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Palladium-Catalyzed β-C–H Arylation of Alkyl Carboxamides with Sterically Hindered Aryl Iodides Using *Ortho*-Sulfinyl Aniline Auxiliaries

Delong Mu,[a] Fang Gao,[a] Gong Chen*[a,b,c] and Gang He*[a,b]

[a]State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China.

[b]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China.

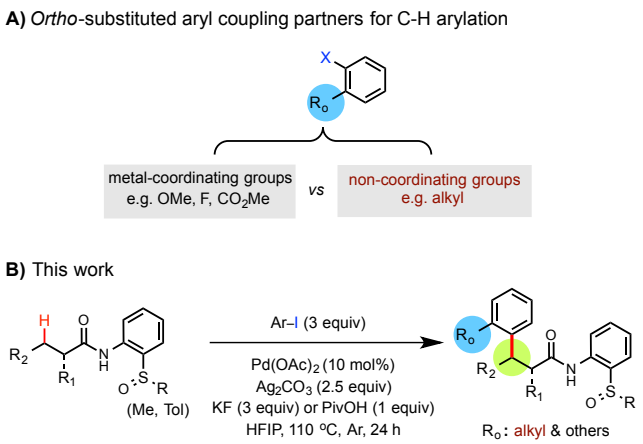
[c]Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, United States.

ABSTRACT: We disclose a pair of *ortho*-sulfinylaniline auxiliaries for palladium-catalyzed β-C-H arylation of alkyl carboxamides. Together, these auxiliaries offer a means to effect efficient β-methyl and methylene C–H bond arylation with sterically hindered aryl iodides. *Ortho*-methylsulfinylaniline (MSOA) enables efficient β-methyl C-H arylation of propanamide substrates with aryl iodides bearing various *ortho*-substituents including alkyl groups. *Ortho*-tosylsulfinylaniline (TSOA) enables β-methylene C-H arylation with *ortho*-substituted aryl iodides. Both amide-linked MSOA and TSOA auxiliaries can be easily removed to give ester products under relatively mild conditions.

KEYWORDS: *sp³ C-H arylation, methylene C-H, hindered aryl iodide, palladium, sulfinylaniline auxiliary*

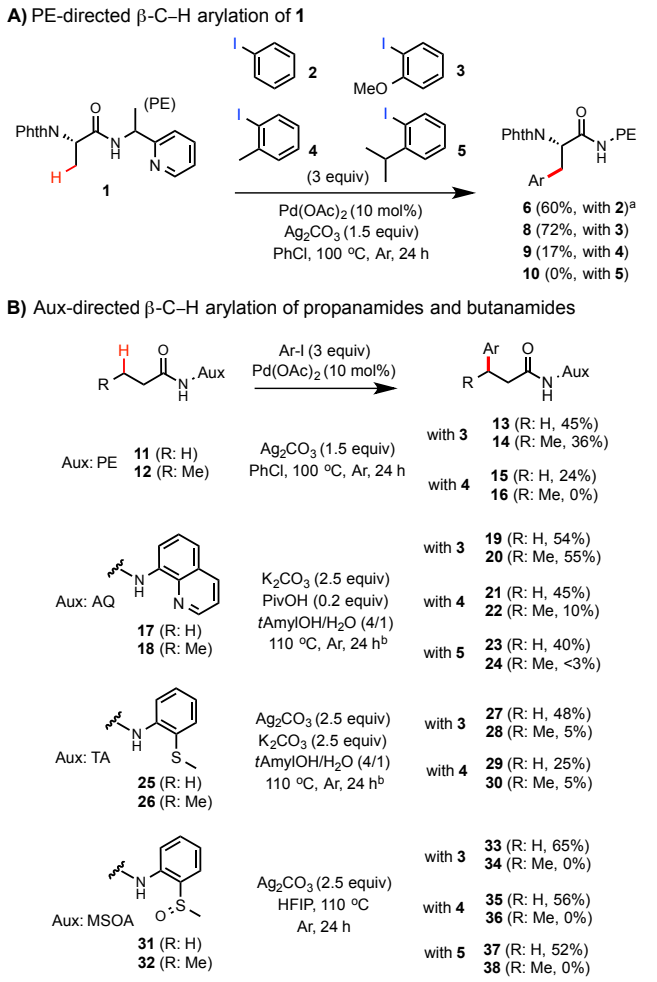
Metal-catalyzed directing group-facilitated C(sp³)-H arylation reactions have been greatly advanced over the past decade.[1] Among these reactions, palladium-catalyzed β-C-H arylation of alkyl carboxamides equipped with amide–linked auxiliary groups has enjoyed the most success, offering increasingly useful methods for the synthesis of β-aryl alkylcarboxamides.[2] However, despite these developments, significant limitations on substrate scope must be overcome to achieve broad application of this reaction strategy. Firstly, in comparison with the widely reported arylation reactions of β-methyl C-H bonds, the arylation of unactivated methylene C-H bonds are considerably more difficult and this transformation is only available to substrates bearing small subset of auxiliary groups.[3,4] Secondly, while the use of sterically unhindered *para*- or *meta*-substituted aryl coupling partners is common, the incorporation of *ortho*-substituted aryl groups presents a significant challenge (Scheme 1A). Using established methods, the amenable *ortho* substituents of aryl coupling partners are mostly limited to groups with metal-coordination ability, e.g. OMe, F, and ester.[5] Successful coupling reactions with aryl reactants bearing non-coordinating *ortho*-substituents have only been sporadically reported for primary C(sp³)-H bonds;[6] efficient arylation of unactivated secondary C(sp³)-H bonds with *ortho*-alkyl aryl partners has not been realized. Herein, we report the development of a pair of new *ortho*-sulfinylaniline auxiliaries for Pd-catalyzed β-C(sp³)-H arylation of alkylcarboxamides with a broad range of sterically hindered aryl iodides (Scheme 1B).[7]

