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Aminoquinoline-directed, cobalt-catalyzed carbonylation of sulfonamide sp^2 C–H bonds†

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We report a method for cobalt-catalyzed, aminoquinoline-directed sp^2 C–H bond carbonylation of sulfonamides. The reactions proceed in a dichloroethane solvent, and employ diisopropyl azodicarboxylate as a carbon monoxide source, $Mn(OAc)_2$ as a cooxidant and potassium pivalate as a base. Halogen, ester, and amide functionalities are compatible with the reaction conditions. This method allows for a short and efficient synthesis of saccharin derivatives.

2-Sulfobenzoic acid imide functionality is important in pharmaceutical and food chemistry (Fig. 1).[1] For example, Repinotan **1** acts as a highly selective 5-HT1A receptor agonist and is effective in counteracting the respiratory depression produced by morphine.[1a] Ipsapirone **2** has been investigated for generalized anxiety disorder treatment.[1b] Another imide of sulfobenzoic acid, supidimide **3**, has been used as a non-teratogenic analogue of thalidomide.[1c] Saccharin **4** is an artificial sweetener,[1d] while 6-nitrosaccharin **5** is its bitter derivative that activates G protein-coupled receptors hT2R44 and hT2R61, which are thought to mediate a bitter taste response in humans.[1d,e]

The most direct synthesis of 2-sulfobenzoic acid imides would involve the direct carbonylation of arylsulfonic acid amides possessing an appropriate directing group, preferably using a first-row transition metal catalyst.[2] While the second-row transition metal-catalyzed carbonylation of C–H bonds has emerged as an efficient synthetic methodology,[3] the use of first-row metals in these reactions is rare.[4] The cobalt-catalyzed carbonylation of azobenzene and Schiff bases disclosed by Murahashi is perhaps the earliest example of directed C–H bond functionalization.[4a] Previously, we have shown that aminoquinoline benzamide carbonylation can be effected at room temperature under 1 atm of CO by employing oxygen from air as the terminal oxidant.[4b] Following this report, several groups have used aminoquinoline to direct cobalt- or nickel-catalyzed sp^2 and sp^3 C–H bond carbonylation.[4c–e] All of these reports describe aminoquinoline amide C–H bond functionalization that results in the synthesis of substituted phthalic acids. Sulfonamide C–H bond carbonylation under first-row transition metal catalysis has not been reported yet.[5a–c] A single paper by the group of Yu describes two examples of palladium-catalyzed C–H carbonylation.[5d] We report here a method for cobalt-catalyzed, aminoquinoline-directed sp^2 C–H bond carbonylation of sulfonamides. The cleavage of the directing group affords saccharin derivatives.

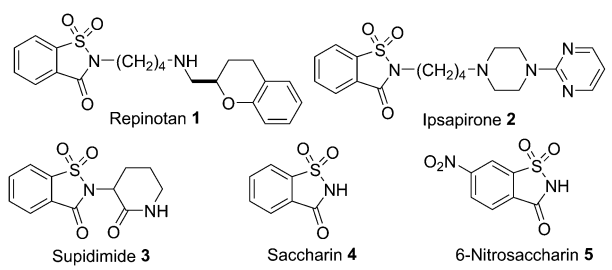

Fig. 1 2-Sulfobenzoic acid imides.

Based on cobalt-catalyzed, aminoquinoline-directed C–H functionalization reactions developed previously by our group,[4b,6] simple cobalt salts were used as catalysts and manganese(II) acetate was chosen as a co-oxidant. Reaction optimization is illustrated in Table 1. The use of carbon monoxide gas gives low conversion to 7 (entry 1). Previously, we have shown that aminoquinoline benzamide carboxylation proceeds efficiently with carbon monoxide at room temperature.[4b] At higher temperatures, required for the corresponding sulfonamide carbonylation, the use of gaseous carbon monoxide is technically challenging. A less volatile source of CO is needed for an efficient reaction. It is known that azodicarboxylate esters decompose at elevated temperatures releasing carbon monoxide,[7a] and dialkyl azodicarboxylates have been used in directed alkoxycarbonylation and carbonylation of sp^2 C–H bonds.[7b,c] When diisopropyl azodicarboxylate (DIAD) was used as a CO source,

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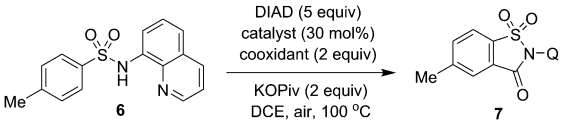
Table 1 Optimization of reaction conditions[a]



