ChemPubSoc Europe

DOI: 10.1002/chem.201500331

CHEMISTRY
A European Journal
Communication

Organic Synthesis

Direct C–H Amidation of Benzoic Acids to Introduce *meta*- and *para*-Amino Groups by Tandem Decarboxylation

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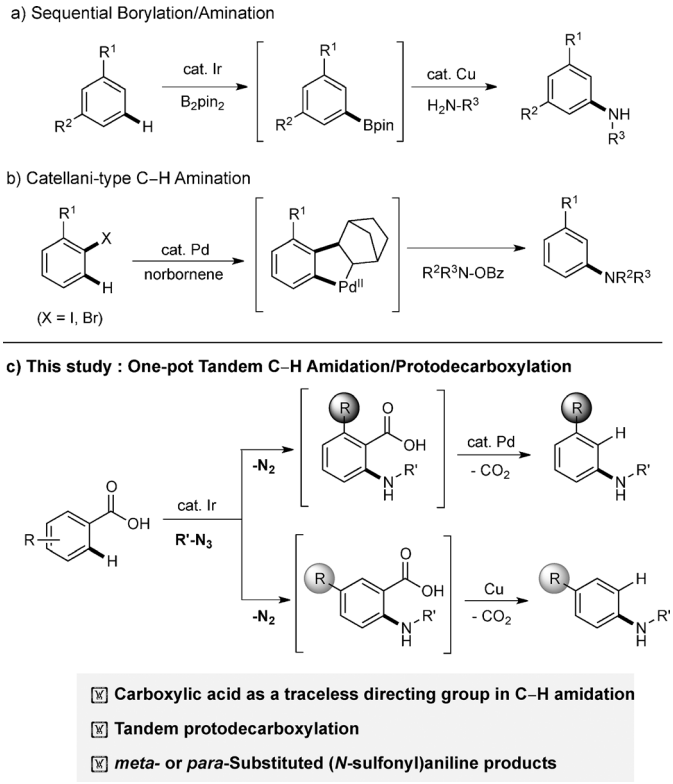
Abstract: The Ir-catalyzed mild C–H amidation of benzoic acids with sulfonyl azides was developed to give reactions with high efficiency and functional-group compatibility. Subsequent protodecarboxylation of *ortho*-amidated benzoic acid products afforded *meta*- or *para*-substituted (*N*-sulfonyl)aniline derivatives, the latter being inaccessible by other C–H functionalization approaches. The decarboxylation step was compatible with the amidation conditions, enabling a convenient one-pot, two-step process.

Preparation of aryl amines is one of the most important reactions in organic synthesis because they are omnipresent as a key unit in natural products, synthetic intermediates, pharmaceuticals, agrochemicals, and electronic materials.[1] As a result, significant research progress has been made in the past few decades, enabling the development of efficient C–N bond forming procedures.[2] Among these, the Buchwald–Hartwig *N*-arylation[3] represents one of the most well-established methods for this purpose. Its broad applicability is unprecedented; the reaction employs aryl (pseudo)halides as starting materials to react with amines, however, it also generates stoichiometric amounts of byproducts such as halide salts. In this regard, direct C–H amination[4] has attracted special attention as (hetero)arenes can be directly employed. Because control of regioselectivity in the C–H amination approach is a challenge, chelation-assisted C–H bond activation is the most widely utilized route, thus giving rise to *ortho*-aminated products.[5] Because of this, the installation of amino groups at the *meta*-position relative to the existing arene substituents has been much less exploited and only a few examples have been reported. For instance, Hartwig and co-workers devised an elegant tandem process for the synthesis of 3,5-disubstituted arylamines that involves Ir-catalyzed borylation of arenes followed by a Cu-catalyzed Chan–Lam type amination (Scheme 1 a).[6] Although this method displays high efficiency and excellent selectivity, substrates are limited to 3,5-disubstituted arenes for securing *meta*-selective borylation. Another creative strategy was disclosed by the Dong group, in which the Pd-catalyzed Catellani-type C–H amination of aryl halides is achieved in the presence of a norbornene cocatalyst (Scheme 1 b).[7] This procedure of employing specially designed amino sources allows selective C–H amination to occur *ortho* to the traceless halide substituents, and, interestingly, the Buchwald–Hartwig type *N*-arylation was not observed.