In the course of our recent total synthesis of hibispeptin A, we discovered that the 2-pyridylethylamine (PE) directing group enabled a challenging Pd-catalyzed arylation of the γ-methyl C-H bond of phthaloyl isoleucine with a sterically hindered *ortho*-benzyloxy aryl iodide, allowing us to prepare a key C_{alkyl}-C_{aryl} linked



Scheme 1. Pd-catalyzed β-C(sp³)-H arylation of alkyl carboxamides with aryl iodides

pseudodipeptide intermediate.[8] Subsequently, we demonstrated the utility of this PE auxiliary with the synthesis of various β-aryl-α-amino acids bearing *ortho*-substituted aryl side chains via β-methyl C-H arylation of phthaloyl alanine precursor **1** (Scheme 2A).[9] While the reaction of **1** with 2-methoxylphenyl iodide **3** proceeded in good yield, the yield of the reaction with 2-iodotoluene **4** dropped substantially, and when 2-isopropylphenyl iodide **5** was evaluated, no arylated product **10** was detected. Furthermore, the β-methyl C-H arylation of conformationally more flexible PE-coupled propanamide **11** with **3** gave notably decreased yield (**13**, Scheme 2B), and β-methylene C-H arylation of PE-coupled butanamide **12** with **4** did not form any product **16**. Clearly, aryl iodide substrates bearing non-coordinating *ortho*-alkyl substituents,

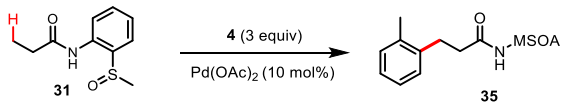


Scheme 2. Comparative studies of different amine-based auxiliaries for β-C(sp^3)-H arylation with aryl iodides. Isolated yields on a 0.2 mmol scale. a) A β-diarylated side product **7** was obtained in 16% yield. No substantial amount of β-diarylated products (< 3%) were detected for the other reactions listed in this Scheme. b) These conditions were optimized for the best results for reaction with **4**. See supporting information for more results under other reactions conditions.

even as small as a methyl group, cannot be efficiently coupled via PE-directed Pd-catalyzed C(sp^3)-H arylation.