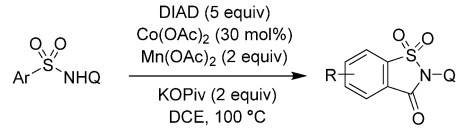
Entry	Catalyst	Cooxidant	Yield of 7, %
1[b]	$Co(OAc)_2$	$Mn(OAc)_2$	<5
2[c,d]	$Co(OAc)_2$	$Mn(OAc)_2$	38
3[d]	$Co(OAc)_2$	$Mn(OAc)_2$	71
4[d]	$Co(acac)_2$	$Mn(OAc)_2$	31
5[d]	$Co(acac)_3$	$Mn(OAc)_2$	25
6[d]	$Co(OAc)_2$	$Mn(OAc)_3{\cdot}2H_2O$	18
7[d]	None	$Mn(OAc)_2$	0
8	$Co(OAc)_2$	None	<5
9[d,e]	$Co(OAc)_2$	$Mn(OAc)_2$	62
10[d,f]	$Co(OAc)_2$	$Mn(OAc)_2$	0

[a] Sulfonamide **6** (0.5 mmol), DIAD (2.5 mmol, added 4 times, 0.625 mmol per time), catalyst (0.15 mmol), cooxidant (1 mmol), KOPiv (1 mmol), DCE (10 mL), 100 °C, 24 h. Yields are isolated yields. Please see the ESI for details. Abbreviations: DIAD = diisopropyl azodicarboxylate, OPiv = pivalate, DCE = 1,2-dichloroethane, acac = acetylacetonate, and Q = 8-quinolinyl. [b] Carbon monoxide was used instead of DIAD. [c] DIAD (2.5 mmol) was added at once at the beginning of the reaction. [d] Reaction vessel periodically opened to air. [e] *tert*-Butyl azodicarboxylate used instead of DIAD. [f] Molybdenum hexacarbonyl used instead of DIAD.

38% yield of **7** was obtained (entry 2). The batchwise addition of DIAD increases the yield to 71% (entry 3). Cobalt(II) and (III) acetylacetonate catalysts afford lower yields compared with those of cobalt(II) acetate (entries 4 and 5). When manganese(III) acetate was used as a cooxidant, the yield decreased to 18% (entry 6). The presence of cobalt is necessary (entry 7), while the reaction under air without any cooxidant gave less than 5% of **7** (entry 8). The reaction under nitrogen gave a substantially lowered product yield. The use of trifluoroethanol as a solvent, which was used for previous cobalt-catalyzed reactions, gave no product. The use of *tert*-butyl azodicarboxylate instead of DIAD gave the product in lower yield (entry 9), while $Mo(CO)_6$ was inefficient as a carbon monoxide source (entry 10).

The reaction scope with respect to substitution in sulfonamides is shown in Table 2. Both electron-rich (entries 1–3, 8 and 12) and electron-poor (entries 5–7 and 9–11) substrates afford products in moderate to good yields. Scaling up of the reaction is feasible without the loss of yields (entry 1). Substitution at the *ortho*-position is tolerated, as sterically hindered 2-methylbenzenesulfonamide gives the product in 55% yield (entry 8). Similar to cobalt-catalyzed aminoquinoline carboxamide carbonylation,[4b] *meta*-substituted substrates react selectively at the less hindered C–H bond (entries 9–14) due to preferential metalation at the less sterically hindered position. The reaction is functional group tolerant, with alkoxy (entry 2), iodo (entry 5), bromo (entry 6), trifluoromethoxy (entry 7), trifluoromethyl (entry 9), chloro (entry 10), fluoro (entry 11), naphthyl (entry 12), unsaturated ester (entry 13), and amide (entry 14) substituents compatible with the reaction conditions. The trifluoroacetylated 1,2,3,4-tetrahydroisoquinoline derivative is carbonylated in 50% yield (entry 14), showing the relevance of the methodology in drug-like molecule derivatization.[8] Nitro-substituted sulfonamides

Table 2 Carbonylation of aminoquinoline sulfonamides[a]