Scheme 1. Synthetic approaches to *meta*- or *para*-substituted anilines.

meta-Substituted arenes can be accessed by employing removable directing groups to guide the selective C–H bond activation, and these are cleaved after the desired C–H functionalization.[8] In fact, this approach to combine *ortho*-functionalization and subsequent removal of directing groups has been successfully applied to reactions using carboxylic acids as a traceless directing group by several research groups.[9] For instance, formal *meta* C–H olefination or arylation was reported independently by Miura and Larrosa.[9a–d] More recently, Gooßen and co-workers developed a synthetic route to aryl

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500331.

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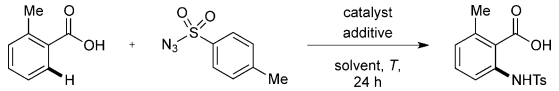
ethers from carboxylic acids by using this strategy.[9f] In these reports, however, only carbon or oxygen groups were introduced *ortho* to the carboxylic acids to obtain *meta*-substituted arenes.

Although *ortho* C–H amidation of benzoic acids was previously reported by Yu,[10] C–N bond formation at the *meta*-position of substituted arenes through this approach has not been reported to the best of our knowledge. Moreover, the traceless C–H functionalization method has never been applied to the synthesis of *para*-substituted amino arenes. In this context, described herein is an advance to access to *meta*- and *para*-substituted (*N*-sulfonyl)anilines through a tandem process, that is, Ir-catalyzed *ortho* C–H amidation of benzoic acids and the subsequent protodecarboxylation by Pd or Cu catalysts (Scheme 1c). As the second stage is compatible with the initial C–H amidation conditions, this tandem procedure could be optimized to be conveniently carried out in one pot.

We commenced our studies by optimizing an amidation reaction of 2-methylbenzoic acid (**1a**) with *p*-toluenesulfonyl azide (**2a**, 1.2 equiv) under various catalytic conditions (Table 1).[11] A moderate yield (35%) of the *ortho*-amidated toluic acid (**3a**) was obtained when $[IrCp^*Cl_2]_2$ was used in the presence of $AgNTf_2$ additive for the in situ generation of a cationic iridium species, whereas no reaction took place with a neutral precursor only (entries 1–2). To our delight, the amidation occurred almost quantitatively in the presence of lithium acetate at 80 °C (entry 3). Remarkably, the desired reaction took place even at room temperature, albeit with slightly lower efficiency (entry 4). Optimal conditions were established with 2 mol% of dimeric iridium precursor $[IrCp^*Cl_2]_2$ at 50 °C in 1,2-dichloroethane (1,2-DCE) to afford the desired product **3a** in high yield (entry 5). LiOAc turned out to be most effective: the use of other acetates resulted in lower efficiency (entries 6–7, and see the Supporting Information for details). The reaction was also found to be sensitive to the choice of solvents: 1,4-dioxane was similar to 1,2-DCE in efficiency, but the reaction was sluggish in polar solvents (entries 8–10). Although the amidation was still significant even with lower amounts of iridium catalyst (entry 11), other previously known catalytic systems such as rhodium, ruthenium, and palladium, were not effective (entries 12–14).[5,10]

With the optimized conditions in hand, we explored the scope of substrates in the reaction with *p*-toluenesulfonyl azide (Table 2). Benzoic acids bearing alkyl, aryl, or alkoxy groups at the *ortho*-position underwent the desired amidation in moderate to high yields (**3a**–**3e**). The reaction of mono- or

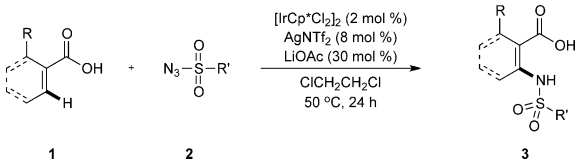
Table 1. Optimization of C–H amidation of benzoic acid.[a]