To address this substrate scope limitation, we then examined the performance of two other well-studied aniline-based bidentate auxiliary groups. The 8-aminoquinoline (AQ) and 2-(methylthio)aniline (TA) auxiliaries were first introduced by Daugulis for Pd-catalyzed C-H arylation with aryl iodides (Scheme 2B).[10] The reactions of aminoquinoline (AQ)-coupled propanamide **17** and butanamide **18** with **3** provided higher yield than the corresponding PE-directed reactions under optimized conditions (**19** *vs* **13**, **20** *vs* **14**). However, the yield of arylation with *ortho*-alkyl substituted aryl iodides **4** and **5** was poor (see **21**-**24**). The 2-(methylthio)aniline auxiliary exhibited comparable reactivity to PE under the optimized conditions (see **27**-**30**). Inspired by recent reports on sulfoxide-based directing groups for Pd-catalyzed C(sp^2)-H functionalization,[11-14] we synthesized 2-methylsulfinyl aniline (MSOA) containing **31**[15] and subjected it to C(sp^3)-H arylation with our panel of *ortho* substituted aryl iodides. To our delight, propanamide **31** gave promising results (see **33**, **35** and **37**) in the presence of Ag_2CO_3 additive in hexafluoroisopropanol

Table 1. β-C-H arylation of propanamide **31** with **4**



entry	reagents (equiv)	solvent	t (°C)	yield (%)[a]
1	Ag_2CO_3 (2.5)	tAmylOH	110	<5
2	Ag_2CO_3 (2.5), K_2CO_3 (2.5)	tAmylOH/ H_2O (4/1)	110	<5
3	Ag_2CO_3 (2.5)	CH_3CN	110	<5
4	Ag_2CO_3 (2.5)	DCE	110	<5
5	Ag_2CO_3 (2.5)	TFE	110	55
6	Ag_2CO_3 (2.5)	tBuOH (F_9)[b]	110	59
7	Ag_2CO_3 (2.5)	HFIP	110	58
8	AgOAc (2.5)	HFIP	110	34
9	Ag_2CO_3 (2.5), K_2CO_3 (2.5)	HFIP	110	53
10	K_2CO_3 (2.5)	HFIP	110	<5
11	Ag_2CO_3 (2.5), KF (3.0)	HFIP	110	74(71)[c]
12	Ag_2CO_3 (2.5), KF (3.0)	HFIP	130	54
13	AgF (2.5)	HFIP	110	59
14	Ag_2CO_3 (2.5), PivOH (1.0)	HFIP	110	35
15	Ag_2CO_3 (2.5), $(BnO)_2PO_2H$ (0.2)	HFIP	110	56
16	Ag_2CO_3 (2.5), KF (3.0), PivOH (1.0)	HFIP	110	49

