JOC The Journal of Organic Chemistry

Article

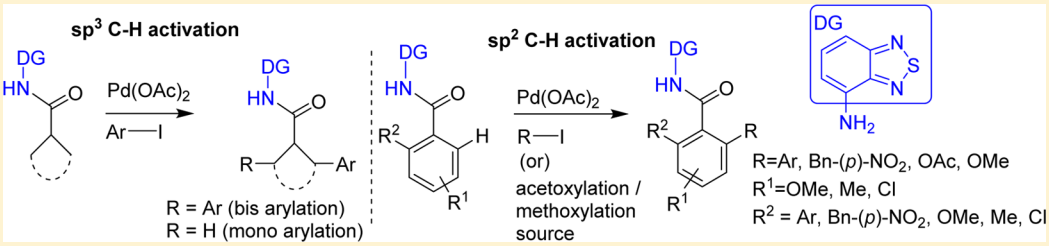
pubs.acs.org/joc

4-Amino-2,1,3-benzothiadiazole as a Removable Bidentate Directing Group for the Pd(II)-Catalyzed Arylation/Oxygenation of sp^2/sp^3 β-C−H Bonds of Carboxamides

Chennakesava Reddy,[†] Narendra Bisht,[†] Ramarao Parella,[†] and Srinivasarao Arulananda Babu*

Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Manauli P.O., Sector 81, SAS Nagar, Knowledge City, Mohali, Punjab 140306, India

Supporting Information



ABSTRACT: In this paper, we report 4-amino-2,1,3-benzothiadiazole (ABTD) as a new bidentate directing group for the Pd(II)-catalyzed sp^2/sp^3 C−H activation/functionalization of various aliphatic/alicyclic/aromatic carboxamide systems. The Pd(II)-catalyzed, ABTD-directed sp^3 C−H arylation/acetoxylation of aliphatic- and alicyclic carboxamides afforded the corresponding β-C−H arylated/acetoxylated carboxamides. The Pd(II)-catalyzed, ABTD-directed sp^3 C−H arylation of cyclobutanecarboxamide with different aryl iodides afforded the corresponding bis β-C−H arylated cyclobutanecarboxamides having *all-cis* stereochemistry with a high degree of stereocontrol. The Pd(II)-catalyzed, ABTD-directed arylation/benzylation/acetoxylation/alkoxylation of *ortho* C(sp^2)−H bonds of various benzamides afforded the corresponding *ortho* C−H arylated/benzylated/oxygenated benzamides. The observed regio- and stereoselectivity in the Pd(II)-catalyzed, ABTD-directed arylation/benzylation of aliphatic/alicyclic carboxamides and benzamides were ascertained from the X-ray structures of representative compounds **5g** (bis-β-C(sp^3)−H arylated cyclobutanecarboxamide) and **7f** (*ortho* C(sp^2)−H arylated benzamide). A brief description on the efficiency, scope, and limitations of bidentate directing group ABTD is reported.

INTRODUCTION

The transition-metal-catalyzed C−H activation followed by a C−C bond-forming process has emerged as a pivotal organic transformation.[1−4] There exist numerous reports dealing with the transition-metal-catalyzed, directing-group-aided or directing-group-free C−H activation/functionalization reactions.[1−4] The functionalization of sp^2 C−H bonds of organic molecules, sp^3 C−H bonds of benzylic systems, α-C(sp^3)−H bonds next to a heteroatom (e.g., THF and pyrrolidine systems), and diazocarbonyl compound based C(sp^3)−H insertion reactions has been extensively studied.[1−4] Apart from these transformations, the functionalization of unactivated sp^3 C−H bonds of organic molecules was considered an arduous task in past decades. However, in recent years, various research groups have shown that the functionalization of unactivated sp^3 C−H bonds of organic molecules is an achievable task.[1−4]

The first paper by Daugulis[5,6] dealing with the Pd(II)-catalyzed, bidentate directing group 8-aminoquinoline (**DG-a**)-assisted arylation of unactivated sp^3 C(β)−H bonds of aliphatic and aromatic carboxamides has provided an inspiring direction to the research area pertaining to the sp^3 C−H activation/functionalization reactions (Figure 1).[1−4,7,8] Concurrently, Yu's work[9a] dealing with the Pd(II)-catalyzed, monodentate directing group 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline (**DG-b**)-assisted functionalization of unactivated sp^3 C−H bonds of organic molecules has provided motivation for synthetic organic chemists (Figure 1). Consequently, while the directing group-free C−H activation/functionalization transformation still remains a challenging and less explored area, the directing group-assisted C−H activation/functionalization tactic has emerged as a dependable method for functionalizing organic molecules with a high degree of site-selectivity.[1−4]

The bidentate directing group 8-aminoquinoline (**DG-a**, Figure 1)[1−4,7,8] was found to be efficient for the functionalization (e.g., arylation, alkylation, acetoxylation) of β-C−H bonds of carboxylic acid and amino acid systems (substrate type 1, Figure 1). However, considering the importance of the C−H activation/functionalization in organic synthesis and to pronounce the availability of other optional bidentate directing groups,[10−13] few other auxiliaries were identified for performing the C−H activation/functionalization of carboxylic acid derivatives and amine systems (substrate type 2, Figure 1).

Received: July 28, 2016
Published: November 17, 2016

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

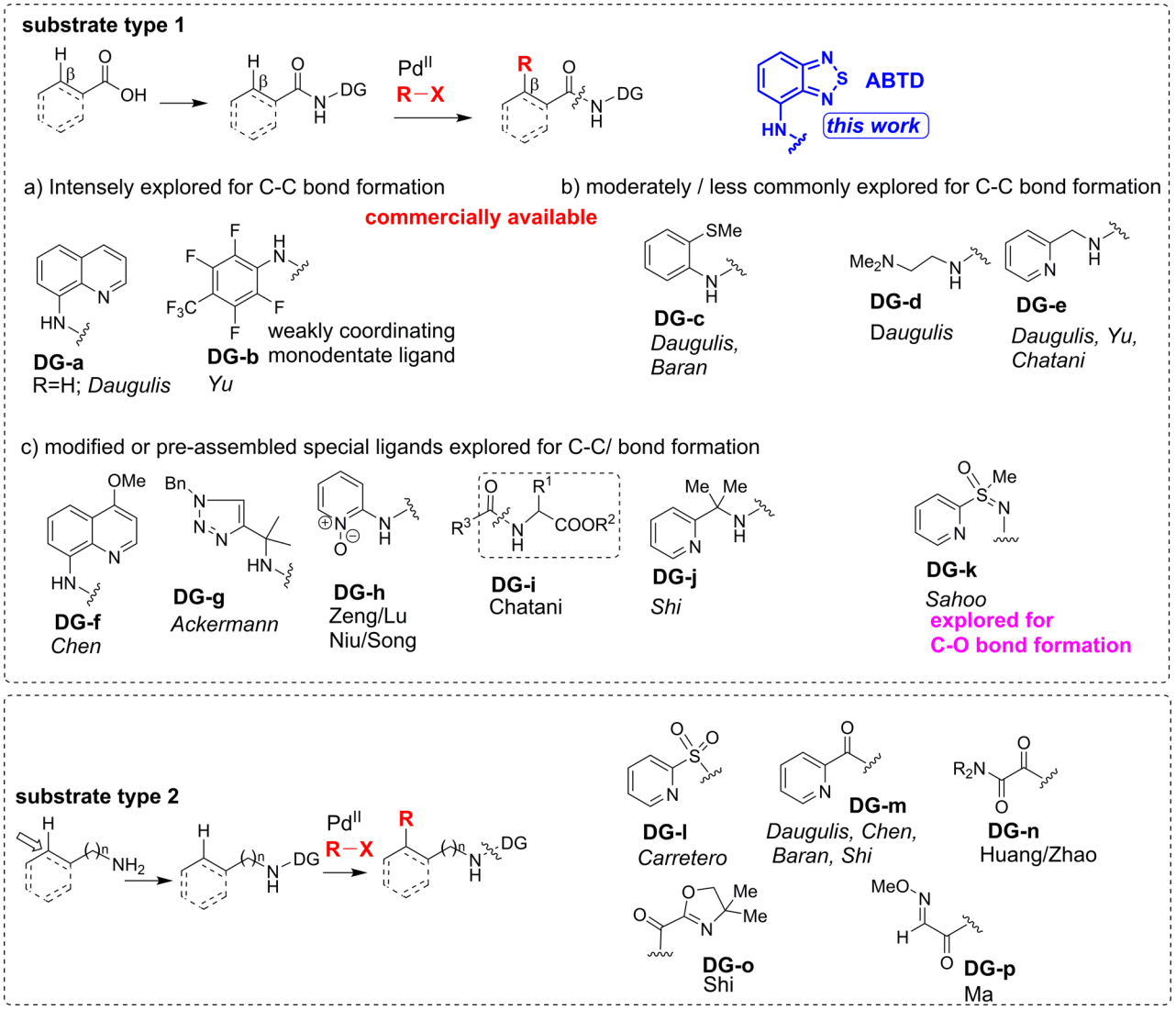


Figure 1. Bidentate directing groups explored for sp^2/sp^3 C−H activation/functionalization.

With regard to substrate type 1, several research groups showed the functionalization of sp^2/sp^3 C−H bonds of carboxylic acid derivatives using the directing group **DG-a** (Figure 1).[1−4] Apart from the popular directing group **DG-a**,[5,6] **DG-c**[6,10a] was found to be a moderately efficient directing group for the C−H activation followed by C−C bond formation, and **DG-c** was not popularly used for the C−H oxygenation reactions.[1−4] Yu's group extensively exploited **DG-b**[6,10a] for C−C bond formation, and to the best of our knowledge, **DG-b** was not popularly used for the C−H oxygenation reactions.[1−4] **DG-d**[6] and **DG-e**[6,11a,b] were less commonly used, and it appears that **DG-d** and **DG-e** are relatively less efficient directing groups for the functionalization of β-C−H bonds of carboxylic acid derivatives (substrate type 1, Figure 1).

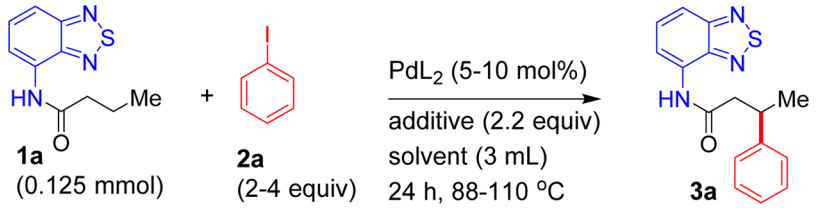
Chen et al. used the modified quinoline-type bidentate directing group **DG-f**[12a] for the γ-C(sp^3)−H amination reactions. Shi[13a] used **DG-g** for performing the palladium-catalyzed substitution/cyclization reactions of amine systems. Ackermann[13b] also used **DG-g** for performing the Fe-catalyzed, Grignard reagent employed arylation of β-C−H bonds of carboxylic acid derivatives. Recently, Niu and Song[12f,g] used the pyridine *N*-oxide-type directing group **Dg-h** for the Pd(II)-catalyzed arylation of β-C(sp^3)−H bonds of aliphatic carboxylic acids. Concurrently, Zeng and Lu[12e] also used the pyridine *N*-oxide-type directing group **Dg-h** for the Pd(II)-catalyzed selective arylation of the β-C(sp^3)−H bond of the propionic acid system.

Recently, Chatani described[11c] the Pd(II)-catalyzed functionalization of *ortho* C−H bonds in *N*-benzoyl α-amino ester derivatives in which both the NH-amido and the ester carbonyl groups of **DG-i** were reported to play a role in the C−H activation/functionalization process. Shi[12c] and Sahoo[13c] have, respectively, introduced the directing groups **Dg-j** and **Dg-k** for the oxidation/oxygenation of β-C(sp^3)−H bonds of aliphatic carboxylic acids. Furthermore, Shi revealed the utility of the directing group **Dg-j** for the Pd(II)-catalyzed selective arylation of sp^3 C−H bonds of alanine and aliphatic carboxylic acid systems.[11e,f] In general, the Pd(II)-catalyzed, bidentate directing group-assisted C−H arylation/functionalization reactions have been performed using silver salts as additives.[1−4] It is to be noted that the Pd(II)-catalyzed, **Dg-j**-directed arylations of methylene sp^3 C−H bonds aliphatic carboxylic acid systems were performed without using any silver salts.[11f]

With regard to substrate type 2, several research groups showed the functionalization of sp^2/sp^3 C−H bonds of various

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Table 1. Optimization Reactions: Pd(II)-Catalyzed, ABTD-Directed Direct Arylation of Methylene C(β)−H Bond of 1a



entry	PdL_2 (mol %)	additive	solvent	T (°C)	yield **3a** (%)
1	$Pd(OAc)_2$ (5)	AgOAc	toluene	110	85
2	$Pd(OAc)_2$ (10)	AgOAc	toluene	110	95
3	$Pd(OAc)_2$(10)	Ag_2CO_3	toluene	110	75
4	$Pd(OAc)_2$(10)	KOAc	toluene	110	<10
5	$Pd(OAc)_2$(10)	$PhI(OAc)_2$	toluene	110	0
6	$PdCl_2$ (10)	AgOAc	toluene	110	84
7	$Pd(TFA)_2$ (10)	AgOAc	toluene	110	40
8	$Pd(OAc)_2$(10)	AgOAc	*t*-amylOH	100	93
9	$Pd(OAc)_2$ (10)	AgOAc	1,2-DCE	85	92
10[a]	$Pd(OAc)_2$(10)	AgOAc	toluene	110	70
11[b]	$Pd(OAc)_2$ (10)	AgOAc	toluene	110	87

[a]2 equiv of **2a** was used. [b]3 equiv of **2a** was used.

amine systems using the bidentate directing group **DG-m** (picolinamide directing group, Figure 1).[4f,6,10a] Additionally, Baran[10b] and Shi[8a] showed the utility of the directing group **DG-m** for the arylation of sp^3 C−H bonds of amine/carboxylic acid systems. Carretero[12b] used the *N*-(2-pyridyl)sulfonyl directing group **DG-l** for the Pd(II)-catalyzed functionalization of sp^3 C−H bonds of amino acid derivatives. Huang and Zhao[13d] used the oxalylamide directing group **DG-n** for the functionalization of C−H bonds of amine systems. Recently, Shi[11d] revealed an oxazoline-carboxylate directing group **DG-o** for the arylation of sp^2/sp^3 C−H bonds of various amine systems. Ma[12d] reported 2-methoxyiminoacetyl directing group **DG-p** (MIA) for the Pd(II)-catalyzed functionalization of sp^3 C−H bonds of amine systems.

The reported bidentate directing groups were efficient and developed with an aim of achieving a high degree of site selectivity in the Pd(II)-catalyzed C−H activation-based C−C/C−O bond-forming reactions involving substrate type 1.[1−4,14−16] Nevertheless, some of the seminal bidentate directing groups (e.g., **DG-g**, **DG-h**, **DG-j**, and **DG-k**) are not commercially available and need to be preassembled by involving a few synthetic steps/transformations.[12c,e−g,13a−c] Additionally, Daugulis et al. revealed[5,6] that the attempts on the Pd(II)-catalyzed C−H arylation of methyl group of propionic acid with the help of the typically used bidentate directing groups (e.g., **DG-a** and **DG-c**) afforded the corresponding monoarylation product (3-arylated propionamide) and bis-arylation product (3,3-bis-arylated propionamide).