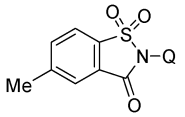
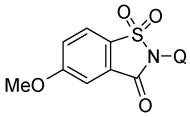
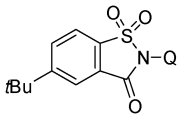
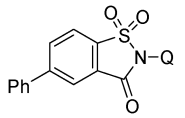
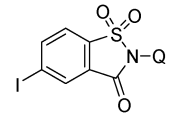
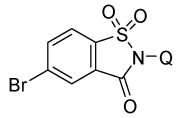
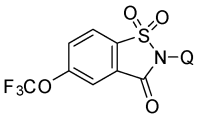
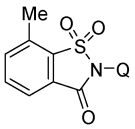
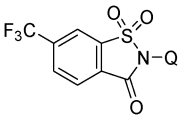
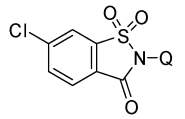
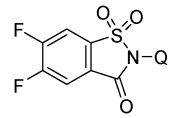
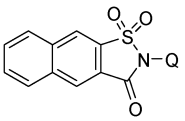
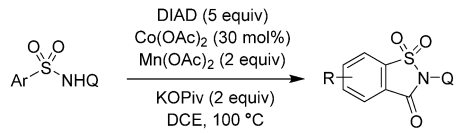
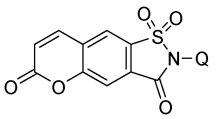
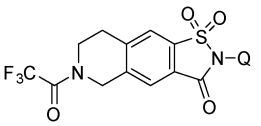
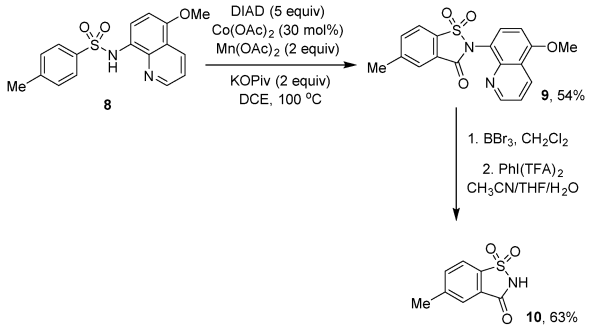
Entry	Ar	Product	Yield, %
1	4-MeC_6H_4		71 68[b]
2	4-$MeOC_6H_4$		59
3	4-*t*BuC_6H_4		72
4	4-PhC_6H_4		57
5	4-IC_6H_4		73
6	4-BrC_6H_4		61
7	4-$CF_3OC_6H_4$		63
8	2-MeC_6H_4		55
9	3-$CF_3C_6H_4$		47
10	3-ClC_6H_4		48
11	3,4-$F_2C_6H_3$		69
12[c]	2-Naphthyl		51

Table 2 (*continued*)



Entry	Ar	Product	Yield, %
13	2-Oxo-2*H*-1-benzo-pyranyl		65
14	2-CF_3CO-tetra-hydroisoquinolinyl		50[d]

[a] Sulfonamide (0.5 mmol), DIAD (2.5 mmol, added 4 times, 0.625 mmol per time), $Co(OAc)_2$ (0.15 mmol), $Mn(OAc)_2$ (1 mmol), KOPiv (1 mmol), DCE (10 mL), 100 °C, 24 h. Yields are isolated yields. Reaction vessel periodically opened to air. Please see the ESI for details. [b] Scale: 2.5 mmol, 30 h. [c] Cobalt(II) chloride (20 mol%) catalyst, DIAD (1.5 mmol), 24 h at 120 °C. [d] Temperature: 85 °C, 30 h.



Scheme 1 Removal of directing group.

did not give any carbonylation product. The reaction mechanism likely includes aminoquinoline-directed cobaltation, carbon monoxide coordination, and migratory insertion followed by reductive elimination from acylcobalt(III) species. Reoxidation to cobalt(III) would complete the catalytic cycle. The reaction mechanism is under investigation and will be published as a full paper.

Chen introduced an 8-amino-5-methoxyquinoline auxiliary that can be oxidatively cleaved.[9] The carbonylation of sulfonamide **8** gave product **9** in 54% yield (Scheme 1). The cleavage of the 5-methoxyaminoquinoline auxiliary under the original conditions employing ceric ammonium nitrate was unsuccessful. However, the removal of the methyl group with BBr_3 followed by oxidation with an iodine(III) reagent afforded methylsaccharin **10** in 63% yield.[10]

In conclusion, we have developed a method for cobalt-catalyzed, aminoquinoline-directed carbonylation of aryl sulfonamides. The reactions proceed in the presence of DIAD as a carbon monoxide source, $Mn(OAc)_2$ as a cooxidant, and employ KOPiv as a base. Functional groups such as halogens, esters, and amides are compatible with the reaction conditions. The removal of the directing group affords saccharin derivatives.

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