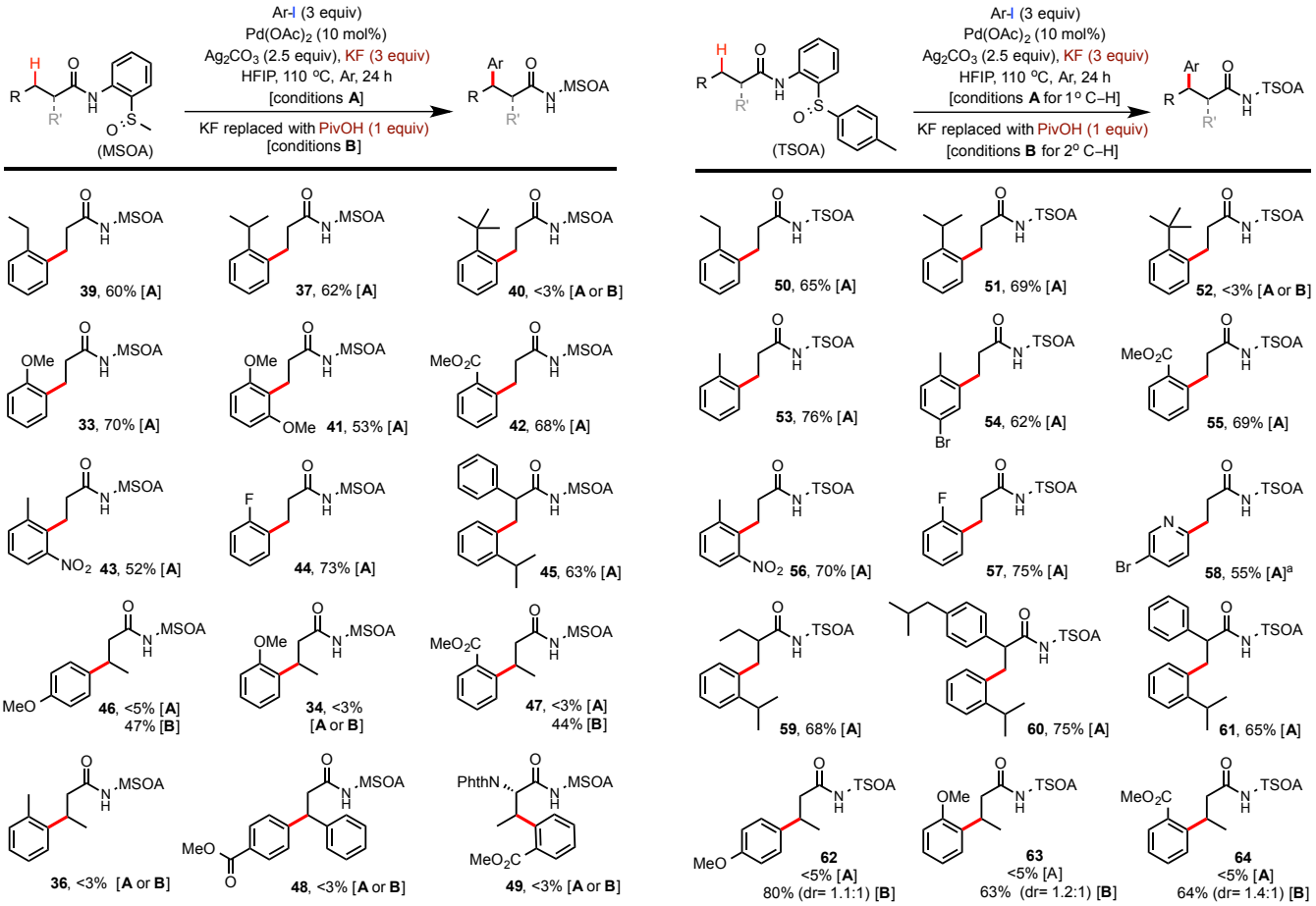
a) Yields are based on ^{1}H-NMR analysis on a 0.2 mmol scale using 1, 1, 2, 2-tetrachloroethane as internal standard; b) perfluoro-*t*-butanol; c) Isolated yield. No β-di-arylated product was formed under the conditions tested above.

(HFIP)[16] solvent at 110 °C. However, MSOA-directed β-methylene C-H arylation of substrate **32** was unsuccessful (see **34**, **36** and **38**).

As seen in Table 1, choice of solvent is critical in the reaction of **31** with **4** (entries 1-7). The reaction performed best in fluorinated alcohols such as trifluoroethanol (TFE), perfluoro-t-butanol and HFIP.[17] We chose HFIP solvent for further reaction optimization due to its relatively lower cost. The use of Ag additive is also required (entry 10 vs 7). Interestingly, the addition of 3 equiv of KF can further improve the reaction, giving **35** in 71% isolated yield (entry 11).[18]

The substrate scope of MSOA-directed β-C(sp^3)-H arylation was then investigated under the optimized conditions **A** (Scheme 3). β-Methyl C-H arylation of **31** with both 2-ethyl and 2-isopropylphenyl iodides gave the desired products in good yields (**39**, **37**). However, arylation with 2-*t*-butylphenyl iodide did not give any product **40**. Aryl iodides bearing coordinating groups such as MeO, CO_2Me and F at the *ortho* position were well tolerated (**33**, **42**, **44**). 2-Methyl-6-nitrophenyl iodide also reacted with **31** to give **43** in good yield. As seen in **46** and **47**, β-methylene C-H arylation of butanamide gave little product under conditions **A**. Interestingly, replacing KF used in conditions **A** with 1 equiv of PivOH (conditions **B**, entry 14 in Table 1) gave improved yield. However, MSOA-directed β-methylene C-H arylation of many other substrates still failed to proceed under either conditions **A** and **B** (see **34**, **36**, **48**).