Given that the research field pertaining to the bidentate directing group directed site-selective sp^3 C−H activation/functionalization reactions is still emerging; the scope and limitations of the bidentate directing groups are yet to be clearly scrutinized. Furthermore, given the importance of the C−H activation/functionalization tactics in organic synthesis, advancing the research area pertaining to the directing group-assisted C−H activation/functionalization reactions by developing new directing groups might (a) ensure the availability of commercially available other optional bidentate directing groups and (b) enhance the understanding with regard to the scope and limitations of bidentate directing groups while executing the site-selective C−H functionalization of suitable substrates. Hence, with a goal of bolstering the sp^2/sp^3 C−H activation/functionalization method,[6−16] we envisaged reporting 4-amino-2,1,3-benzothiadiazole (ABTD)[17] as a new bidentate directing group for the Pd(II)-catalyzed, sp^2/sp^3 C−H activation/functionalization of various aliphatic/alicyclic/aromatic carboxamide systems. The results from our investigation on the Pd(II)-catalyzed, ABTD-directed arylation/acetoxylation of β-C(sp^3)−H bonds of aliphatic/alicyclic carboxamides and arylation/benzylation/acetoxylation/methoxylation of *ortho* C(sp^2)−H bonds of various benzamides are reported.[18]

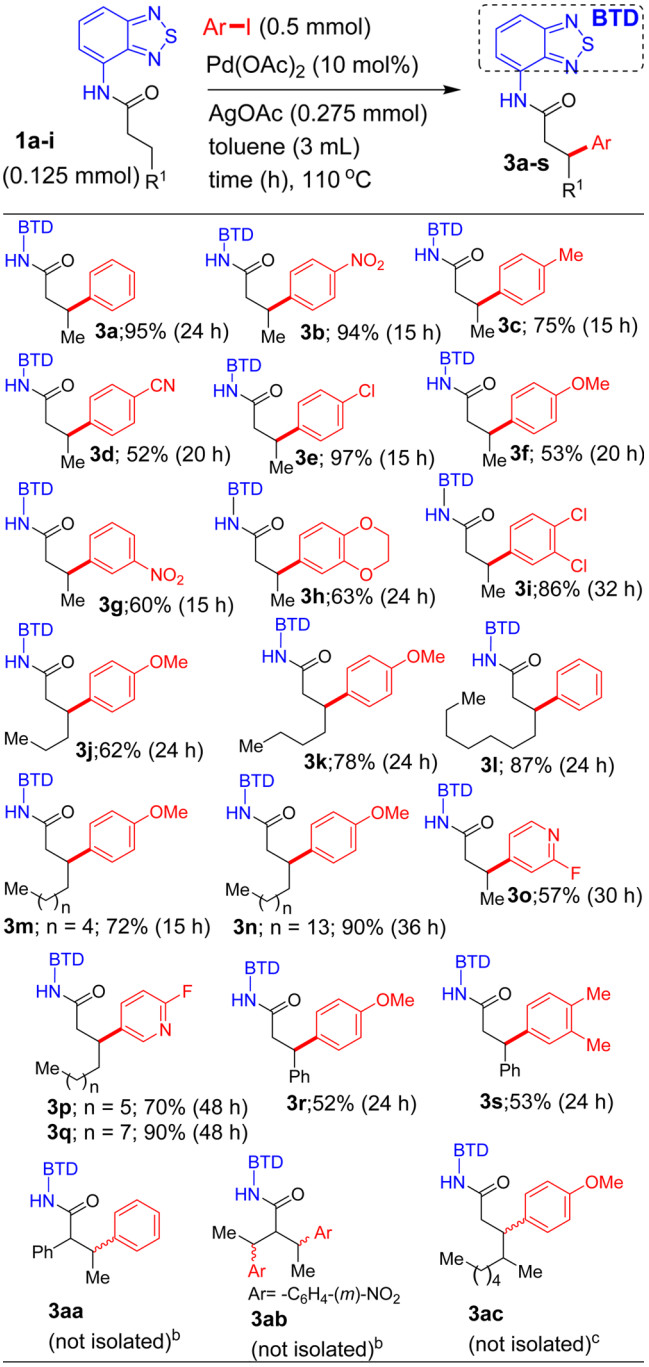
RESULTS AND DISCUSSION

To explore ABTD as a directing group for the Pd(II)-catalyzed C−H activation and direct arylation of carboxamides, initially we assembled carboxamide **1a** from butanoyl chloride and ABTD. We then carried out the optimization reactions using carboxamide **1a**, and Table 1 shows the results for the Pd(II)-catalyzed sp^3 C−H arylation of **1a** with **2a** in the presence of various palladium catalysts and additives in different solvents. The reaction of a mixture of **1a** (1 equiv), PhI (**2a**, 4 equiv), $Pd(OAc)_2$ catalyst (5 or 10 mol %), and AgOAc additive in toluene at 110 °C afforded the methylene C(β)−H arylated product **3a** in 85−95% yields (entries 1 and 2, Table 1). The Pd(II)-catalyzed sp^3 C−H arylation of **1a** with **2a** using additional additives, such as Ag_2CO_3 or KOAc, furnished the product **3a** in 75 and <10% yields, respectively (entries 3 and 4, Table 1). The use of $PhI(OAc)_2$ as an additive failed to give the product **3a** (entry 5, Table 1). The arylation of **1a** with **2a** in the presence of other palladium catalysts, such as $PdCl_2$ or $Pd(TFA)_2$, furnished the product **3a** in 84 and 40% yields, respectively (entries 6 and 7, Table 1). The Pd(II)-catalyzed sp^3 C−H arylation of **1a** with **2a** in other solvents, such as, *tert*-amylOH or 1,2-DCE, furnished the product **3a** in 93 and 92% yields, respectively (entries 8 and 9, Table 1). The sp^3 C−H arylation of **1a** with 2 or 3 equiv of **2a** afforded the product **3a** in 70 and 87% yields, respectively (entries 10 and 11, Table 1).

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

We then examined the generality of the Pd(II)-catalyzed, ABTD-directed arylation of methylene C(β)−H bonds of various aliphatic carboxamides (Table 2). Using the optimized reaction conditions, we carried out the $Pd(OAc)_2$/AgOAc catalytic system-based, ABTD-directed C−H arylation of **1a** with different aryl iodides that possessed electron-donating or electron-withdrawing groups at the *para*/*meta* position of the aryl ring in the corresponding aryl iodides. Accordingly, a variety of corresponding β-C−H arylated butanamides **3a−g** were obtained in 52−97% yields (Table 2). The β-C−H arylated butanamides **3h** (63%) and **3i** (86%) were obtained from the Pd(II)-catalyzed, ABTD-directed arylation of methylene C(β)−H bond of **1a** with the corresponding disubstituted aryl iodides (Table 2).

Table 2. Scope and Generality of the Pd(II)-Catalyzed, ABTD-Directed Direct Arylation of Methylene C(β)−H Bonds of Various Aliphatic Carboxamide[a],[14d]



[a]The β-C−H-arylated carboxamides **3a−s** were obtained from their respective starting materials **1a−i**. [b]The reactions were carried out using the corresponding starting materials **1aa** and **1ab**, and products **3aa** and **3ab** could not be isolated as the corresponding reactions gave a complex mixture. [c]The reaction was performed using the starting material **1ac**, and a negligible amount of product formation was observed.

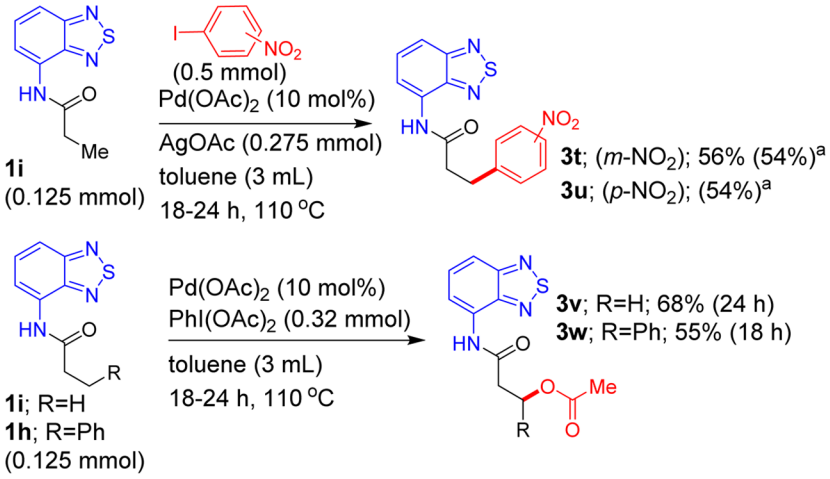
Next, we performed the $Pd(OAc)_2$/AgOAc catalytic system-based, ABTD-directed arylation of methylene C(β)−H bonds of various aliphatic carboxamides **1b−f** with different aryl iodides, which furnished the corresponding β-C−H arylated carboxamides **3j−n** in 62−90% yields (Table 2). We then performed the Pd(II)-catalyzed, ABTD-directed arylations of methylene C(β)−H bonds of substrates **1a,d,g** with a heteroaryl iodide (e.g., 2-fluoro-5-iodopyridine), which afforded the corresponding β-C−H arylated carboxamides **3o−q** in 57−90% yields (Table 2). Subsequently, we performed the Pd(II)-catalyzed, ABTD-directed C−H arylation of mono-β-arylated propionamide **1h** with 1-iodo-4-methoxybenzene and 4-iodo-1,2-dimethylbenzene to afford the corresponding β'-aryl β-aryl propionamides **3r,s** in 52 and 53% yields, respectively (Table 2). We also performed the diastereoselective Pd(II)-catalyzed β-C−H arylation reactions using branched carboxamides **1aa−ac** to obtain the corresponding β-C−H arylated products **3aa−3ac**; however, these reactions were not fruitful.

We also performed the $Pd(OAc)_2$/AgOAc catalytic system based, ABTD-directed arylation of methyl C(β)−H bond of propionamide **1i** with 1-iodo-3-nitrobenzene and 1-iodo-4-nitrobenzene, which furnished the corresponding monoarylated propionamides **3t,u** in 54−56% yield (Scheme 1). In these reactions, the corresponding bis-arylated propionamides were not obtained in characterizable amounts. Furthermore, we wished to attempt the acetoxylation of the sp^3 C−H bond of the aliphatic carboxamide system with the help of the ABTD bidentate directing group. In this regard, we performed the Pd(II)-catalyzed, ABTD-directed C−H acetoxylation of propionamides **1i,h** with $PhI(OAc)_2$, which gave the corresponding β-C−H acetoxylated propionamides **3v,w** in 68 and 55% yields, respectively (Scheme 1).

Next, we were interested in exploring the diastereoselective Pd(II)-catalyzed C−H arylation of alicyclic carboxamides with the help of the ABTD bidentate directing group. In this regard, initially we performed the Pd(II)-catalyzed, ABTD-directed C−H arylation of cyclopropanecarboxamide **1j** with 1-iodo-3-nitrobenzene. This reaction gave the mono-β-C−H-arylated product **4a** in 27% yield (*cis* isomer) and bis-β-C−H-arylated product **4aA** in 14% yield (*all-cis* isomer, Table 3). Similarly, the Pd(II)-catalyzed, ABTD-directed C−H arylation of cyclopropanecarboxamide **1j** with 4-iodoacetophenone furnished the corresponding mono-β-C−H-arylated product **4b** in 28% yield (*cis* isomer) and bis-β-C−H-arylated product **4bB** in <10% yield (*all-cis* isomer, Table 3). Then, we envisaged to attempt the diastereoselective Pd(II)-catalyzed C−H arylation/alkylation of cyclobutanecarboxamide **1k** with the help of the ABTD bidentate directing group. Initially, we performed the Pd(II)-catalyzed, ABTD-directed C−H alkylation of cyclobutanecarboxamide **1k** with ethyl iodoacetate, which furnished the substituted cyclobutanecarboxamide **4c** in 44% yield (Table 3). Next, we performed the Pd(II)-catalyzed, ABTD-directed C−H arylation of **1k** with 1-iodo-3-nitrobenzene, 3-fluoro-1-iodo-

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Scheme 1. Pd(II)-Catalyzed, ABTD-Directed β-C−H Arylation of 1i and β-C−H Acetoxylation of 1i,h



[a]The reaction was performed using 0.15 mmol of 1-iodo-3-nitrobenzene for 18 h.

benzene, and 1-iodo-2-nitrobenzene. These reactions afforded the corresponding bis-β-C−H-arylated cyclobutanecarboxamides **5a−c** having the *all-cis* stereochemistry in 56−95% yields (Table 3). Similarly, the Pd(II)-catalyzed, ABTD-directed C−H arylation of **1k** with various aryl iodides that possessed electron-donating or electron-withdrawing groups at the *para* position of the aryl ring in the corresponding aryl iodides successfully furnished the corresponding bis-β-C−H-arylated cyclobutanecarboxamides **5d−i** having the *all-cis* stereochemistry in 79−98% yields (Table 3).

Furthermore, the Pd(II)-catalyzed, ABTD-directed C−H arylation of cyclobutanecarboxamide **1k** with disubstituted aryl- and heteroaryl iodides proceeded smoothly to afford the corresponding bis-β-C−H-arylated cyclobutanecarboxamides **5j−m** having *all-cis* stereochemistry in 58−98% yields (Table 3). It is worth mentioning that the C−H arylation of **1k** selectively occurred at both β-positions of cyclobutanecarboxamide **1k** with the help of the ABTD bidentate directing group, and the corresponding bis-β-C−H-arylated/alkylated carboxamides **4**/**5** were obtained with high diastereoselectivity. Notably, the double β-C−H arylations of cyclobutanecarboxamide **1k** have led to the assembly of various trisubstituted cyclobutanecarboxamide scaffolds having the *all-cis* stereochemistry, which are analogous to the naturally occurring bioactive cyclobutanes.[10a] The observed *cis* stereochemistry and structure of the cyclopropanes **4a**, **4b**, **4aA**, and **4bB** and cyclobutanes **5a−m** were assigned on the basis of the similarity of the NMR spectral pattern of these compounds with the previous works dealing with the bidentate directing group-directed diastereoselective *cis* C−H arylation of cyclopropanecarboxamide[15a,e,f] and cyclobutanecarboxamide[10a,14c] systems, respectively. Additionally, the X-ray structure analysis of **5g** (see the Supporting Information for the X-ray structure of **5g**) clearly revealed that compound **5g** has the *cis* stereochemistry in accordance with the previous reports.[10a,14c] The stereochemistry of compound **4c**[16d,e] was assigned on the basis of the stereochemistry of compounds **5a−m**.

Having explored the Pd(II)-catalyzed direct arylation of sp^3 C(β)−H bonds of aliphatic and alicyclic carboxamides using the ABTD directing group, next we wished to perform the Pd(II)-catalyzed direct arylation of *ortho* C(sp^2)−H bonds of aromatic carboxamides using the ABTD bidentate directing group. In this regard, we assembled benzamides **6a** and **8a** from their corresponding benzoyl chlorides and ABTD. We then performed the optimization reactions using benzamides **6a** and **8a**. Table 4 shows the results for the ABTD-directed monoarylation of the *ortho* C(sp^2)−H bond of benzamide **6a** and bis arylation of *ortho* C(sp^2)−H bonds of benzamide **8a** in the presence of various palladium catalysts and additives in different solvents.

The arylation reaction of the *ortho* C(sp^2)−H bond of benzamide **6a** with 1-ethyl-4-iodobenzene in the presence of 10 mol % of the Pd(OAc)$_2$ catalyst and AgOAc additive in toluene at 110 °C afforded the mono C−H arylated benzamide **7a** in a maximum yield of 70% (entry 2, Table 4). Similarly, the Pd(II)-catalyzed arylation of *ortho* C(sp^2)−H bonds of benzamide **8a** with 1-ethyl-4-iodobenzene afforded the bis-C−H-arylated benzamide **9a** in a maximum yield of 75% (entry 2, Table 4). Apart from these reactions, the other optimization reactions comprising the mono- and bis-arylation of *ortho* C(sp^2)−H bonds of the corresponding benzamides **6a** and **8a** in the presence of other palladium catalysts or additives or solvents were not fruitful (entries 1 and 3−11, Table 4). Next, to examine the generality of this work, we planned to perform the arylation of *ortho* C(sp^2)−H bonds of various 2/3-substituted-benzamides **6a−e**, which were prepared from the ABTD directing group (Table 5). Using the optimized reaction conditions (entry 2, Table 4), we attempted the Pd(OAc)$_2$/AgOAc-catalytic system-based, ABTD-directed arylation of *ortho* C(sp^2)−H bonds of 2/3-substituted-benzamides **6a−d** with different aryl iodides that possessed electron-donating or electron-withdrawing groups at the *para*/*meta* position of the aryl ring in the corresponding aryl iodides. These reactions afforded a wide range of the corresponding mono C−H arylated benzamides **7a−n** in 50−77% yields (Table 5). The arylation of the *meta*-substituted benzamide **6e** with 1-iodo-4-methoxybenzene afforded the corresponding mono- and bis-arylated benzamides **7o** and **7o′** in 44 and <10% yields. Further, the arylation of **6e** with 1-iodo-3-nitrobenzene afforded the corresponding mono- and bis-arylated benzamides **7p** (<10%) and **7p′** (<20%) in low yields (Table 5).