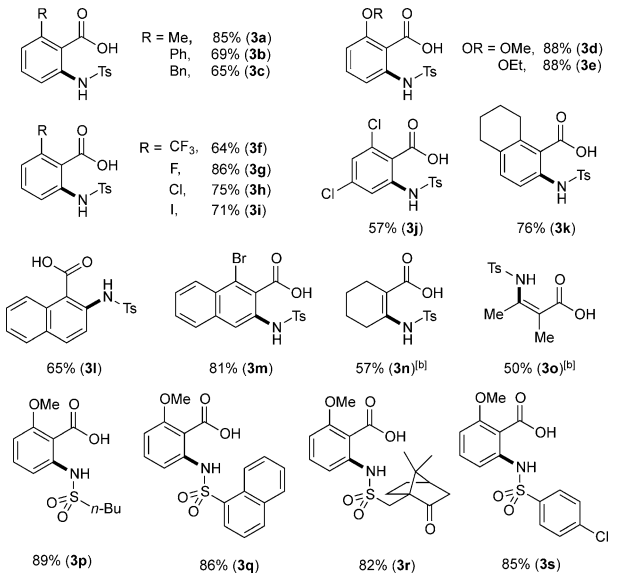


Entry	Catalytic system (mol%)	Additives (mol%)	Solvent	T [°C]	Yield [%][b]
1	$[IrCp^*Cl_2]_2$ (4)	–	1,2-DCE	80	N.R.
2	$[IrCp^*Cl_2]_2$ (4)/$AgNTf_2$ (16)	–	1,2-DCE	80	35
3	$[IrCp^*Cl_2]_2$ (4)/$AgNTf_2$ (16)	LiOAc (30)	1,2-DCE	80	95
4	$[IrCp^*Cl_2]_2$(4)/$AgNTf_2$ (16)	LiOAc (30)	1,2-DCE	25	75
5	**$[IrCp^*Cl_2]_2$ (2)/$AgNTf_2$ (8)**	**LiOAc (30)**	**1,2-DCE**	**50**	**92**
6	$[IrCp^*Cl_2]_2$ (2)/$AgNTf_2$ (8)	NaOAc (30)	1,2-DCE	50	78
7	$[IrCp^*Cl_2]_2$ (2)/$AgNTf_2$ (8)	KOAc (30)	1,2-DCE	50	55
8	$[IrCp^*Cl_2]_2$ (2)/$AgNTf_2$ (8)	LiOAc (30)	1,4-dioxane	50	91
9	$[IrCp^*Cl_2]_2$ (2)/$AgNTf_2$ (8)	LiOAc (30)	DMSO	50	<5
10	$[IrCp^*Cl_2]_2$ (2)/$AgNTf_2$ (8)	LiOAc (30)	DMF	50	32
11	$[IrCp^*Cl_2]_2$ (1)/$AgNTf_2$ (4)	LiOAc (30)	1,2-DCE	50	63
12	$[RhCp^*Cl_2]_2$ (2)/$AgSbF_6$ (8)	LiOAc (30)	1,2-DCE	50	N.R.
13	$[Ru(p\text{-cymene})Cl_2]_2$ (2)/$AgNTf_2$ (8)	LiOAc (30)	1,2-DCE	50	N.R.
14	$[Pd(OAc)_2]$	–	1,2-DCE	50	N.R.

[a] Reaction conditions: **1a** (0.20 mmol) and **2a** (1.2 equiv) in solvent (0.5 mL). [b] ^1H NMR yield of crude reaction mixture ($Cl_2CHCHCl_2$ as an internal standard). N.R. = no reaction.

Table 2. Substrate scope of carboxylic acids in the C–H amidation.[a]





[a] Reaction conditions: **1** (0.20 mmol) and **2** (1.2 equiv) in 1,2-dichloroethane (0.5 mL). Yields of isolated products are given. [b] AgOAc was used instead of LiOAc at 25 °C.