To further improve the directing ability of *ortho*-sulfinyl aniline auxiliary, we then examined various analogs of MSOA. We were pleased to find that *ortho*-tolylsulfinyl aniline (TSOA) gave notably improved results (Scheme 4). The β-methyl C-H arylation of TSOA-coupled propanamide with various *ortho* alkyl substituted aryl iodides gave good yields. As seen in **59**, the arylation reactions



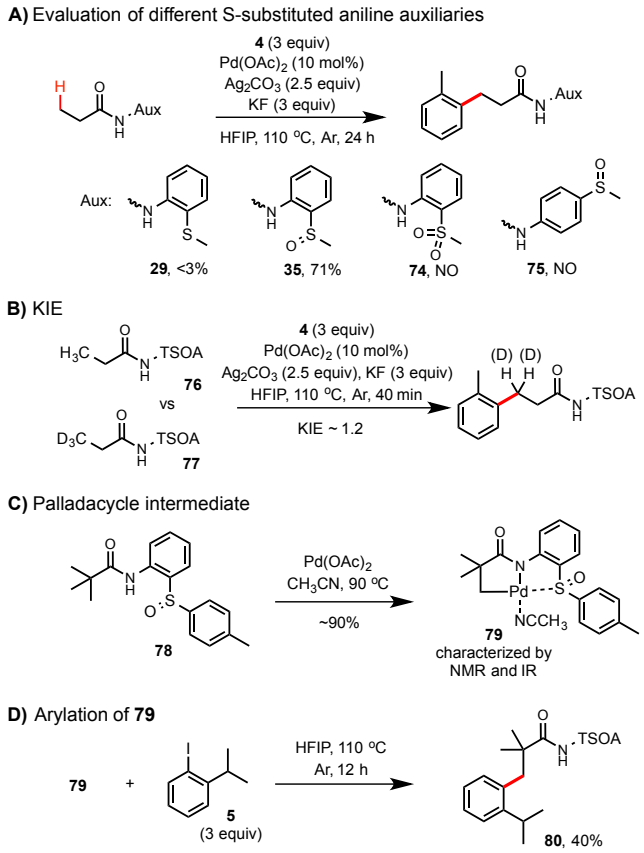
Scheme 3. Substrate scope of Pd-catalyzed MSOA-directed β-C(sp^3)-H arylation. Isolated yield on a 0.2 mmol scale.

Scheme 4. Substrates scope of Pd-catalyzed TSOA-directed β-C(sp^3)-H arylation. Isolated yields on a 0.2 mmol scale. a) *t*-Amyl-OH was used instead of HFIP. b) 120 °C.

with 2-isopropylphenyl iodide **5** proceeded with selectivity for β-methyl over methylene C-H bond functionalization. In the absence of reactive β-methyl groups, the TSOA directing group enables β-methylene C-H arylation with aryl iodides carrying coordinating groups such as MeO, F, CO_2Me, and ketones at the *ortho* position under conditions **B** (see **62-70**). However, β-methylene C-H arylations with *ortho*-alkyl aryl iodides gave lower yield. Nevertheless, an 18% yield of product **71**, represents a notable improvement relative to the results obtained from existing methylene C-H arylation systems (see **71** vs **24** in Scheme 2).