After investigating the Pd(II)-catalyzed, ABTD-directed monoarylation of *ortho* C(sp^2)−H bond of benzamides **6a−e**, we planned to extend the substrate scope by examining the bis arylation of *ortho* C(sp^2)−H bonds of benzamides **8a−d**. Accordingly, using the optimized reaction conditions (entry 2,

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Table 3. Diastereoselective Pd(II)-Catalyzed, ABTD-Directed Arylation of Methylene C(β)−H Bonds of Cyclopropane and Cyclobutane Systems

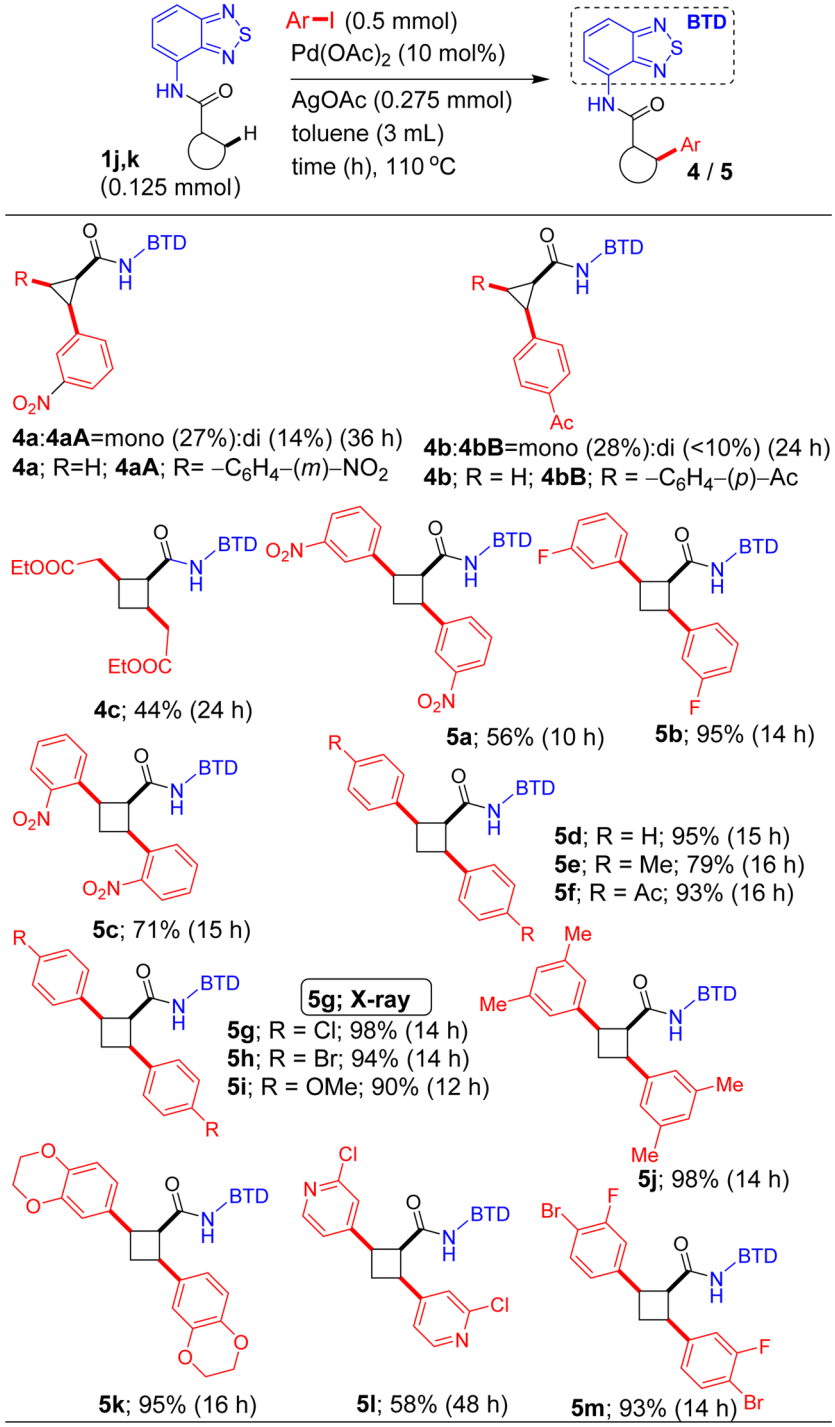
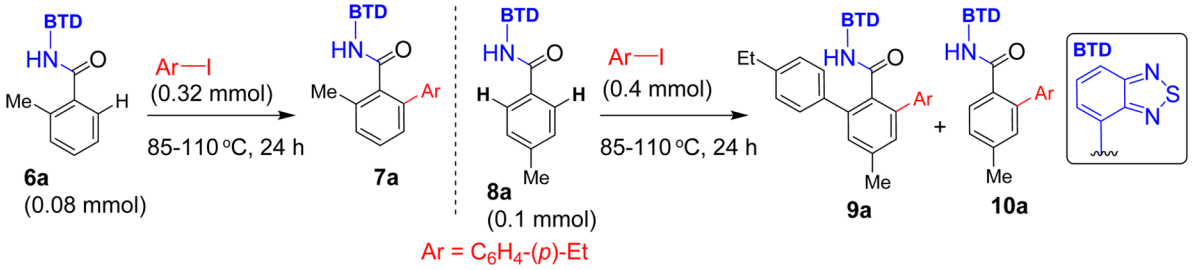


Table 4), we attempted the $Pd(OAc)_2$/AgOAc-catalytic system-based, ABTD-directed arylation of *ortho* C(sp^2)−H bonds of benzamides **8a−d** with several aryl iodides that possessed electron-donating or electron-withdrawing groups at the *para*/*meta* position of the aryl ring in the corresponding aryl iodides. These reactions furnished a wide range of bis-C−H-arylated benzamides **9a−m** in 42−75% yields, respectively (Table 5).

Next, we focused our attention on exploring the Pd(II)-catalyzed direct benzylation of *ortho* C(sp^2)−H bonds of benzamides with the help of the ABTD bidentate directing group. In this regard, initially, we carried out the $Pd(OAc)_2$/AgOAc-catalytic system-based, ABTD-directed *ortho* C−H benzylation of **6a**/**6c**/**6d** with 1-(bromomethyl)-4-nitrobenzene (**10**). These reactions afforded the corresponding *ortho* C−H-benzylated benzamides **11a−c** in 47−65% yields, respectively (Scheme 2). Having performed the Pd(II)-catalyzed monobenzylation of the *ortho* C(sp^2)−H bond of **6a**/**6c**/**6d**, we then performed the Pd(II)-catalyzed, ABTD-directed bis benzylation of *ortho* C(sp^2)−H bonds of benzamides **8a**/**8c**/**8d**/**6e** with **10**. These reactions furnished the corresponding bis *ortho*-C−H benzylated benzamides **12a−c** and **12d′** in 30−58% yields, respectively (Scheme 2).

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Table 4. Optimization Reactions: Pd(II)-Catalyzed, ABTD-Directed Arylation of *Ortho* C(sp^2)−H Bonds of Benzamides 6a/8a[a−c]



entry	6a (or) 8a (1 equiv)	PdL_2 (10 mol %)	solvent (3 mL)	additive (2.2 equiv)	*T* (°C)	7a (or) 9a: yield (%)
1	**6a**	nil	toluene	AgOAc	110	**7a**: 0
2	**8a**					**9a**: 0
3	**6a**	$Pd(OAc)_2$	toluene	AgOAc	110	**7a**: 70
4	**8a**					**9a**: 75
5	**6a**	$PdCl_2$	toluene	AgOAc	110	**7a**: 24
6	**8a**					**9a**: 50
7	**6a**	$Pd(PPh_3)_4$	toluene	AgOAc	110	**7a**: < 5
8	**8a**					**9a**: < 5
9	**6a**	$Pd(TFA)_2$	toluene	AgOAc	110	**7a**: < 5
10	**8a**					**9a**: < 5
11	**6a**	$Pd(OAc)_2$	toluene	Ag_2CO_3	110	**7a**: 0
12	**8a**					**9a**: 0
13	**6a**	$Pd(OAc)_2$	toluene	$PhI(OAc)_2$	110	**7a**: 0
14	**8a**					**9a**: 0
15	**6a**	$Pd(OAc)_2$	toluene	KOAc	110	**7a**: < 5
16	**8a**					**9a**: < 5
17	**6a**	$Pd(OAc)_2$	1,4-dioxane	AgOAc	100	**7a**: 30
18	**8a**					**9a**: < 5
19	**6a**	$Pd(OAc)_2$	^{t}amylOH	AgOAc	110	**7a**: 0
20	**8a**					**9a**: 0
21	**6a**	$Pd(OAc)_2$	^{t}BuOH	AgOAc	85	**7a**: 0
22	**8a**					**9a**: 0

[a]The reaction conditions given in any row correspond to the independent reactions carried out with **6a** and **8a**. [b]The product **7a** was obtained from the corresponding reactions involving substrate **6a**. [c]The product **9a** was obtained from the corresponding reactions involving substrate **8a**. The product **10a** was not observed in the reactions involving the substrate **8a**.

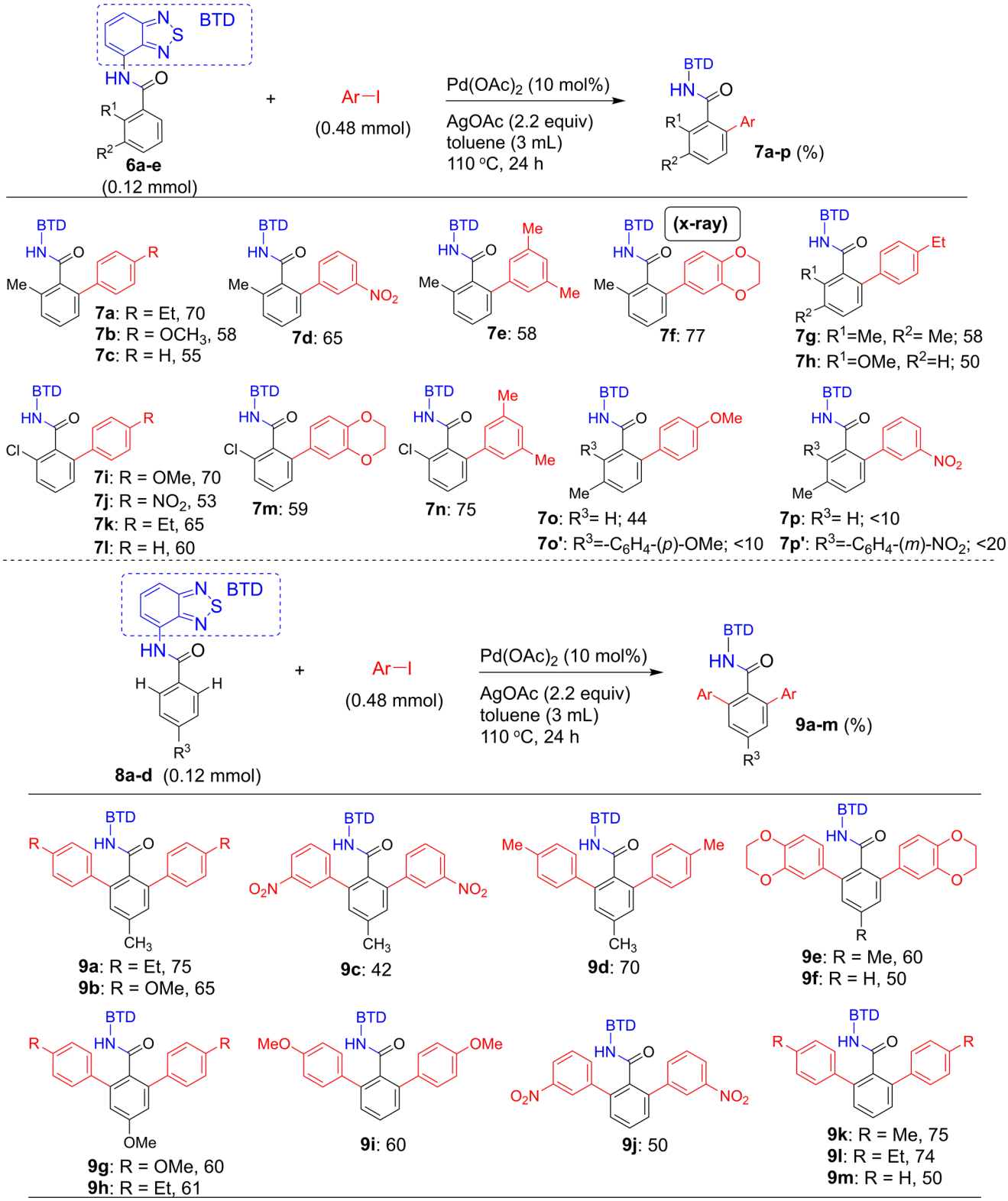
The C−H arylated/benzylated compounds **7a−p**, **9a−m**, **11a−c**, **12a−c**, and **12d′** obtained from the Pd(II)-catalyzed, ABTD-directed arylation/benzylation of *ortho* C−H bonds of the corresponding substrates **6a−e** and **8a−d** were characterized on the basis of their NMR spectra and HRMS data. For example, a comparison of the ^{1}H NMR spectra of substrate **6b** and carboxamide **7g** was performed. The corresponding distinct doublet peaks of the *meta* and *para* protons of *ortho* C−H-arylated carboxamide **7g** revealed that the arylation occurred at the *ortho* C−H bond of the 2,3-dimethylbenzamide system **6b**. Similarly, a comparison the ^{1}H NMR spectra of substrate **8a** and carboxamides **9d**/**12a** was performed. The corresponding distinct singlet peak of the *meta* protons of the bis *ortho* C−H arylated/benzylated 4-methylbenzamide systems **9d**/**12a** revealed that the arylation/benzylation occurred at both the *ortho* C−H bonds of the 4-methylbenzamide system **8a**. Additionally, the observed regioselectivity in the reactions comprising the Pd(II)-catalyzed, ABTD-directed *ortho* C(sp^2)−H arylation/benzylation of benzamides **6a−e** and **8a−d** was unambiguously confirmed from the X-ray structure of a representative *ortho* C−H-arylated benzamide **7f** (see the Supporting Information for the X-ray structure of **7f**).

Next, it was envisaged to carry out a brief comparison on the efficiency, scope, and limitations of the 4-amino-2,1,3-benzothiadiazole (ABTD) bidentate directing group with the other seminal bidentate directing groups used for performing the Pd(II)-catalyzed arylation/acetoxylation of carboxylic acid derivatives. Accordingly, Schemes 3−6 reveal a comparison of the propensity of the ABTD directing group with the typical bidentate directing groups reported for the Pd(II)-catalyzed arylation of cyclobutanecarboxamide system **13** (Scheme 3). The expected bis-C−H-arylated cyclobutanecarboxamides **14−16** did not form in the Pd(II)-catalyzed C−H arylation of their corresponding starting materials. The reason for this may be that the respective bidentate directing groups linked with the cyclobutanecarboxamides **13** have not assisted the arylation of C−H bond of the corresponding cyclobutanecarboxamides **13**.

Typically, the Pd(II)-catalyzed C−H arylations of carboxylic acid derivatives have been performed using the 8-aminoquinoline, 2-(methylthio)aniline, and N^1,N^1-dimethylethane bidentate directing groups.[3,5,6] Using these bidentate directing groups, our laboratory reported the Pd(II)-catalyzed diastereoselective double *β*-C−H activation and arylation of cyclobutanecarboxamides.[14c] A comparison of the efficiencies of these bidentate directing groups with the ABTD directing group with regard to the diastereoselective *β*-C−H arylation of cyclobutane system was carried out. It was found that the ABTD bidentate directing group is relatively more efficient

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Table 5. Substrate Scope and Generality of the Pd(II)-Catalyzed, ABTD-Directed Arylation of the *Ortho* C(sp^2)−H Bond of Benzamides 6a−e and 8a−d[a,b]



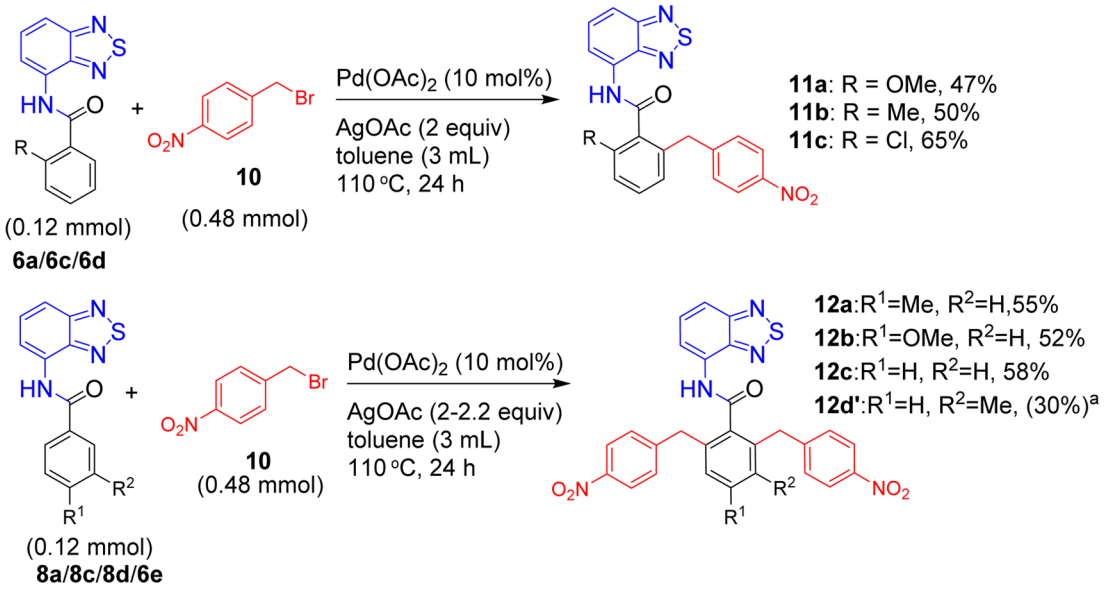
[a]The substrates used are as follows: **6a**, R^1 = Me, R^2 = H; **6b**, R^1 = Me, R^2 = Me; **6c**, R^1 = OMe, R^2 = H; **6d**, R^1 = Cl, R^2 = H; **6e**, R^1 = H, R^2 = Me. [b]The substrates used are as follows: **8a**, R^3 = Me; **8b**, R^3 = Cl; **8c**, R^3 = OMe; **8d**, R^3 = H.

than the 2-(methylthio)aniline and N^1,N^1-dimethylethane-1,2-diamine directing groups, and the efficiency of the 4-amino-2,1,3-benzothiadiazole directing group was comparable to the 8-aminoquinoline bidentate directing group (Scheme 3).

Furthermore, the results shown in Scheme 4 provided additional input with regard to the assistance provided by the ABTD bidentate directing group for the selective mono β-C−H arylation of the methyl group of propionamide. Daugulis et al.