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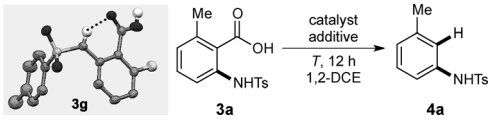
disubstituted halide-containing substrates was also facile (**3f**–**3j**), indicating that the amidation was not significantly influenced by the electronic variation of substrates. The sulfonamidated product of tetrahydronaphthalene carboxylic acid was formed in high yield (**3k**), a product that is known to be a potent inhibitor of methionine aminopeptidase-2 (MetAP-2).[12] Reactions with naphthoic acids also proceeded smoothly (**3l**–**3m**). Significantly, olefinic C–H bonds could also be amidated in acceptable yields by using carboxylic acid as a directing group (**3n**–**3o**). It is noteworthy that the amidation of tiglic acid took place at room temperature (**3o**). In addition, the scope of sulfonyl azides that underwent reaction was broad enough to include alkyl, naphthyl, camphor, and halide-substituted phenyl derivatives, and all of which were found to be highly suitable amido sources (**3p**–**3s**). On the other hand, other amino sources such as alkyl-, aryl-, and phosphoryl azides were not reactive, leading to negligible product yields (<5%), only acyl azides showed moderate reactivity, but still with insufficient efficiency (~30% yields).

As a proof of concept, we were curious to see whether decarboxylation of amidated products could be achieved. Considering the fact that amidated products obtained in this study have an intramolecular hydrogen-bond between the carboxylic acid and sulfonamide groups (the X-ray structure of **3g** is shown in Table 3), it was uncertain at the initial stage if the desired defunctionalization would indeed take place.[13] We were delighted to observe that protodecarboxylation of **3a** was mediated efficiently by a [Pd(OAc)$_2$] catalyst at 120 °C (Table 3, entry 2).[14] However, known procedures using silver species were not successfully adapted (entries 4–5).[15]

Table 3. Optimization of protodecarboxylation.[a]



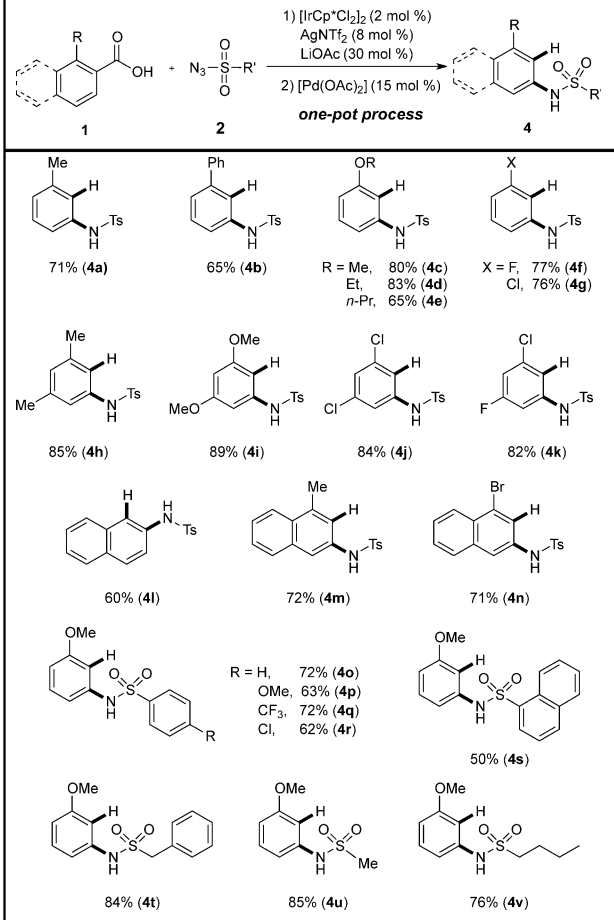
3g 3a 4a

Entry	Catalyst (mol%)	Additive	T [°C]	Yield [%][b]
1	[Pd(OAc)$_2$] (15)	–	100	52
2	**[Pd(OAc)$_2$] (15)**	–	**120**	**84**
3	[Pd(O$_2$CCF$_3$)$_2$] (10)	TFA (10.0 equiv)	120	24
4	Ag$_2$CO$_3$ (10)	–	120	<5
5	AgOAc (20)	K$_2$CO$_3$ (15 mol%)	120	<5

[a] Reaction conditions: **3a** (0.10 mmol) in 1,2-dichloroethane (0.5 mL). [b] ^{1}H NMR yield of crude reaction mixture (Cl$_2$CHCHCl$_2$ as an internal standard).