We have performed some preliminary mechanistic studies. As shown in Scheme 5A, both *ortho*-sulfonylaniline (**74**) and *para*-sulfinyl aniline (**75**) auxiliaries failed to deliver arylated product under the standard reaction conditions, suggesting the *ortho*-sulfinyl group of aniline is critical to exert the directing ability. We speculate that the higher yields of arylated product obtained using *ortho*-sulfinyl auxiliary **31** as compared to *ortho*-thiomethyl aniline **25** results from stabilization of the auxiliary-catalyst complex via a π backbonding interaction.[19-21] A small kinetic isotope effect (KIE) value (K_H/K_D ~ 1.2) was observed via the parallel β-methyl C-H arylation of **76** and **77** with **4** under the conditions **A**, suggesting that C-H palladation is not the turnover limiting step (Scheme 5B). We obtained palladacycle intermediate **79** from the reaction of stoichiometric amounts of pivalamide **78** and $Pd(OAc)_2$ in acetonitrile. Palladacycle **79** was characterized by ^{1}H-NMR and IR spectroscopy (Scheme 5C).[22] When 2-isopropyl-iodobenzene **5** was added to compound **79**, arylated product **80** was formed in moderate yield (Scheme 5D). Based on these results, we propose that the catalytic cycle of *ortho*-sulfinylaniline-directed C-H arylation features a sequence of C–H palladation, oxidative addition with aryl iodide, and reductive elimination.

As shown in Scheme 6A, enantioenriched TSOA* **83** was prepared following a known procedure.[12h] TSOA*-directed β-C-H arylation of **84** with methyl 4-iodobenzoate proceeded with moderate diastereoselectivity (dr = 3:1) under the general conditions **B**.[23] The TSOA group of **85** was removed by treatment with HCl in



Scheme 5. Mechanism studies.

MeOH at 100 °C to give the corresponding methyl ester **86** in excellent yield (Scheme 6B). The MSOA group of **35** can also be removed under the same conditions to give ester **87** in good yield.

In summary, *ortho*-sulfinyl aniline-based auxiliaries MSOA and TSOA are uniquely effective at facilitating palladium-catalyzed β-C-H arylation of alkyl carboxamides with sterically hindered aryl iodides. The structurally simpler MSOA auxiliary enables efficient β-methyl C-H arylation of propanamide with aryl iodides carrying various *ortho*-substituents including those bearing *ortho* alkyl groups. The TSOA auxiliary enables more challenging β-methylene C-H arylation with various *ortho*-substituted aryl iodides. We suspect that π acidity of sulfoxides may contribute to the directing ability of these auxiliaries. Both MSOA and TSOA auxiliaries can be easily removed under relatively mild acidic conditions. We are investigating the use of these auxiliaries in other Pd-catalyzed C-H functionalization reactions.

ASSOCIATED CONTENT

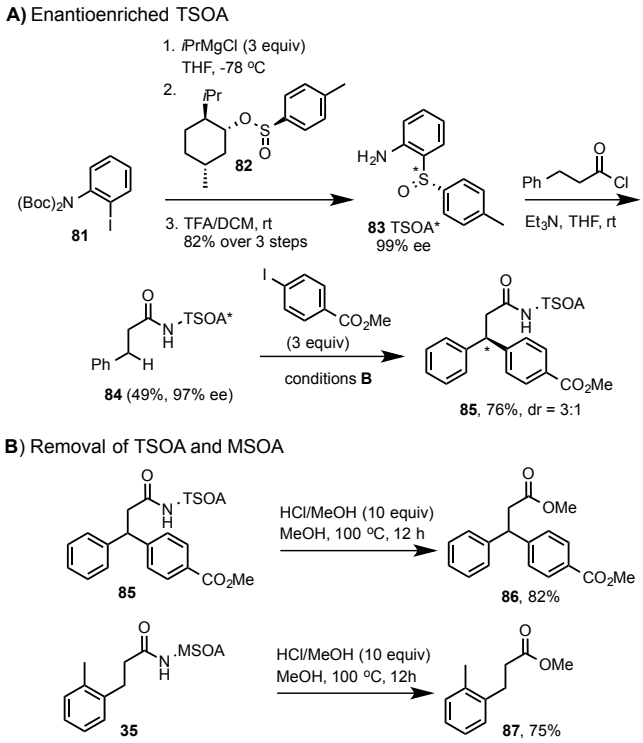
Supporting Information

Additional experimental procedures and spectroscopic data for all new compounds are supplied. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

hegang@nankai.edu.cn, gongchen@nankai.edu.cn, guc11@psu.edu



Scheme 6. Application of enantioenriched TSOA auxiliary.

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