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Scheme 2. Pd(II)-Catalyzed, ABTD-Directed Mono- and Bis-benzylation of *Ortho* C(sp²)−H Bonds of Benzamides 6 and 8[a]



[a]The benzylation of **6e** afforded the bis-benzylated product **12d′** along with the corresponding monobenzylated product **12d** in <10% yield. Our efforts to isolate compound **12d** in pure form were not fruitful.

revealed[5,6] that the attempts on the Pd(II)-catalyzed C−H arylation of methyl group of propionamide with the help of the typically used bidentate directing groups (e.g., 8-aminoquinoline and 2-(methylthio)aniline) afforded the corresponding 3-arylated propionamide (monoarylation product) and 3,3-bis-arylated propionamide (bis arylation product).[5,6] In the present investigation, the Pd(OAc)/AgOAc-catalytic system-based C−H arylation of butyramide **20a** (assembled from the 2-aminopyridine directing group) and propionamide **20b** (assembled from the N^1,N^1-dimethylethane-1,2-diamine directing group) did not give the expected products **21a**, **21b**, and **21b′** (Scheme 4).

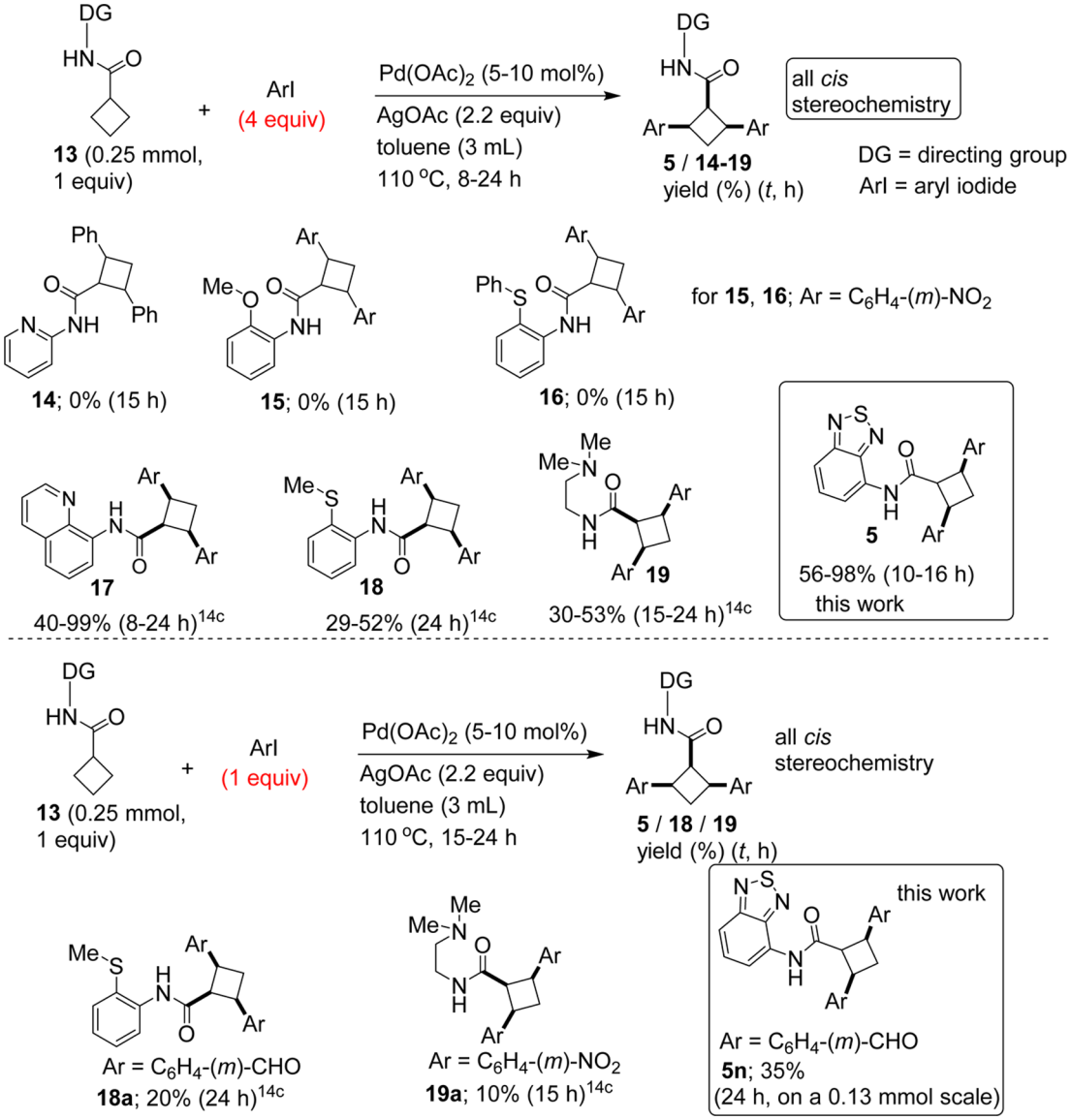
The Pd(II)-catalyzed C−H arylation of **20c**, which was assembled from the 2-(methylthio)aniline bidentate directing group, afforded the monoarylation product **21c** in low yield (30%. Scheme 4). However, the Pd(II)-catalyzed C−H arylation of **20d**, which was assembled from the 8-aminoquinoline bidentate directing group, afforded the corresponding monoarylation products **21d**/**21e** (21−40%) and bis arylation product **21d′**/**21e′** (17−18%, Scheme 4). Nonetheless, the Pd(II)-catalyzed C−H arylation of **1i**, which was assembled from the ABTD bidentate directing group, selectively afforded the monoarylation products **3t**/**3x** in good yields (up to 56%, Schemes 1 and 4). Furthermore, we observed that the ABTD-directed C−H arylation of **6a** selectively afforded the monoarylation product **7a** in 70% yield (Scheme 5). On the other hand, the 8-aminoquinoline-directed C−H arylation of **20i** afforded the bis arylation product **22a** in 53% yield along with the compound **22b** in 5−10% yield (Scheme 5).[16f]

Additionally, we performed the Pd(II)-catalyzed, ABTD-directed *β*-C−H acetoxylation of substrate **1i** with $PhI(OAc)_2$, which afforded the corresponding C−H acetoxylated products **3v**/**3w** in 55−68% yields (Scheme 6). However, the Pd(II)-catalyzed *β*-C−H acetoxylation of the corresponding carboxamides **20a**−**c**, directed by the respective bidentate directing groups, was not fruitful (Scheme 6). We also performed the Pd(II)-catalyzed, ABTD-directed *β*-C−H acetoxylation of substrates **6c**,**d**, which afforded the corresponding C−H-acetoxylated **25a**,**b** in 86−89% yields, respectively (Scheme 6). Similarly, the Pd(II)-catalyzed, ABTD-directed *β*-C−H methoxylation of **6b**,**d** afforded the corresponding C−H methoxylated products **25c**,**d** in 64−71% yields, respectively. A comparison of the Pd(II)-catalyzed ABTD directing group-based C−H acetoxylation/alkoxylation reactions with the seminal works[8b−e] dealing on the C−H acetoxylation/alkoxylation using typical bidentate directing groups was shown in Scheme 6. The ABTD directing group-based C−H acetoxylation/alkoxylation of benzamides **6b**−**d** afforded the products **25a**−**d** in good yields involving relatively simple reaction conditions. Overall, the results presented in Schemes 3−6 have afforded a brief comparison on the adeptness, scope, and limitations of the ABTD bidentate directing group with regard to the other seminal bidentate directing groups used for performing the Pd(II)-catalyzed C−H arylation/benzylation/acetoxylation of carboxylic acid derivatives.

Finally, we also attempted the removal of the ABTD bidentate directing group after the C−H arylation of reactions using representative C−H-arylated carboxamides (Scheme 7). Initially, we attempted the amide hydrolysis reaction of **9m** with aq H_2SO_4, which afforded the 9-fluorenone derivative **27** (Scheme 7), and in this reaction, the corresponding carboxylic acid was not obtained in a characterizable amount. After the removal of the directing group, the corresponding carboxylic acid underwent an intramolecular Friedel−Crafts acylation to directly afford the compound **27** under the experimental conditions. The base-mediated amide hydrolysis of **5g** and **5h** furnished the corresponding trisubstituted cyclobutanecarboxylic acids **28a** and **28b** (Scheme 7). The stereochemistry of carboxylic acids **28a** and **28b** was assigned by comparing the NMR spectral data of **28a** and **28b** with the previous work,[14c] which also revealed the occurrence of epimerization at the carbonyl group containing stereocenter of **28a** and **28b**[14c] under the experimental conditions. The removal of the ABTD bidentate directing group from **3a** and **3e** under the base-mediated hydrolysis reaction conditions gave the corresponding *β*-arylbutyric acids **28c** and **28d** (Scheme 7).

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Scheme 3. Comparison of ABTD with the Pivotal Bidentate Directing Groups Reported for the Pd(II)-Catalyzed Arylation of Cyclobutanecarboxamide[14c]



CONCLUSION

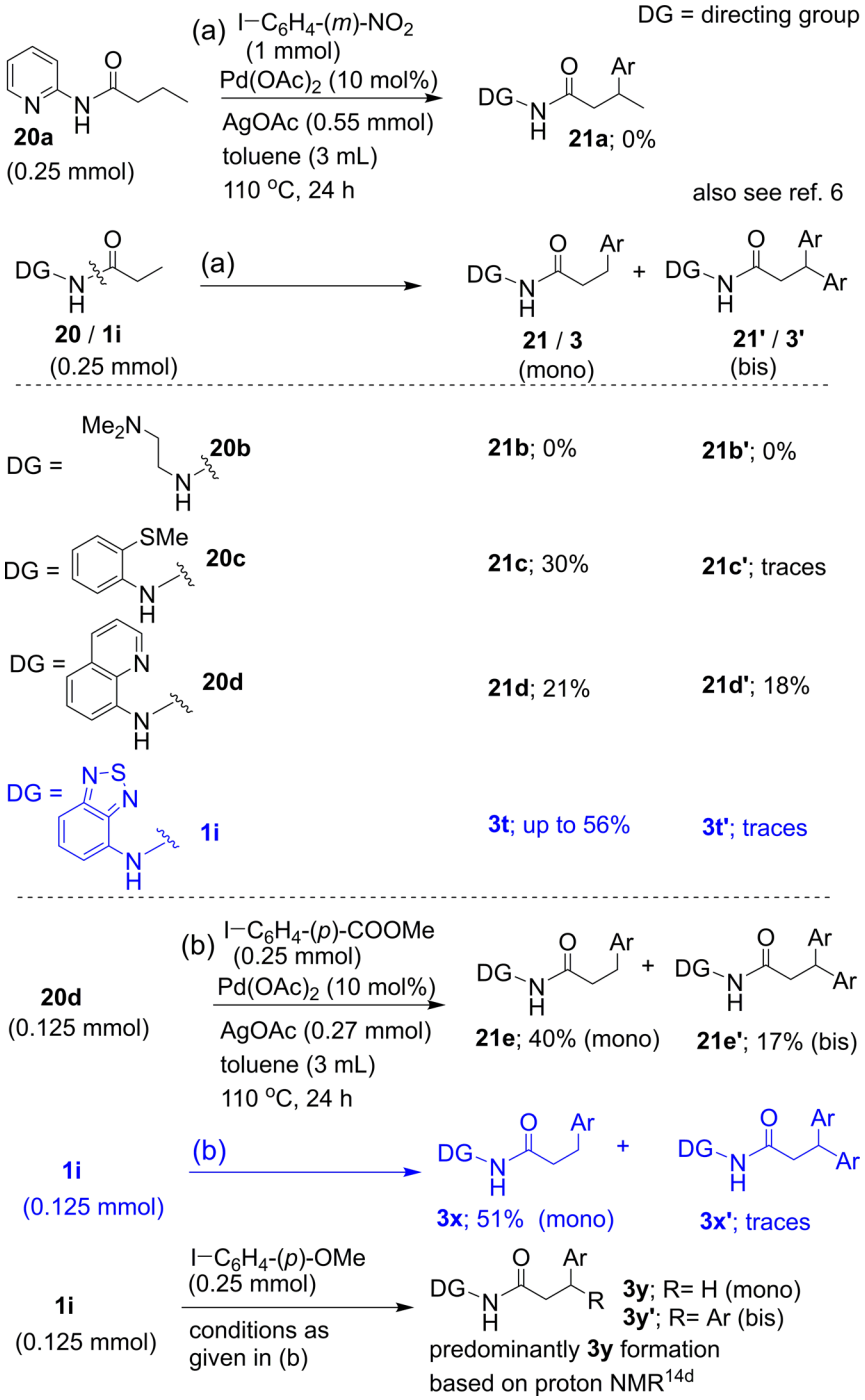
In summary, we have shown 4-amino-2,1,3-benzothiadiazole as a new bidentate directing group for the $Pd(OAc)_2$/AgOAc catalytic system-based sp^2/sp^3 C−H activation/functionalization and C−C/C−O bond formation. The ABTD directing group directed the Pd(II)-catalyzed C−H arylation/acetoxylation to occur at the β-position of various aliphatic/alicyclic carboxamides and benzamides. Various examples comprising the β-C−H arylated/acetoxylated carboxamides and trisubstituted cyclobutanecarboxamide scaffolds having the *all-cis* stereochemistry were synthesized in good yields. Further, the Pd(II)-catalyzed, ABTD-directed arylation and benzylation of *ortho* C(sp^2)−H bonds of various benzamides afforded the corresponding mono/bis β-C−H arylated/benzylated benzamides in good yields. A brief description on the efficiency, scope, and limitations of the ABTD bidentate directing group was presented by comparing the efficiency of ABTD with other seminal bidentate directing groups. Finally, we have also shown the removal of the ABTD directing group from representative C−H arylated compounds. It is to be noted that the research field pertaining to the bidentate directing group-directed site-selective sp^3 C−H activation/functionalization is still emerging. Hence, advancing the research area pertaining to the directing group-assisted sp^2/sp^3 C−H activation/functionalization reactions by developing new directing groups/substrates will enhance understanding with regard to the scope and limitations of the directing groups while exercising the site-selective C−H functionalization. Hence, we believe that ABTD might serve as an optional directing group when the site-selective C−H activation/functionalization of suitable carboxylic acid substrates is explored.

EXPERIMENTAL SECTION

General Methods. IR spectra of compounds were recorded as thin films or KBr pellets. ^1H and $^{13}C\{^1H\}$ NMR spectra of all compounds were recorded on 400 and 100 MHz spectrometers, respectively (using TMS as an internal standard). HRMS measurements were obtained from a QTOF mass analyzer using the electrospray ionization (ESI) method. Column chromatography was carried out using silica gel 100−200 mesh. Reactions were performed in anhydrous solvent under

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Scheme 4. Comparison of ABTD with the Other Pivotal Directing Groups Used for the Mono β-C−H Arylation of Propionic Acid[6,14d]

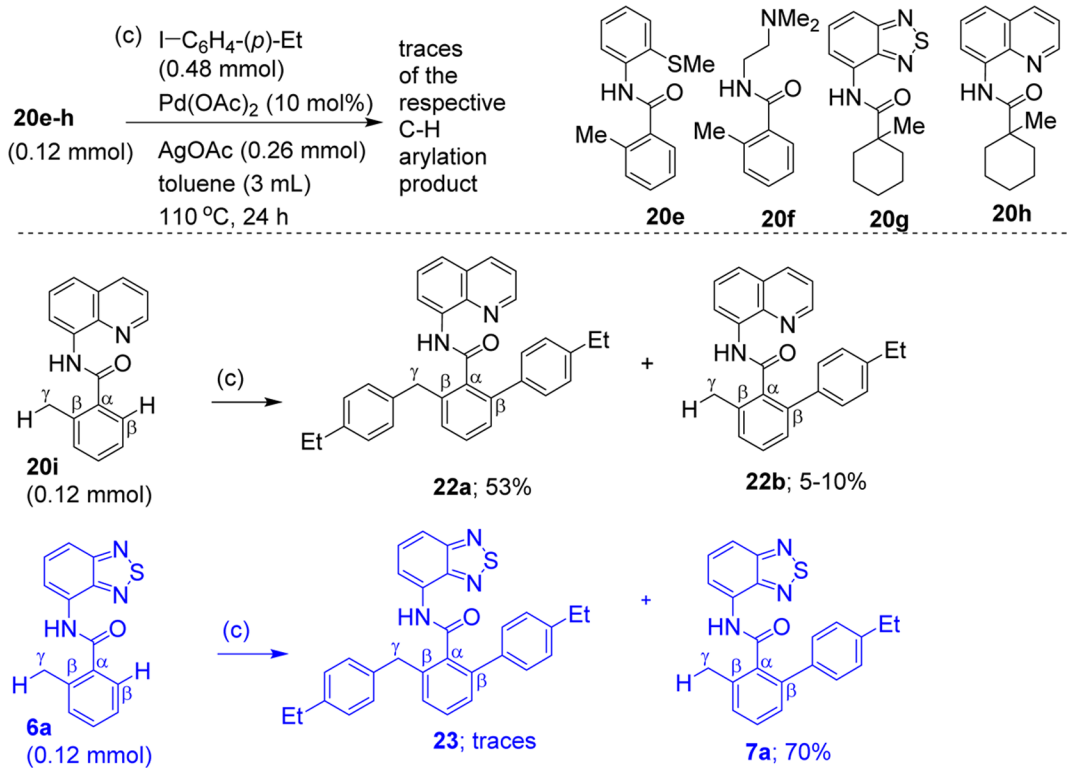


a nitrogen atmosphere. Isolated yields of all compounds were reported, and yields of all compounds reported here were not optimized. Compounds **3a−i** and **3o** were obtained from substrate **1a**. Compounds **3j**, **3k**, **3l**, **3m**, and **3n** were obtained from the corresponding substrates **1b**, **1c**, **1d**, **1e**, and **1f**. Compounds **3p**, **3q**, **3r**, and **3s** were obtained from the corresponding substrates **1d**, **1g**, and **1h**. Compounds **4a/4aA** and **4b/4bB** were obtained from substrate **1j**. Compounds **5a−m** were obtained from substrate **1k**. Compounds **27**,[20a] **28a**,[14c] **28b**,[14c] **28c**,[19] **28d**,[19] **20a**,[20b] **20b**,[6] **20c**,[6] **20d**,[6] and **21d**[20c] are reported in the literature. The reactions shown in Scheme 3 for comparing the efficiency of the ABTD with other popular bidentate directing groups are reported by our group.[14c] General procedures for the preparation of required carboxamide starting materials and C−H arylation/benzylation/oxygenation of carboxamides are given below. See the respective Schemes 1−7 and Tables 1−5 for exact reaction conditions and starting materials/reagents used.