The Pd-mediated protodecarboxylation procedure was then examined to see whether it is compatible with the Ir-catalyzed C–H amidation conditions. We were pleased to find that the two reactions could be carried out *in one pot* without the need to isolate the amidated products for the subsequent decarboxylation process. Indeed, the decarboxylation occurred smoothly just by adding the palladium catalyst (15 mol%) to the amidation reaction mixture and then allowing the reaction to occur for 12 h at 120 °C. It should be noted that the overall yields for the one-pot, two-step procedure were similar or better than those obtained from two separate reactions by isolating the amidated intermediates. As a result, a tandem process consisting of two catalytic reactions could be applied to a wide range of carboxylic acid substrates (Table 4).

Table 4. Substrate scope for the tandem C–H amidation and decarboxylation.[a]



[a] Reaction conditions: 1) **1** (0.20 mmol) and **2** (1.2 equiv) in 1,2-dichloroethane (0.5 mL) at 50 °C for 24 h; 2) 120 °C for 12 h. Yields of isolated products are given.

The one-pot protocol of C–H amidation and subsequent protodecarboxylation proceeded smoothly with most of the substrates examined in good to excellent product yields. Electronic variation of substrates was not influential on the reaction efficiency, and both electron-donating and -withdrawing groups were compatible in each step of the amidation and decarboxylation (**4a**–**4g**). The one-pot procedure was successfully applied to 2,4-disubstituted benzoic acids, leading to 3,5-disubstituted (*N*-sulfonyl)anilines in high yields regardless of the electronic properties (**4h**–**4k**). It should be mentioned that although these products could also be obtained by using the Hartwig tandem process of borylation and amidation, monosubstituted anilines cannot be accessed by this approach. Naphthoic acids were reacted under the optimized conditions to give naphthalene sulfonamides bearing various substituents

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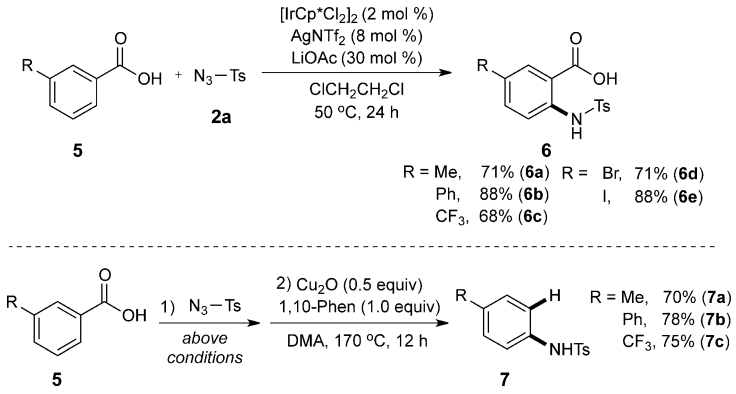

Scheme 2. Amidation of 3-substituted benzoic acids and tandem one-pot procedure to afford *para*-substituted (*N*-sulfonyl)anilines. Reaction conditions: 1) **5** (0.20 mmol) and **2a** (1.2 equiv) in 1,2-dichloroethane (0.5 mL); 2) after amidation was complete, the solvent was removed and replaced with DMA (0.5 mL). Yields of isolated products are given.

(**4l**–**4n**). Again, a labile bromo group was well tolerated under the Pd-catalyzed decarboxylation conditions (**4n**). We were also curious to see whether this tandem process would work with various types of sulfonyl azides. Both arene and alkane sulfonamides were completely compatible with the Pd-catalyzed protodecarboxylation conditions (**4o**–**4v**). In addition, the reaction efficiency was not influenced by the electronic property of the arene sulfonamide moiety (**4o**–**4r**).

With successful results in obtaining *meta*-substituted (*N*-sulfonyl)anilines, we were next curious to extend this approach to the formation of *para*-substituted (*N*-sulfonyl)anilines.

It was envisioned that the key to success would be regioselective C–H amidation of *meta*-substituted benzoic acids. Unlike 2-substituted benzoic acids, there are two reactive C–H bonds present for possible amidation in the case of 3-substituted benzoic acids. In this regard, we anticipated that the difference in steric congestion between the two C–H bonds in 3-substituted benzoic acids would lead to the preferential activation at the less sterically hindered site, thus leading to regioselective amidation. We were quite pleased to observe that this prediction turned out to be the case (Scheme 2, top). Indeed, Ir-catalyzed amidation of 3-methylbenzoic acid with *p*-toluenesulfonyl azide proceeded exclusively at the 6-position without reacting at the sterically more congested 2-position (**6a**). This reactivity and selectivity were maintained in other substrates bearing C-3 substituents, such as phenyl (**6b**), trifluoromethyl (**6c**), bromo (**6d**), and iodo groups (**6e**). In all the cases examined, the desired products were obtained in satisfactory yields by using 2 mol% of iridium catalyst at 50 °C.