General Procedure for the Synthesis of Carboxamides 1a−k and 1aa−ac (Procedure A). A dry RB flask containing benzo[*c*]-[1,2,5]thiadiazol-4-amine (1 mmol) and Et_3N (1.1 mmol) was stirred for 5−10 min under a nitrogen atmosphere. Then to the reaction flask was added anhydrous DCM (4 mL) followed by dropwise addition of the corresponding acid chloride (1 mmol). The reaction mixture was stirred for 12 h. After this period, the reaction mixture was diluted with dichloromethane (3−5 mL) and washed once with water (5−7 mL) and twice with saturated aqueous $NaHCO_3$ solution (3−5 mL). The

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Scheme 5. Typical Comparison of ABTD with Other Pivotal Directing Groups Used for the C−H Arylation Carboxamides



combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo, and purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh, EtOAc/hexanes) furnished the corresponding carboxamides **1a−k** and **1aa−ac**.

General Procedure for the C−H Functionalization of Carboxamides 1a−k, 1aa−ac, and 20a−h (Procedure B). An appropriate carboxamide (0.125 mmol, 1 equiv), $Pd(OAc)_2$ (2.8 mg, 10 mol %), an appropriate aryl iodide (0.5 mmol, 4 equiv), and AgOAc (45.9 mg, 0.275 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 110 °C for 12−48 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuo, and purification of the resulting reaction mixture through column chromatography furnished the corresponding C−H arylated carboxamides **3a−s**, **4a**, **4aA**, **4b**, **4bB**, **5a−m**, **21**, and **22** (see the corresponding tables and schemes for specific examples).

General Procedure for the Selective Monoarylation of Carboxamide 1i (Procedure C). An appropriate amide (0.125 mmol, 1 equiv), $Pd(OAc)_2$ (2.8 mg, 10 mol %), an appropriate aryl iodide (0.15 mmol, 1.2 equiv), and AgOAc (45.9 mg, 0.275 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 110 °C for 18−24 h under nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuo, and purification of the resulting reaction mixture through column chromatography furnished the corresponding C−H-arylated amides **3t,u,x** (see the corresponding scheme for specific examples).

General Procedure for the C−H Acetoxylation of Carboxamides 1h,i/20a−c (Procedure D). An appropriate amide (0.125 mmol, 1 equiv), $Pd(OAc)_2$ (2.8 mg, 10 mol %), $PhI(OAc)_2$ (0.32 mmol, 2.5 equiv), and anhydrous toluene (3 mL) was heated at 110 °C for 18−24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuo, and purification of the resulting reaction mixture through column chromatography furnished the corresponding *β*-acetoxylated amides **3v,w** (see the corresponding schemes for specific examples).

Procedure for the Alkylation of 1k and the Preparation of 4c (Procedure E). Cyclobutanecarboxamide **1k** (0.125 mmol), $Pd(OAc)_2$ (2.8 mg, 10 mol %), ethyl iodoacetate (80 mg, 0.37 mmol), Ag_2CO_3 (75 mg, 0.27 mmol), and $(BnO)_2PO_2H$ (7 mg, 20 mol %) in anhydrous *tert*-amyl alcohol (2 mL) was heated at 110 °C for 24 h under a nitrogen atmosphere. After the reaction period, the mixture was concentrated in vacuo, and purification of the crude residue by column chromatography on silica gel furnished the corresponding *β*-alkylated carboxamide **4c**.

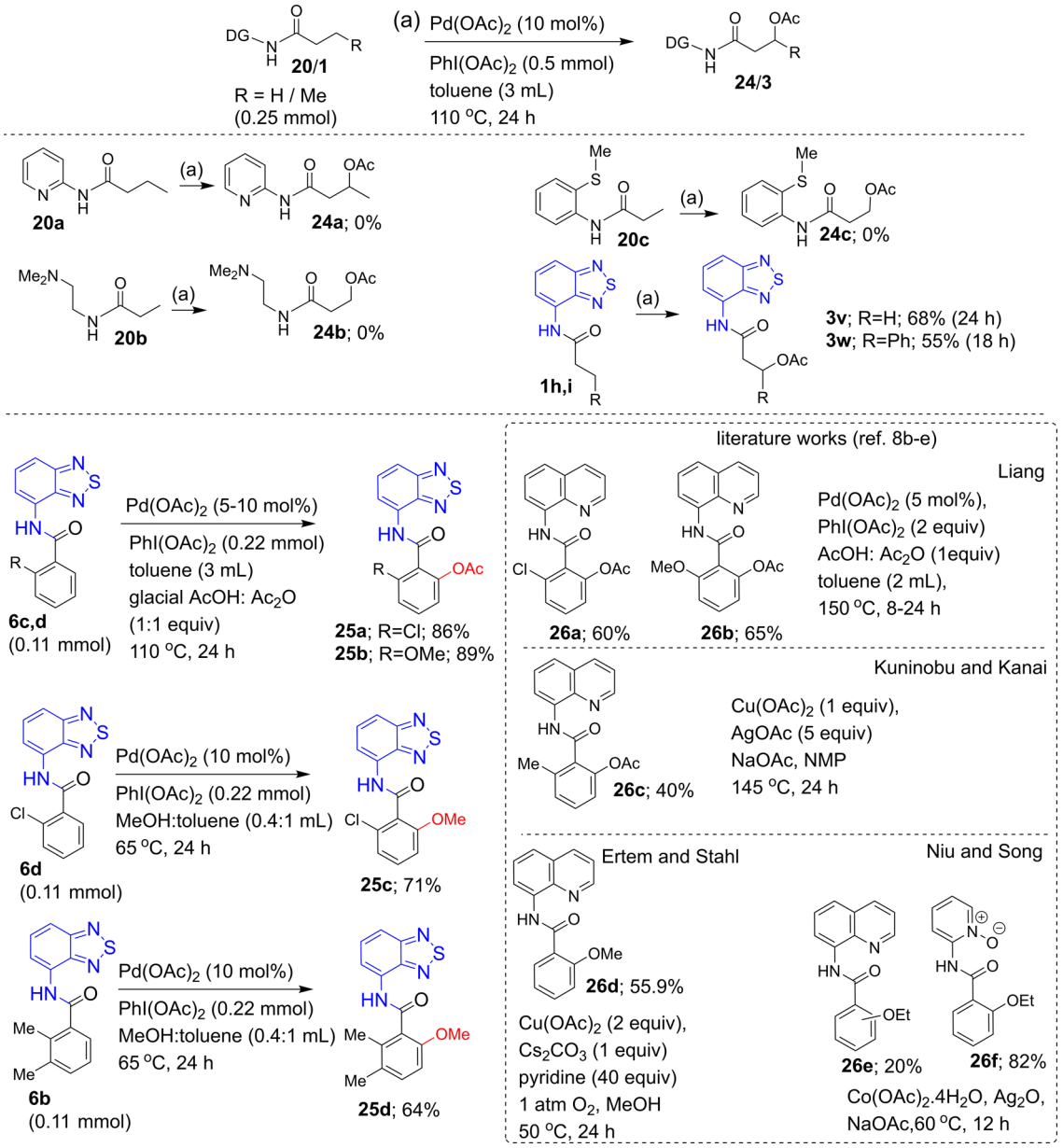
General Procedure for the Hydrolysis of C−H-Arylated Carboxamides 5g,h, and 3a,e (Procedure F). A solution of the corresponding carboxamide (0.1 mmol) and NaOH (10−15 equiv) in ethanol (3−4 mL) was heated at 85 °C for 18−24 h. After this period, the reaction mixture was diluted with water (3−4 mL) and extracted with DCM (2 × 10 mL), and then the aqueous layer was acidified with 1 N HCl to obtain pH ∼2. The resulting aqueous layers were extracted with DCM (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4 followed by the evaporation of the solvent in vacuo, resulting the corresponding pure carboxylic acids **28a−d**.

General Procedure for the Synthesis of Benzamides/Carboxamides 6d, 8a, 8b, 8d, and 20a−d (Procedure G). A dry flask containing 4-amino-2,1,3-benzothiadiazole (1 mmol, 151 mg) and Et_3N (1.1 mmol, 115 mg) was stirred for 5−10 min under a nitrogen atmosphere. Then to the reaction flask was added anhydrous DCM (4 mL) followed by dropwise addition of an appropriate acid chloride (1 mmol). The resulting mixture was stirred at rt for 12 h. After this period, the reaction mixture was diluted with dichloromethane and washed once with water and twice with saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo, and purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh, EtOAc/hexanes = 1:4) furnished the corresponding benzamides **6d**, **8a**, **8b**, **8d**, and **20a−d**.

General Procedure for the Synthesis of Benzamides 6a−c, 6e, and 8c (Procedure H). The corresponding carboxylic acid (3 mmol) was dissolved in dry DCM (12−15 mL) by adding two to three drops of dry DMF to the reaction mixture, oxalyl chloride (1.5 equiv, 563 mg) was added at 0 °C, and then the reaction mixture was stirred and allowed to attain rt over a period of 6−8 h under a nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuo to remove excess oxalyl chloride and solvent. The resultant

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Scheme 6. Comparison of ABTD with Other Seminal Works on the C−H Acetoxylation/Alkoxylation of Carboxamides



acid chloride was dissolved in DCM (12 −15 mL). Then, this DCM solution was added to a separate flask containing 4-amino-2,1,3-benzothiadiazole (2 mmol, 302 mg) and Et_3N (1.5 equiv, 454 mg) in DCM (3 mL) at 0 °C. After this, the resultant reaction mixture was stirred and allowed to attain rt over the period of 6−8 h under a nitrogen atmosphere. After this period, the reaction mixture was diluted with dichloromethane and then washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the resulting reaction mixture by column chromatography (silica gel, 100−200 mesh, EtOAc/hexanes = 1:4) furnished benzamides **6a**−**6c**, **6e**, and **8c**.

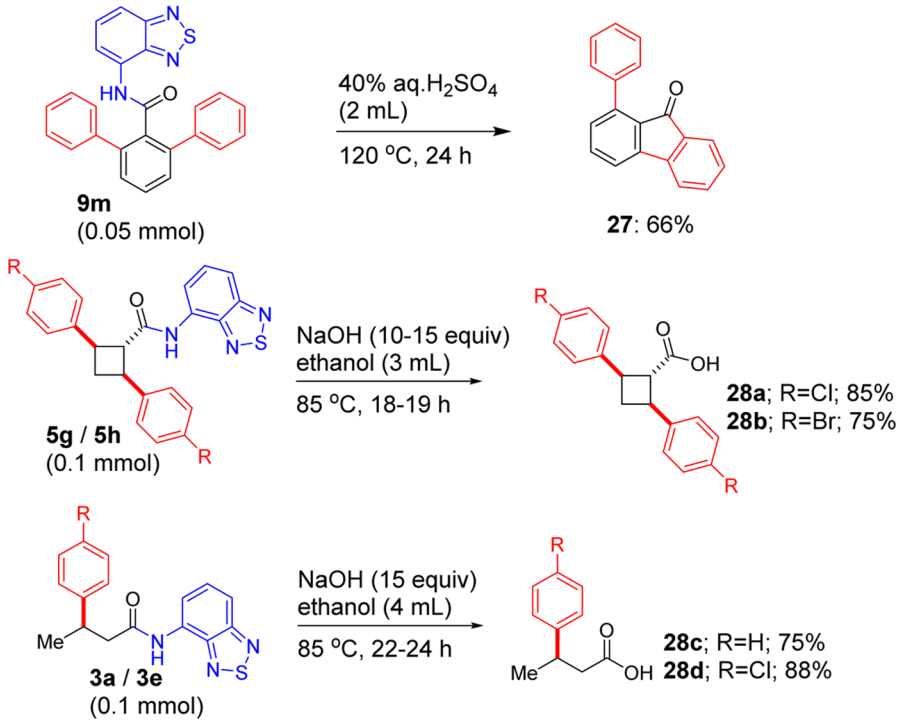
General Procedure for the Pd(II)-Catalyzed, ABTD-Directed *Ortho* C(sp^2)−H Arylation and Benzylation of Benzamides 6a−e and 8a−d (Procedure I). An appropriate benzamide **6**/**8** (0.12 mmol, 1 equiv), $Pd(OAc)_2$ (10 mol %, 2.7 mg), an appropriate aryl iodide or 1-(bromomethyl)-4-nitrobenzene (0.36−0.48 mmol, 4 equiv), and AgOAc (0.24−0.264 mmol, 2−2.2 equiv, 40−43.8 mg,) in anhydrous toluene (3 mL) was heated at 110 °C for 24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuo, and purification of the resulting reaction mixture by column chromatography furnished the corresponding *ortho* C(sp^2)−H arylated/benzylated benzamides **7**/**9**/**11**/**12** (see the corresponding tables and schemes for specific examples).

Procedure for the Synthesis of the Compound 27 (Procedure J). The bis-arylated benzamide **9m** (0.05 mmol, 20 mg) and 40% aq H_2SO_4 (2 mL) were heated at 120 °C for 24 h. After this period, the reaction mixture was diluted with water and extracted with ether (2 × 10 mL), the combined organic layers were dried over Na_2SO_4, and then the solvent was removed under vacuum. The crude reaction mixture was purified by column chromatography on silica gel to afford the compound **27**.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)butyramide (**1a**).* Following the general procedure A, **1a** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a colorless solid: R_f = 0.54 (EtOAc/hexanes = 1:5); yield 90% (200 mg); mp 86−88 °C; IR (KBr) 3053, 1698, 1547, 1264, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, 1H, J = 7.3 Hz), 8.50 (br s, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.60 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.3 Hz), 2.53 (t, 2H, J = 7.4 Hz), 1.90−1.81 (m, 2H), 1.07 (t, 3H, J = 7.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.8, 154.7, 147.7, 131.2, 129.9, 115.6, 114.9, 39.8, 19.0, 13.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{10}H_{12}N_3OS$

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Scheme 7. Removal of the ABTD Directing Group after the β-C−H Arylation of Carboxamides.[14e]