We next examined the feasibility of a tandem one-pot process consisting of C–H amidation followed by protodecarboxylation of the obtained products, **6**. Although a palladium catalyst system had been successfully applied to amidated compounds obtained from *ortho*-substituted benzoic acids (Table 4), we found that Cu_2O (0.5 equiv) was required to mediate the protodecarboxylation process of amidated products derived from 3-substituted benzoic acids.[16] More pleasingly, the two separate reactions could be conveniently carried in one pot with a slight modification of the second reaction: 1,2-dichloroethane, used in the amidation, was replaced by dimethylacetamide (DMA) for the subsequent decarboxylation step. With this combined protocol, *para*-substituted (*N*-sulfonyl)aniline products (**7a**–**7c**) were obtained in satisfactory overall yields (Scheme 2, bottom). It is worthwhile to mention that, to our best knowledge, this is the first example preparing *para*-substituted amidated compounds by using C–H functionalization approaches. In fact, neither the Hartwig or Dong's approaches can provide this type of products.[6,7]

In conclusion, we have developed a new approach to *meta*- and *para*-substituted (*N*-sulfonyl)anilines. Carboxylic acids were utilized as traceless directing groups in the Ir-catalyzed direct C–H amidation of arenes with sulfonyl azides under mild conditions. Subsequent protodecarboxylation of the carboxylic acid group in the amidated products was catalyzed by palladium or copper species. The two tandem reactions were optimized to enable them to be carried out conveniently in one pot without need to isolate the *ortho*-amidated benzoic acid intermediates.

Experimental Section

Representative tandem procedure

ortho-Toluic acid (**1a**, 0.20 mmol), *p*-toluenesulfonyl azide (**2a**, 0.24 mmol), $[IrCp^*Cl_2]_2$ (3.2 mg, 2.0 mol%), $AgNTf_2$ (6.2 mg, 8.0 mol%), LiOAc (4.0 mg, 30 mol%) and 1,2-dichloroethane (0.5 mL) were placed in a screw-capped vial equipped with a Spinvane triangular stir bar. The reaction mixture was stirred at 50 °C in a pre-heated oil bath for 24 h. After cooling to room temperature, $[Pd(OAc)_2]$ (6.6 mg, 15 mol%) was added and the resulting mixture was stirred at 120 °C for an additional 12 h. Upon cooling, the mixture was filtered through a pad of Celite and washed with EtOAc (3×10 mL). Solvents were removed under reduced pressure, and the residue was purified by silica-gel chromatography (*n*-hexane/EtOAc = 8:1, v/v) to give **4a** (37 mg, 71%).

Acknowledgements

This research was supported by the Institute for Basic Science in Korea (IBS-R010-D1).

Keywords: C–H amidation · decarboxylation · *meta*- and *para*-substituted anilines · tandem processes · traceless directing groups

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Received: January 26, 2015
Published online on ■■ ■■, 0000

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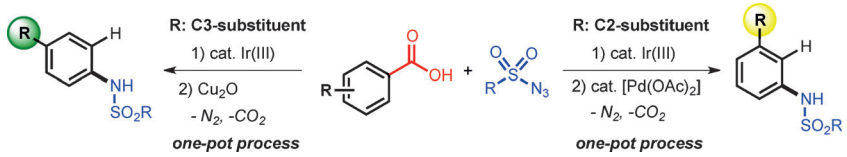
Direct C–H Amidation of Benzoic Acids to Introduce *meta*- and *para*-Amino Groups by Tandem Decarboxylation



Without a trace: Carboxylic acids are used as traceless directing groups in the Ir-catalyzed direct C–H amidation of arenes with sulfonyl azides under mild conditions. The tandem protodecarboxylation of the *ortho*-amidated benzoic acid products afforded *meta*- or *para*-substituted (*N*-sulfonyl)anilines, which are difficult to obtain by other C–H functionalization approaches.

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