222.0701, found 222.0695. The NH proton is perhaps merged with the doublet peak at δ 8.50 in the ^{1}H NMR spectrum.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)hexanamide (**1b**).* Following the general procedure A, **1b** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a colorless solid; R_f = 0.50 (EtOAc/hexanes = 1:5); yield 70% (174 mg); mp 98−100 °C; IR (KBr) 3396, 1662, 1521, 1257, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, 1H, J = 7.4 Hz), 8.50 (br s, 1H), 7.68 (dd, 1H, J_1 = 8.9 Hz, J_2 = 1.0 Hz), 7.60 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.4 Hz), 2.55 (t, 2H, J = 7.4 Hz), 1.86−1.78 (m, 2H), 1.45−1.37 (m, 4H), 0.96−0.93 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.0, 154.7, 147.7, 131.2, 130.0, 115.6, 114.9, 37.9, 31.4, 25.2, 22.4, 14.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{12}H_{16}N_3OS$ 250.1014, found 250.1017. The NH proton is perhaps merged with the doublet peak at δ 8.51 in the ^{1}H NMR spectrum.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)heptanamide (**1c**).* Following the general procedure A, **1c** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 15:85) as a pale yellow solid: R_f = 0.52 (EtOAc/hexanes = 1:5); yield 98% (258 mg); mp 79−81 °C; IR (KBr) 3312, 2935, 2358, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 8.48 (d, 1H, J = 7.5 Hz), 7.64 (dd, 1H, J_1 = 8.9 Hz, J_2 = 1.0 Hz), 7.56 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.5 Hz), 2.54 (t, 2H, J = 7.5 Hz), 1.83−1.75 (m, 2H), 1.44−1.38 (m, 2H), 1.36−1.30 (m, 4H), 0.89 (t, 3H, J = 7.1 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.9, 154.7, 147.7, 131.1, 130.0, 115.5, 114.9, 37.9, 31.6, 28.9, 25.4, 22.5, 14.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{18}N_3OS$ 264.1171, found 264.1174. The NH proton is perhaps merged with the doublet peak at δ 8.49 in the ^{1}H NMR spectrum.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)decanamide (**1d**).* Following the general procedure A, **1d** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a colorless solid: R_f = 0.53 (EtOAc/hexanes = 1:5); yield 73% (223 mg); mp 89−91 °C; IR (KBr) 3307, 1666, 1522, 1407, 1276, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, 1H, J = 7.4 Hz), 8.49 (br s, 1H), 7.68 (dd, 1H, J_1 = 8.8 Hz, J_2 = 1.0 Hz), 7.61 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 2.55 (t, 2H, J = 7.4 Hz), 1.85−1.78 (m, 2H), 1.46−1.28 (m, 12H), 0.89 (t, 3H, J = 6.7 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.9, 154.7, 147.7, 131.2, 130.0, 115.6, 114.9, 37.9, 31.9, 29.4, 29.4, 29.3, 29.2, 25.5, 22.7, 14.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{24}N_3OS$ 306.1640, found 306.1647.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)nonanamide (**1e**).* Following the general procedure A, **1e** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 15:85) as a colorless solid: R_f = 0.53 (EtOAc/hexanes = 1:5); yield 81% (236 mg); mp 80−82 °C; IR (KBr) 3309, 2916, 1657, 1409 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 8.45 (d, 1H, J = 7.3 Hz), 7.62−7.59 (m, 1H), 7.56−7.51 (m, 1H), 2.52 (t, 2H, J = 7.4 Hz), 1.81−1.74 (m, 2H), 1.41−1.24 (m, 10H), 0.85 (t, 3H, J = 6.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.0, 154.7, 147.7, 131.1, 129.9, 115.5, 114.9, 37.9, 31.8, 29.3, 29.2, 29.1, 25.5, 22.6, 14.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{22}N_3OS$ 292.1484, found 292.1480.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)stearamide (**1f**).* Following the general procedure A, **1f** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a colorless solid: R_f = 0.55 (EtOAc/hexanes = 1:5); yield 98% (409 mg); mp 99−101 °C; IR (KBr) 3054, 1548, 1422, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, 1H, J = 7.5 Hz), 8.50 (br s, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.59 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.5 Hz), 2.55 (t, 2H, J = 7.5 Hz), 1.85−1.77 (m, 2H), 1.43−1.26 (m, 28H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.9, 154.7, 147.7, 131.2, 130.0, 115.6, 114.8, 37.9, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 25.5, 22.7, 14.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{24}H_{40}N_3OS$ 418.2892, found 418.2889. The NH proton is perhaps merged with the doublet peak at δ 8.50 in the ^{1}H NMR spectrum.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)dodecanamide (**1g**).* Following the general procedure A, **1g** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 15:85) as a pale yellow solid: R_f = 0.51 (EtOAc/hexanes = 1:5); yield 75% (249 mg); mp 83−85 °C; IR (KBr) 3054, 2305, 1421, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, 1H, J = 6.8 Hz), 8.51 (br s, 1H), 7.66 (dd, 1H, J_1 = 8.8 Hz, J_2 = 1.0 Hz), 7.59 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 2.55 (t, 2H, J = 7.5 Hz), 1.85−1.77 (m, 2H), 1.44−1.26 (m, 16H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.0, 154.7, 147.7, 131.2, 130.0, 115.6, 114.9, 37.9, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.5, 22.7, 14.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{28}N_3OS$: 334.1953, found 334.1949. The NH proton is perhaps merged with the doublet peak at δ 8.50 in the ^{1}H NMR spectrum.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-phenylpropanamide (**1h**).* Following the general procedure A, **1h** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 15:85) as

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

a colorless solid: R_f = 0.58 (EtOAc/hexanes = 1:5); yield 90% (254 mg); mp 114−116 °C; IR (KBr) 3318, 2962, 1547, 1409 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, 1H, J = 7.3 Hz), 8.44 (br s, 1H), 7.69 (d, 1H, J = 8.7 Hz), 7.61 (dd, 1H, J_1 = 8.7 Hz, J_2 = 7.3 Hz), 7.35−7.29 (m, 4H), 7.25−7.22 (m, 1H), 3.15 (t, 2H, J = 7.4 Hz), 2.88 (t, 2H, J = 7.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.8, 154.7, 147.7, 140.4, 131.1, 129.8, 128.7, 128.4, 126.5, 115.8, 115.0, 39.5, 31.3; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{14}N_3OS$ 284.0858, found 284.0850.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)propionamide (**1i**).* Following the general procedure A, **1i** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.55 (EtOAc/hexanes = 1:5); yield 80% (166 mg); mp 129−131 °C; IR (KBr) 3323, 1667, 1524, 1278, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, 1H, J = 7.2 Hz), 8.50 (br s, 1H), 7.67 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.9 Hz), 7.60 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.2 Hz), 2.59 (q, 2H, J = 7.6 Hz), 1.34 (t, 3H, J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.5, 154.7, 147.7, 131.2, 130.0, 115.6, 114.8, 30.9, 9.5; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_9H_{10}N_3OS$ 208.0545, found 208.0541. The NH proton is perhaps merged with the doublet peak at δ 8.50 in the ^{1}H NMR spectrum.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)cyclopropanecarboxamide (**1j**).* Following the general procedure A, **1j** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a colorless solid: R_f = 0.56 (EtOAc/hexanes = 1:5); yield 70% (153 mg); mp 142−144 °C; IR (KBr) 3314, 1656, 1558, 1419, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.46 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.0 Hz), 7.68 (dd, 1H, J_1 = 8.8 Hz, J_2 = 1.0 Hz), 7.60 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 1.80−1.71 (m, 1H), 1.21−1.75 (m, 2H), 1.0−0.95 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.4, 154.8, 147.7, 131.2, 130.1, 115.5, 114.8, 16.1, 8.6; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{10}H_{10}N_3OS$ 220.0545, found 220.0540.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)cyclobutanecarboxamide (**1k**).* Following the general procedure A, **1k** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a colorless solid: R_f = 0.56 (EtOAc/hexanes = 1:5); yield 95% (221 mg); mp 169−171 °C; IR (KBr) 3399, 1656, 1555, 1257, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, 1H, J = 7.2 Hz), 8.39 (br s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.59 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.2 Hz), 3.41−3.32 (m, 1H), 2.53−2.43 (m, 2H), 2.37−2.29 (m, 2H), 2.11−1.97 (m, 2H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.7, 154.7, 147.7, 131.2, 130.0, 115.5, 114.8, 41.0, 25.4, 18.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{11}H_{12}N_3OS$ 234.0701, found 234.0710.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-phenylbutanamide (**1aa**).* Following the general procedure A, **1aa** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a pale yellow viscous liquid: yield 85% (252 mg); R_f (EtOAc/hexanes = 1:4) 0.78; IR (DCM) 3389, 2965, 1694, 1546, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (br s, 1H), 8.50 (d, 1H, J = 6.7 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.56 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.47−7.45 (m, 2H), 7.41 (t, 2H, J = 7.2 Hz); 7.32 (t, 1H, J = 7.2 Hz), 3.61 (t, 1H, J = 7.6 Hz), 2.39−2.32 (m, 1H), 2.01−1.94 (m, 1H), 1.00 (t, 3H, J = 7.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 172.2, 154.7, 147.7, 139.1, 131.1, 129.9, 129.1, 128.0, 127.7, 115.7, 114.7, 56.4, 26.4, 12.4; HRMS (ESI) calcd for $C_{16}H_{16}N_3OS$ [M + H]$^+$ 298.1014, found 298.1002.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-ethylbutanamide (**1ab**).* Following the general procedure A, **1ab** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a pale yellow solid: yield 87% (656 mg); mp 60−62 °C; R_f (EtOAc/hexanes = 1:4) 0.75; IR (DCM) 3321, 3056, 2964, 1693,748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.55 (d, 1H, J = 7.3 Hz), 8.50 (br s, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.60 (dd, 1H, J_1 = 8.0, J_2 = 7.4 Hz), 2.32−2.25 (m, 1H), 1.86−1.75 (m, 2H), 1.71−1.61 (m, 2H), 1.00 (t, 6H, J = 7.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 174.9, 154.7, 147.8, 131.2, 129.9, 115.6, 115.0, 52.4, 25.8, 12.1; HRMS (ESI) calcd for $C_{12}H_{16}N_3OS$ [M + H]$^+$ 250.1014, found 250.1003.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4-methylnonanamide (**1ac**).* TFollowing the general procedure A, **1ac** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a pale yellow solid: yield 90% (274 mg); mp 90−92 °C; R_f (EtOAc/hexanes = 1:4) 0.80; IR (DCM) 3314, 2919, 1667, 1523, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (br s, 1H), 8.42 (d, 1H, J = 7.3 Hz), 7.56 (d, 1H, J = 8.8 Hz), 7.48 (dd, 1H, J_1 = 8.0, J_2 = 7.4 Hz), 2.58−2.44 (m, 2H), 1.83−1.76 (m, 1H), 1.61−1.52 (m, 1H), 1.49−1.45 (m, 1H), 1.32−1.18 (m, 7H), 1.14−1.08 (m, 1H), 0.89 (d, 3H, J = 6.6 Hz), 0.83 (t, 3H, J = 7.1 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 172.1, 154.7, 147.6, 131.0, 129.9, 115.4, 114.9, 36.7, 35.6, 32.5, 32.4, 32.1, 26.6, 22.7, 19.4, 14.1; HRMS (ESI) calcd for $C_{16}H_{24}N_3OS$ [M + H]$^+$ 306.1640, found 306.1627.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-phenylbutanamide (**3a**).* Following the general procedure B, **3a** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a brown liquid: R_f = 0.55 (EtOAc/hexanes = 1:5); yield 95% (35 mg); IR (DCM) 3321, 1696, 1543, 1517, 1408, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, 1H, J = 7.4 Hz), 8.35 (br s, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.58 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.34−7.32 (m, 4H), 7.25−7.19 (m, 1H), 3.53−3.44 (m, 1H), 2.87 (dd, 1H, J_1 = 14.5 Hz, J_2 = 7.1 Hz), 2.78 (dd, 1H, J_1 = 14.5 Hz, J_2 = 7.7 Hz), 1.44 (d, 3H, J = 7.1 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.4, 154.7, 147.6, 145.4, 131.1, 129.8, 128.8, 126.8, 126.6, 115.7, 114.9, 46.7, 36.9, 21.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{16}N_3OS$ 298.1014, found 298.1008.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-nitrophenyl)butanamide (**3b**).* Following the general procedure B, **3b** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a brown liquid: R_f = 0.46 (EtOAc/hexanes = 1:5); yield 94% (40 mg); IR (DCM) 3387, 1547, 1516, 1408, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, 1H, J = 7.4 Hz), 8.38 (br s, 1H), 8.19 (d, 2H, J = 8.8 Hz), 7.68 (d, 1H, J = 8.3 Hz), 7.59 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.50 (d, 2H, J = 8.8 Hz), 3.67−3.61 (m, 1H), 2.87 (d, 2H, J = 7.4 Hz), 1.47 (d, 3H, J = 7.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.4, 154.7, 153.2, 147.6, 146.7, 131.0, 129.5, 127.8, 124.0, 116.0, 115.2, 45.8, 36.6, 21.6; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{15}N_4O_3S$ 343.0865, found 343.0871.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(p-tolyl)butanamide (**3c**).* Following the general procedure B, **3c** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a pale yellow solid: R_f = 0.57 (EtOAc/hexanes = 1:5); yield 75% (29 mg); mp 91−93 °C; IR (KBr) 3398, 1695, 1546, 1408, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, 1H, J = 7.3 Hz), 8.33 (br s, 1H), 7.67 (d, 1H, J = 8.2 Hz), 7.59 (dd, 1H, J_1 = 8.6 Hz, J_2 = 7.4 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.14 (d, 2H, J = 8.0 Hz), 3.47−3.42 (m, 1H), 2.85 (dd, 1H, J_1 = 14.5 Hz, J_2 = 7.2 Hz), 2.76 (dd, 1H, J_1 = 14.5 Hz, J_2 = 7.4 Hz), 2.32 (s, 3H), 1.42 (d, 3H, J = 7.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 154.7, 147.6, 142.4, 136.2, 131.2, 129.8, 129.4, 126.6, 115.7, 114.9, 46.8, 36.5, 22.0, 21.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{18}N_3OS$ 312.1171, found 312.1176.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-cyanophenyl)butanamide (**3d**).* Following the general procedure B, **3d** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.49 (EtOAc/hexanes = 1:5); yield 52% (21 mg); mp 146−148 °C; IR (KBr) 3392, 1609, 1546, 1408, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, J = 7.4 Hz), 8.35 (br s, 1H), 7.69 (d, 1H, J = 8.8 Hz), 7.62 (d, 2H, J = 8.4 Hz), 7.58 (d, 1H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.4 Hz), 3.60−3.54 (m, 1H), 2.83 (dd, 2H, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 1.44 (d, 3H, J = 7.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.5, 154.7, 151.0, 147.6, 132.6, 131.0, 129.5, 127.7, 118.9, 116.0, 115.1, 110.5, 45.8, 36.8, 21.5; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{15}N_4OS$ 323.0967, found 323.0960.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-chlorophenyl)butanamide (**3e**).* Following the general procedure B, **3e** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.55 (EtOAc/hexanes = 1:5); yield 97% (40 mg); mp 98−100 °C; IR (KBr) 3401, 1651, 1546, 1409, 1274, 679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, 1H, J = 7.3 Hz), 8.30 (br s, 1H), 7.68 (d, 1H, J = 8.8 Hz), 7.58 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.3 Hz), 7.30−7.24 (m, 4H), 3.50−3.44 (m, 1H), 2.84−2.76 (m, 2H), 1.41 (d, 3H, J = 7.0 Hz);

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.0, 154.7, 147.6, 143.9, 132.3, 131.0, 129.6, 128.9, 128.2, 115.8, 115.0, 46.5, 36.3, 21.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{15}ClN_3OS$ 332.0624, found 332.0629.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-methoxyphenyl)-butanamide (**3f**).* Following the general procedure B, **3f** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.55 (EtOAc/hexanes = 1:5); yield 53% (22 mg); mp 93−95 °C; IR (KBr) 3401, 1611, 1512, 1408, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, 1H, J = 7.3 Hz), 8.33 (br s, 1H), 7.66 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.9 Hz), 7.58 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.3 Hz), 7.24 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.6 Hz), 3.77 (s, 3H), 3.46−3.40 (m, 1H), 2.84−2.72 (m, 2H), 1.40 (d, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.6, 158.2, 154.7, 147.6, 137.5, 131.1, 129.8, 127.7, 115.7, 114.9, 114.1, 55.2, 47.0, 36.2, 22.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2S$ 328.1120, found 328.1131.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(3-nitrophenyl)butanamide (**3g**).* Following the general procedure B, **3g** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a brown liquid: R_f = 0.47 (EtOAc/hexanes = 1:5); yield 60% (26 mg); IR (DCM) 3374, 1696, 1526, 1349, 897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1H, J = 7.5 Hz), 8.42 (br s, 1H), 8.21 (t, 1H, J = 1.9 Hz), 8.09−8.06 (m, 1H), 7.67 (dd, 2H, J_1 = 8.8 Hz, J_2 = 0.8 Hz), 7.57 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.5 Hz), 7.48 (t, 1H, J = 7.9 Hz), 3.67−3.61 (m, 1H), 2.94−2.83 (m, 2H), 1.48 (d, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 154.7, 148.5, 147.6, 147.5, 133.6, 131.0, 129.6, 129.5, 121.8, 121.6, 116.0, 115.1, 45.8, 36.4, 21.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{15}N_4O_3S$ 343.0865, found 343.0858. The NH proton is perhaps merged with the doublet peak at δ 8.42 in the ^1H NMR spectrum.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(2,3-dihydrobenzo[b][1,4]-dioxin-6-yl)butanamide (**3h**).* Following the general procedure B, **3h** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a colorless liquid: R_f = 0.54 (EtOAc/hexanes = 1:4); yield 63% (28 mg); IR (DCM) 3404, 1683, 1546, 1408, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, 1H, J = 7.3 Hz), 8.33 (br s, 1H), 7.66 (d, 1H, J = 8.3 Hz), 7.59 (dd, 1H, J_1 = 8.7 Hz, J_2 = 7.4 Hz), 6.83−6.79 (m, 3H), 4.24−4.21 (m, 4H), 3.39−3.34 (m, 1H), 2.81 (dd, 1H, J_1 = 14.5 Hz, J_2 = 7.4 Hz), 2.72 (dd, 1H, J_1 = 14.5 Hz, J_2 = 7.4 Hz), 1.38 (d, 3H, J = 6.9 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 154.7, 147.6, 143.6, 142.2, 138.8, 131.1, 129.8, 119.7, 117.5, 115.7, 115.4, 114.9, 64.4, 64.3, 46.8, 36.3, 22.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{18}N_3O_3S$ 356.1069, found 356.1068.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(3,4-dichlorophenyl)-butanamide (**3i**).* Following the general procedure B, **3i** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a brown viscous liquid: R_f = 0.57 (EtOAc/hexanes = 1:5); yield 86% (39 mg); IR (neat) 3400, 1421, 1265, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, 1H, J = 7.4 Hz), 8.33 (br s, 1H), 7.68 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.7 Hz), 7.58 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.41 (d, 1H, J = 2.0 Hz), 7.37 (d, 1H, J = 8.2 Hz), 7.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.0 Hz), 3.46 (m, 1H), 2.80−2.77 (m, 2H), 1.41 (d, 3H, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.6, 154.6, 147.6, 145.7, 132.7, 131.0, 130.6, 130.5, 129.5, 128.9, 126.4, 115.9, 115.1, 46.1, 36.1, 21.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{14}Cl_2N_3OS$ 366.0235, found 366.0223.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-methoxyphenyl)-hexanamide (**3j**).* Following the general procedure B, **3j** was obtained from the carboxamide **1b** after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a brown liquid: R_f = 0.55 (EtOAc/hexanes = 1:5); yield 62% (28 mg); IR (DCM) 3406, 1693, 1547, 1408, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, 1H, J = 7.2 Hz), 8.27 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.9 Hz, J_2 = 0.9 Hz), 7.56 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.2 Hz), 7.20 (d, 2H, J = 8.7 Hz), 6.84 (d, 2H, J = 8.7 Hz), 3.76 (s, 3H), 3.27−3.20 (m, 1H), 2.83 (dd, 1H, J_1 = 14.5 Hz, J_2 = 6.4 Hz), 2.75 (dd, 1H, J_1 = 14.5 Hz, J_2 = 8.4 Hz), 1.79−1.62 (m, 2H), 1.30−1.19 (m, 2H), 0.89 (t, 3H, J = 7.3 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 158.2, 154.7, 147.6, 135.8, 131.1, 129.8, 128.3, 115.6, 114.8, 114.1, 55.2, 45.9, 41.7, 38.6, 20.5, 14.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{22}N_3O_2S$ 356.1433, found 356.1423.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-methoxyphenyl)-heptanamide (**3k**).* Following the general procedure B, **3k** was obtained from the carboxamide **1c** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a yellow liquid: R_f = 0.56 (EtOAc/hexanes = 1:5); yield 78% (36 mg); IR (DCM) 3054, 1547, 1421, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, J = 7.4 Hz), 8.26 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.8 Hz), 7.56 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.20 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 3.76 (s, 3H), 3.23−3.19 (m, 1H), 2.83 (dd, 1H, J_1 = 14.5 Hz, J_2 = 6.4 Hz), 2.75 (dd, 1H, J_1 = 14.5 Hz, J_2 = 8.4 Hz), 1.80−1.66 (m, 2H), 1.35−1.14 (m, 4H), 0.85 (t, 3H, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 158.2, 154.7, 147.6, 135.9, 131.1, 129.8, 128.3, 115.6, 114.8, 114.1, 55.2, 46.0, 41.9, 36.1, 29.6, 22.6, 14.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{24}N_3O_2S$ 370.1589, found 370.1580.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-phenyldecanamide (**3l**).* Following the general procedure B, **3l** was obtained from the carboxamide **1d** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a yellow viscous liquid: R_f = 0.55 (EtOAc/hexanes = 1:5); yield 87% (41 mg); IR (neat) 3393, 2928, 2366, 1546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, J = 7.3 Hz), 8.30 (br s, 1H), 7.64 (d, 1H, J = 8.6 Hz), 7.56 (dd, 1H, J_1 = 8.6 Hz, J_2 = 7.3 Hz), 7.33−7.21 (m, 4H), 7.20−7.17 (m, 1H), 3.31−3.24 (m, 1H), 2.89−2.77 (m, 2H), 1.80−1.70 (m, 2H), 1.28−1.22 (m, 10H), 0.86 (t, 3H, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 154.7, 147.6, 144.0, 131.1, 129.8, 128.7, 127.4, 126.6, 115.6, 114.9, 45.7, 42.7, 36.3, 31.8, 29.5, 29.2, 27.4, 22.6, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{28}N_3OS$ 382.1953, found 382.1960.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-methoxyphenyl)-nonanamide (**3m**).* Following the general procedure B, **3m** was obtained from the carboxamide **1e** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a yellow viscous liquid: R_f = 0.56 (EtOAc/hexanes = 1:5); yield 72% (36 mg); IR (neat) 3339, 2364, 1513, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, J = 7.4 Hz), 8.26 (br s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.56 (t, 1H, J = 8.8 Hz, J_2 = 7.4 Hz), 7.20 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 3.77 (s, 3H), 3.23−3.18 (m, 1H), 2.83 (dd, 1H, J_1 = 14.5 Hz, J_2 = 6.4 Hz), 2.75 (dd, 1H, J_1 = 14.5 Hz, J_2 = 8.6 Hz), 1.76−1.69 (m, 2H), 1.30−1.20 (m, 8H), 0.86 (t, 3H, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 158.2, 154.7, 147.6, 135.9, 131.1, 129.8, 128.3, 115.6, 114.8, 114.1, 55.2, 46.0, 42.0, 36.4, 31.7, 29.2, 27.4, 22.6, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_2S$ 398.1902, found 398.1896.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-methoxyphenyl)-octadecanamide (**3n**).* Following the general procedure B, **3n** was obtained from the carboxamide **1f** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.56 (EtOAc/hexanes = 1:5); yield 90% (59 mg); mp 63−65 °C; IR (KBr) 3406, 1693, 1547, 1408, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, J = 7.4 Hz), 8.26 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.9 Hz), 7.56 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.20 (d, 2H, J = 8.7 Hz), 6.84 (d, 2H, J = 8.7 Hz), 3.76 (s, 3H), 3.23−3.19 (m, 1H), 2.83 (dd, 1H, J_1 = 14.5 Hz, J_2 = 6.4 Hz), 2.74 (dd, 1H, J_1 = 14.5 Hz, J_2 = 8.5 Hz), 1.76−1.66 (m, 2H), 1.33−1.22 (m, 26H), 0.90 (t, 3H, J = 6.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 158.2, 154.7, 147.6, 135.9, 131.1, 129.8, 128.3, 115.6, 114.8, 114.1, 55.2, 46.0, 42.0, 36.4, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 27.4, 22.7, 14.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{31}H_{46}N_3O_2S$ 524.3311, found 524.3300.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(2-fluoropyridin-4-yl)-butanamide (**3o**).* Following the general procedure B, **3o** was obtained from the carboxamide **1a** after purification by column chromatography on silica gel (EtOAc/hexanes = 2:3) as a yellow thick liquid: R_f = 0.48 (EtOAc/hexanes = 1:3); yield 57% (22 mg); IR (neat) 3304, 2966, 1695, 1545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, 1H, J = 7.3 Hz), 8.38 (br s, 1H), 8.20 (d, 1H, J = 2.4 Hz), 7.78−7.74 (m, 1H), 7.70 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.9 Hz), 7.60 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.3 Hz), 6.91 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.4 Hz),

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

3.59−3.54 (m, 1H), 2.83 (d, 2H, J = 7.2 Hz), 1.45 (d, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 162.6 (d, J_{C-F} = 236.4 Hz), 154.7, 147.6, 146.1 (d, J_{C-F} = 14.5 Hz), 139.7 (d, J_{C-F} = 7.6 Hz), 138.4 (d, J_{C-F} = 4.5 Hz), 131.0, 129.5, 116.0, 115.2, 109.5 (d, J_{C-F} = 37.1 Hz), 46.1, 33.5, 21.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}FN_4OS$ 317.0872, found 317.0865.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(6-fluoropyridin-3-yl)-decanamide (**3p**).* Following the general procedure B, **3p** was obtained from the carboxamide **1d** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow thick liquid: R_f = 0.50 (EtOAc/hexanes = 1:3); yield 70% (35 mg); IR (KBr) 3054, 2349, 1547, 1265, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, 1H, J = 7.4 Hz), 8.35 (br s, 1H), 8.15 (d, 1H, J = 2.2 Hz), 7.74−7.70 (m, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.57 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 6.90 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.9 Hz), 3.39−3.32 (m, 1H), 2.91 (dd, 1H, J_1 = 15.0 Hz, J_2 = 6.3 Hz), 2.75 (dd, 1H, J_1 = 15.0 Hz, J_2 = 8.5 Hz), 1.86−1.67 (m, 2H), 1.33−1.24 (m, 10H), 0.86 (t, 3H, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 162.6 (d, J_{C-F} = 236.5 Hz), 154.7, 147.6, 146.7 (d, J_{C-F} = 14.2 Hz), 140.1 (d, J_{C-F} = 7.6 Hz), 136.9 (d, J_{C-F} = 4.4 Hz), 131.0, 129.5, 116.0, 115.1, 109.5 (d, J_{C-F} = 37.2 Hz), 44.9, 39.1, 35.9, 31.7, 29.3, 29.1, 27.3, 22.6, 14.1; HRMS (ESI) m/z $[M - H]^+$ calcd for $C_{21}H_{24}FN_4OS$ 399.1655, found 399.1640.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(6-fluoropyridin-3-yl)-dodecanamide (**3q**).* Following the general procedure B, **3q** was obtained from the carboxamide **1g** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a yellow thick liquid: R_f = 0.51 (EtOAc/hexanes = 1:3); yield 90% (48 mg); IR (KBr) 2926, 1693, 1547, 1408, 1274, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, 1H, J = 7.4 Hz), 8.33 (br s, 1H), 8.16 (d, 1H, J = 2.2 Hz), 7.75−7.72 (m, 1H), 7.68 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.8 Hz), 7.58 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 6.90 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.9 Hz), 3.38−3.34 (m, 1H), 2.91 (dd, 1H, J_1 = 15.0 Hz, J_2 = 6.3 Hz), 2.76 (dd, 1H, J_1 = 15.0 Hz, J_2 = 8.5 Hz), 1.84−1.79 (m, 1H), 1.73−1.67 (m, 2H), 1.31−1.13 (m, 13H), 0.88 (t, 3H, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 162.6 (d, J_{C-F} = 236.4 Hz), 154.7, 147.6, 146.7 (d, J_{C-F} = 14.3 Hz), 140.1 (d, J_{C-F} = 7.8 Hz), 137.0 (d, J_{C-F} = 4.4 Hz), 131.0, 129.4, 116.0, 115.2, 109.5 (d, J_{C-F} = 37.1 Hz), 44.9, 39.1, 35.1, 31.8, 29.5, 29.4, 29.4, 29.3, 27.3, 22.7, 14.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{30}FN_4OS$ 429.2124, found 429.2112.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-methoxyphenyl)-3-phenylpropanamide (**3r**).* Following the general procedure B, **3r** was obtained from the carboxamide **1h** after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a brown liquid: R_f = 0.54 (EtOAc/hexanes = 1:5); yield 52% (26 mg); IR (DCM) 3326, 1696, 1546, 1512, 1408, 1272, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, 1H, J = 7.3 Hz), 8.38 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.9 Hz), 7.55 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.3 Hz), 7.34−7.29 (m, 4H), 7.25 (d, 2H, J = 8.6 Hz), 7.22−7.18 (m, 1H), 6.84 (d, 2H, J = 8.6 Hz), 4.71 (t, 1H, J = 7.8 Hz), 3.76 (s, 3H), 3.27 (d, 2H, J = 7.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 158.3, 154.6, 147.6, 143.7, 135.4, 131.1, 129.7, 128.7, 128.7, 127.6, 126.6, 115.7, 115.0, 114.1, 55.2, 46.4, 44.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{20}N_3O_2S$ 390.1276, found 390.1268.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(3,4-dimethylphenyl)-3-phenylpropanamide (**3s**).* Following the general procedure B, **3s** was obtained from the carboxamide **1h** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a reddish brown liquid: R_f = 0.56 (EtOAc/hexanes = 1:5); yield 53% (25 mg); IR (neat) 3397, 2349, 1546, 1409, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, 1H, J = 7.4 Hz), 8.38 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.8 Hz), 7.56 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.36−7.30 (m, 4H), 7.22−7.18 (m, 1H), 7.10−7.07 (m, 3H), 4.68 (t, 1H, J = 7.8 Hz), 3.29 (d, 2H, J = 7.8 Hz), 2.22 (s, 3H), 2.20 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 154.7, 147.6, 143.7, 140.7, 136.9, 135.0, 131.1, 130.0, 129.8, 129.1, 128.7, 127.6, 126.6, 124.8, 115.7, 115.0, 46.9, 44.4, 19.9, 19.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{22}N_3OS$ 388.1484, found 388.1472.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(3-nitrophenyl)propanamide (**3t**).* Following the general procedure C, **3t** was obtained from the carboxamide **1i** after purification by column chromatography on silica gel (EtOAc/hexanes = 35:65) as a pale yellow solid: R_f = 0.50 (EtOAc/hexanes = 1:4); yield 56% (23 mg); mp 134−136 °C; IR (KBr) 3055, 2306, 1266, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, 1H, J = 7.4 Hz), 8.46 (br s, 1H), 8.19 (s, 1H), 8.10 (d, 1H, J = 8.2 Hz), 7.71 (d, 1H, J = 8.8 Hz), 7.66 (d, 1H, J = 7.6 Hz), 7.62 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.49 (t, 1H, J = 7.9 Hz), 3.27 (t, 2H, J = 7.4 Hz), 2.95 (t, 2H, J = 7.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 154.7, 148.5, 147.6, 142.4, 134.9, 131.0, 129.6, 123.3, 121.7, 116.0, 115.2, 38.5, 30.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_4O_3S$ 329.0708, found 329.0699.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-(4-nitrophenyl)propanamide (**3u**).* Following the general procedure C, **3u** was obtained from the carboxamide **1i** after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a pale yellow solid: R_f = 0.48 (EtOAc/hexanes = 1:4); yield 54% (22 mg); mp 180−182 °C; IR (KBr) 3384, 2342, 1516, 1344 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, 1H, J = 7.3 Hz), 8.44 (br s, 1H), 8.19 (d, 2H, J = 8.7 Hz), 7.71 (dd, 1H, J_1 = 8.9 Hz, J_2 = 0.8 Hz), 7.62 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.3 Hz), 7.48 (d, 2H, J = 8.7 Hz), 3.26 (t, 2H, J = 8.7 Hz), 2.94 (t, 2H, J = 8.7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 154.9, 148.4, 147.8, 146.9, 131.2, 129.7, 129.6, 124.1, 116.3, 115.4, 38.6, 31.0; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{12}N_4NaO_3S$ 351.0528, found 351.0515.

*3-(Benzo[c][1,2,5]thiadiazol-4-ylamino)-3-oxopropyl Acetate (**3v**).* Following the general procedure D, **3v** was obtained from the carboxamide **1i** after purification by column chromatography on silica gel (EtOAc/hexanes = 2:3) as a pale yellow solid: R_f = 0.49 (EtOAc/hexanes = 1:3); yield 68% (23 mg); mp 122−124 °C; IR (KBr) 3327, 2365, 1736, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.51 (d, 1H, J = 7.4 Hz), 7.71 (dd, 1H, J_1 = 8.9 Hz, J_2 = 0.9 Hz), 7.62 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.4 Hz), 4.52 (t, 1H, J = 5.9 Hz), 2.91 (t, 2H, J = 5.9 Hz), 2.20 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 168.7, 154.7, 147.7, 131.1, 129.7, 116.0, 115.2, 60.2, 37.0, 21.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{12}N_3O_3S$ 266.0599, found 266.0591.

*3-(Benzo[c][1,2,5]thiadiazol-4-ylamino)-3-oxo-1-phenylpropyl Acetate (**3w**).* Following the general procedure D, **3w** was obtained from the carboxamide **1h** after purification by column chromatography on silica gel (EtOAc/hexanes = 35:65) as a yellow solid: R_f = 0.50 (EtOAc/hexanes = 1:4); yield 55% (25 mg); mp 133−135 °C; IR (KBr) 2349, 1547, 1262, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.49 (d, 1H, J = 7.4 Hz), 7.72 (d, 1H, J = 8.8 Hz), 7.64−7.60 (m, 1H), 7.46−7.44 (m, 2H), 7.41−7.33 (m, 3H), 6.31 (dd, 1H, J_1 = 8.7 Hz, J_2 = 4.4 Hz), 3.20 (dd, 1H, J_1 = 15.1 Hz, J_2 = 8.7 Hz), 3.01 (dd, 1H, J_1 = 15.1 Hz, J_2 = 4.4 Hz), 2.17 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 167.8, 154.7, 147.7, 139.2, 131.1, 129.6, 128.8, 128.5, 126.2, 116.0, 115.3, 72.6, 44.9, 21.2; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{15}N_3NaO_3S$ 364.0732, found 364.0719.

*Methyl 4-(3-(Benzo[c][1,2,5]thiadiazol-4-ylamino)-3-oxopropyl)-benzoate (**3x**).* Following the general procedure C, **3x** was obtained from the carboxamide **1i** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a yellow viscous liquid: R_f = 0.48 (EtOAc/hexanes = 1:4); yield 51% (22 mg); IR (DCM) 3054, 1719, 1422, 1265, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.49 (d, 1H, J = 7.2 Hz), 8.43 (br s, 1H), 7.99 (d, 2H, J = 7.5 Hz), 7.69 (d, 1H, J = 8.8 Hz), 7.61 (t, 1H, J = 7.5 Hz), 7.37 (d, 2H, J = 7.5 Hz), 3.91 (s, 3H), 3.20 (t, 2H, J = 7.4 Hz), 2.91 (t, 2H, J = 7.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 170.3, 167.0, 154.7, 147.6, 145.8, 131.1, 130.0, 129.7, 128.4, 115.9, 115.1, 52.0, 38.8, 31.2; HRMS (ESI) calcd for $C_{17}H_{16}N_3O_3S$ $[M + H]^+$ 342.0912, found 342.0897.

(1R,2S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-(3-nitrophenyl)-cyclopropanecarboxamide (**4a**).* Following the general procedure B, **4a** was obtained from the carboxamide **1j** after purification by column chromatography on silica gel (EtOAc/hexanes = 35:65) as a pale yellow solid: R_f = 0.54 (EtOAc/hexanes = 1:5); yield 27% (11 mg); mp 149−151 °C; IR (KBr) 3369, 2364, 1527, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 8.24 (t, 1H, J = 1.8 Hz), 8.20 (d, 1H, J = 7.5 Hz), 8.08−8.05 (m, 1H), 7.69−7.66 (m, 1H), 7.64 (d, 1H, J = 8.8 Hz), 7.49 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.5 Hz), 7.46−7.42 (m,

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

1H), 2.77 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.6 Hz), 2.40−2.34 (m, 1H), 2.03−1.99 (m, 1H), 1.64−1.58 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.6, 154.7, 148.0, 147.5, 138.5, 135.3, 131.1, 129.7, 128.9, 124.5, 121.9, 115.7, 114.9, 25.7, 24.9, 11.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{13}N_4O_3S$ 341.0708, found 341.0704.

(1S,2R*,3S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,3-bis(3-nitrophenyl)cyclopropanecarboxamide (**4aA**).* Following the general procedure B, **4aA** was obtained from the carboxamide **1j** after purification by column chromatography on silica gel (EtOAc/hexanes =2:3) as a red yellow solid; R_f = 0.42 (EtOAc/hexanes = 1:4); yield 14% (8 mg); mp 175−177 °C; IR (KBr) 3367, 2366, 1527, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 8.27 (d, 1H, J = 7.4 Hz), 8.20−8.19 (m, 2H), 8.12−8.09 (m, 2H), 7.67 (d, 1H, J = 8.8 Hz), 7.52 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.5 Hz), 7.51−7.48 (m, 2H), 7.39 (t, 2H, J = 7.9 Hz), 3.27 (d, 2H, J = 9.1 Hz), 2.88 (t, 1H, J = 9.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 154.7, 147.8, 147.5, 136.8, 135.2, 131.0, 129.4, 128.6, 126.2, 122.1, 116.1, 115.3, 29.0, 28.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{16}N_5O_5S$: 462.0872, found 462.0858.

(1R,2S*)-2-(4-Acetylphenyl)-N-(benzo[c][1,2,5]thiadiazol-4-yl)-cyclopropanecarboxamide (**4b**).* Following the general procedure B, **4b** was obtained from the carboxamide **1j** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:1) as a pale yellow solid: R_f = 0.53 (EtOAc/hexanes = 1:2); yield 28% (12 mg); mp 119−121 °C; IR (KBr) 3340, 2366, 1685, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (br s, 1H), 8.24 (d, 1H, J = 7.4 Hz), 7.87 (d, 2H, J = 8.0 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.49 (t, 1H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.0 Hz), 2.73 (dd, 1H, J_1 = 16.9 Hz, J_2 = 8.5 Hz), 2.56 (s, 3H), 2.36 (dd, 1H, J_1 = 14.1 Hz, J_2 = 8.0 Hz), 2.00 (dd, 1H, J_1 = 12.6 Hz, J_2 = 5.7 Hz), 1.56 (dd, 1H, J_1 = 13.6 Hz, J_2 = 8.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 167.7, 154.7, 147.5, 142.1, 135.6, 131.1, 129.8, 129.3, 128.2, 115.6, 114.8, 26.6, 26.2, 25.3, 11.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{16}N_3O_2S$ 338.0963, found 338.0959. The corresponding diarylated compound **4bB** could not be isolated in pure form.

Diethyl 2,2′-((1R,2R*,3S*)-2-(Benzo[c][1,2,5]thiadiazol-4-ylcarbamoyl)cyclobutane-1,3-diyl)diacetate (**4c**).* Following the general procedure E, **4c** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a pale yellow solid: R_f = 0.50 (EtOAc/hexanes = 1:4); yield 44% (22 mg); mp 53−55 °C; IR (KBr) 3338, 2364, 1734, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, 1H, J = 7.3 Hz), 8.50 (br s, 1H), 7.69 (d, 1H, J = 8.8 Hz), 7.60 (t, 1H, J = 8.8 Hz), 4.05−3.93 (m, 4H), 3.62−3.58 (m, 1H), 3.07−2.96 (m, 2H), 2.82 (dd, 2H, J_1 = 16.7 Hz, J_2 = 9.6 Hz), 2.60 (dd, 2H, J_1 = 16.7 Hz, J_2 = 6.2 Hz), 2.36−2.29 (m, 1H), 2.10 (dd, 1H, J_1 = 21.4 Hz, J_2 = 10.7 Hz), 1.08 (t, 6H, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.8, 171.5, 154.8, 147.7, 131.1, 129.9, 115.7, 114.8, 60.3, 48.5, 35.4, 32.6, 31.5, 14.0; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{23}N_3NaO_5S$ 428.1256, found 428.1248.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(3-nitrophenyl)cyclobutanecarboxamide (**5a**).* Following the general procedure B, **5a** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.47 (EtOAc/hexanes = 1:4); yield 56% (34 mg); mp 190−192 °C; IR (KBr) 3380, 1524, 1410, 1348, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 8.21 (t, 2H, J = 1.9 Hz), 8.01−7.98 (m, 2H), 7.87 (d, 1H, J = 7.2 Hz), 7.68 (d, 2H, J = 7.8 Hz), 7.54 (dd, 1H, J_1 = 8.9 Hz, J_2 = 0.7 Hz), 7.42 (t, 2H, J = 7.9 Hz), 7.33 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.2 Hz), 4.30−4.17 (m, 3H), 3.61 (dd, 1H, J_1 = 21.7 Hz, J_2 = 10.8 Hz), 2.92−2.87 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 154.4, 148.2, 147.3, 141.9, 133.1, 130.7, 129.2, 128.7, 122.0, 121.7, 116.1, 115.2, 54.0, 38.4, 29.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{18}N_5O_5S$ 476.1029, found 476.1020.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(3-fluorophenyl)cyclobutanecarboxamide (**5b**).* Following the general procedure B, **5b** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.47 (EtOAc/hexanes = 1:5); yield 95% (50 mg); mp 181−183 °C; IR (KBr) 3054, 2306, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.99 (d, 1H, J = 7.4 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.36 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.22−7.16 (m, 2H), 7.10 (br s, 1H), 7.08 (br s, 1H), 7.06−7.04 (m, 1H), 7.03−7.02 (m, 1H), 6.83−6.78 (m, 2H), 4.13−4.03 (m, 3H), 3.49−3.41 (m, 1H), 2.78−2.71 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 162.8 (d, J_{C-F} = 244.2 Hz), 154.5, 147.5, 142.7 (d, J_{C-F} = 7.2 Hz), 130.9, 129.7 (d, J_{C-F} = 8.2 Hz), 129.2, 122.5 (d, J_{C-F} = 2.5 Hz), 115.5, 115.1, 114.0 (d, J_{C-F} = 23.3 Hz), 113.3 (d, J_{C-F} = 20.9 Hz), 54.1, 38.6, 29.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{18}F_2N_3OS$ 422.1139, found 422.1151.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(2-nitrophenyl)cyclobutanecarboxamide (**5c**).* Following the general procedure B, **5c** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a pale yellow solid: R_f = 0.48 (EtOAc/hexanes = 1:4); yield 71% (42 mg); mp 171−173 °C; IR (KBr) 3393, 3055, 1523, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 7.82 (dd, 2H, J_1 = 8.1 Hz, J_2 = 1.2 Hz), 7.78 (d, 1H, J = 8.1 Hz), 7.65 (d, 2H, J = 7.8 Hz), 7.60−7.56 (m, 2H), 7.50 (d, 1H, J = 8.8 Hz), 7.31−7.26 (m, 3H), 4.68 (td, 1H, J_1 = 8.1 Hz, J_2 = 3.3 Hz), 4.42−4.35 (m, 2H), 3.57 (dd, 1H, J_1 = 21.7 Hz, J_2 = 10.9 Hz), 2.75−2.68 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.8, 154.4, 148.8, 147.4, 135.1, 133.1, 130.5, 129.7, 129.0, 127.5, 124.6, 115.6, 114.8, 55.2, 36.1, 27.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{18}N_5O_5S$ 476.1029, found 476.1043.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-diphenylcyclobutanecarboxamide (**5d**).* Following the general procedure B, **5d** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a pale yellow solid: R_f = 0.55 (EtOAc/hexanes = 1:5); yield 95% (45 mg); mp 171−173 °C; IR (KBr) 3358, 2360, 1667, 1544 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.98 (d, 1H, J = 7.5 Hz), 7.52 (d, 1H, J = 8.8 Hz), 7.35−7.32 (m, 5H), 7.28−7.23 (m, 4H), 7.11 (t, 2H, J = 7.5 Hz), 4.12−4.09 (m, 3H), 3.57−3.49 (m, 1H), 2.79−2.72 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.1, 154.5, 147.6, 140.2, 131.0, 129.4, 128.2, 126.9, 126.3, 115.2, 114.9, 54.4, 39.0, 29.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{20}N_3OS$ 386.1327, found 386.1320.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-di-p-tolylcyclobutanecarboxamide (**5e**).* Following the general procedure B, **5e** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a pale yellow solid: R_f = 0.52 (EtOAc/hexanes = 1:5); yield 79% (41 mg); mp 199−201 °C; IR (KBr) 3054, 2349, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 8.04 (d, 1H, J = 7.4 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.36 (t, 1H, J = 8.2 Hz), 7.22 (d, 4H, J = 7.7 Hz), 7.04 (d, 4H, J = 7.7 Hz), 4.07−4.03 (m, 3H), 3.49−3.41 (m, 1H), 2.74−2.67 (m, 1H), 2.22 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 154.5, 147.6, 137.1, 135.7, 131.1, 129.6 128.9, 126.9, 115.1, 114.9, 54.5, 38.8, 29.9, 21.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{24}N_3OS$ 414.1640, found 414.1632.

(1S,2R*,4S*)-2,4-Bis(4-acetylphenyl)-N-(benzo[c][1,2,5]-thiadiazol-4-yl)cyclobutanecarboxamide (**5f**).* Following the general procedure B, **5f** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes =2:3) as a pale yellow solid: R_f = 0.55 (EtOAc/hexanes = 1:1); yield 93% (54 mg); mp 226−228 °C; IR (KBr) 3338, 2366, 1677, 1543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 7.94 (d, 1H, J = 7.5 Hz), 7.84 (d, 4H, J = 8.4 Hz), 7.56 (d, 1H, J = 8.9 Hz), 7.40 (d, 4H, J = 8.4 Hz), 7.33 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.5 Hz), 4.25−4.11 (m, 3H), 3.57 (dd, 1H, J_1 = 21.7 Hz, J_2 = 11.0 Hz), 2.85−2.78 (m, 1H), 2.51 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 168.5, 154.5, 147.5, 145.8, 135.3, 130.9, 129.1, 128.4, 127.0, 115.7, 115.1, 54.3, 39.0, 29.6, 26.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{24}N_3O_3S$ 470.1538, found 470.1545.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(4-chlorophenyl)cyclobutanecarboxamide (**5g**).* Following the general procedure B, **5g** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.55 (EtOAc/hexanes = 1:4); yield 98% (55 mg); mp 189−191 °C; IR (KBr) 3297, 1661, 1549, 816

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.99 (d, 1H, J = 7.4 Hz), 7.56 (d, 1H, J = 8.8 Hz), 7.37 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.25 (d, 4H, J = 8.6 Hz), 7.21 (d, 4H, J = 8.6 Hz), 4.07−3.99 (m, 3H), 3.48−3.40 (m, 1H), 2.76−2.68 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.7, 154.6, 147.5, 138,5, 132.2, 131.0, 129.2, 128.4, 128.3, 115.7, 115.1, 54.2, 38.4, 29.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{23}H_{18}Cl_2N_3OS$: 454.0548, found 454.0536.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(4-bromophenyl)cyclobutanecarboxamide (**5h**).* Following the general procedure B, **5h** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.55 (EtOAc/hexanes = 1:4); yield 94% (63 mg); mp 202−204 °C; IR (KBr) 3293, 2366, 1547, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.99 (d, 1H, J = 7.2 Hz), 7.57 (d, 1H, J = 8.9 Hz), 7.38 (dd, 1H, J_1 = 8.9 Hz, J_2 = 7.2 Hz), 7.36 (d, 4H, J = 8.5 Hz), 7.19 (d, 4H, J = 8.5 Hz), 4.09−3.97 (m, 3H), 3.42 (dd, 1H, J_1 = 21.5 Hz, J_2 = 10.6 Hz), 2.75−2.68 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.6, 154.6, 147.5, 139.0, 131.3, 130.9, 129.1, 128.7, 120.3, 115.7, 115.1, 54.1, 38.5, 29.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{23}H_{18}Br_2N_3OS$ 541.9537, found 541.9549.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(4-methoxyphenyl)cyclobutanecarboxamide (**5i**).* Following the general procedure B, **5i** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 30:70) as a brown liquid: R_f = 0.52 (EtOAc/hexanes = 1:5); yield 90% (50 mg); IR (DCM) 2933, 1545, 1512, 1247, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 8.04 (dd, 1H, J_1 = 7.4 Hz, J_2 = 0.5 Hz), 7.52 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.5 Hz), 7.37 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 7.27 (d, 4H, J = 8.7 Hz), 6.78 (d, 4H, J = 8.7 Hz), 4.05−3.99 (m, 3H), 3.71 (s, 6H), 3.47−3.39 (m, 1H), 2.73−2.68 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.4, 158.0, 154.6, 147.6, 132.2, 131.1, 129.6, 128.1, 115.2, 114.9, 113.6, 55.2, 54.6, 38.5, 30.2; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{25}H_{23}N_3NaO_3S$ 468.1358, found 468.1381.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(3,5-dimethylphenyl)cyclobutanecarboxamide (**5j**).* Following the general procedure B, **5j** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a pale yellow solid: R_f = 0.57 (EtOAc/hexanes = 1:5); yield 98% (54 mg); mp 98−100 °C; IR (KBr) 3338, 2918, 2365, 1546 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 8.05 (d, 1H, J = 7.4 Hz), 7.54 (d, 1H, J = 8.8 Hz), 7.39 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 6.94 (br s, 4H), 6.71 (br s, 2H), 4.09−3.98 (m, 3H), 3.41 (dd, 1H, J_1 = 21.6 Hz, J_2 = 10.8 Hz), 2.73−2.66 (m, 1H), 2.19 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.5, 154.5, 147.6, 140.0, 137.6, 131.1, 129.6, 128.0, 124.7, 115.0, 114.7, 54.5, 38.9, 29.7, 21.3; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{28}N_3OS$ 442.1953, found 442.1941.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)cyclobutanecarboxamide (**5k**).* Following the general procedure B, **5k** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 2:3) as a reddish yellow solid: R_f = 0.46 (EtOAc/hexanes = 1:2); yield 95% (59 mg); mp 203−205 °C; IR (KBr) 3367, 2365, 1508, 1286 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 8.08 (d, 1H, J = 7.4 Hz), 7.55 (d, 1H, J = 8.8 Hz), 7.40 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.4 Hz), 6.83 (d, 2H, J = 2.0 Hz), 6.79 (2H, dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 6.71 (d, 2H, J = 8.3 Hz), 4.14 (s, 8H), 4.01−3.90 (m, 3H), 3.31 (dd, 1H, J_1 = 21.7 Hz, J_2 = 10.7 Hz), 2.68−2.61 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.2, 154.6, 147.6, 143.2, 142.0, 133.4, 131.1, 129.6, 120.0, 117.0, 115.9, 115.1, 114.8, 64.2, 64.2, 54.4, 38.4, 30.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{24}N_3O_5S$ 502.1437, found 502.1425.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(2-chloropyridin-4-yl)cyclobutanecarboxamide (**5l**).* Following the general procedure B, **5l** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 70:30) as a pale yellow solid: R_f = 0.45 (EtOAc/hexanes = 1:1); yield 58% (33 mg); mp 169−171 °C; IR (KBr) 3287, 2366, 1545, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 8.23 (d, 2H, J = 5.1 Hz), 7.96 (d, 1H, J = 7.4 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.43 (dd, 1H, J_1 = 8.8 Hz, J_2 = 7.5 Hz), 7.26 (s, 2H), 7.13 (d, 2H, J = 5.0 Hz), 4.22−4.17 (m, 1H), 4.07−4.00 (m, 2H), 3.45 (dd, 1H, J_1 = 21.7 Hz, J_2 = 10.9 Hz), 2.80−2.74 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 154.6, 152.1, 151.8, 149.5, 147.5, 130.8, 128.5, 122.7, 120.8, 116.5, 115.7, 53.5, 37.8, 28.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{16}Cl_2N_5OS$ 456.0453, found 456.0440.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(4-bromo-3-fluorophenyl)cyclobutanecarboxamide (**5m**).* Following the general procedure B, **5m** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a pale yellow solid: R_f = 0.51 (EtOAc/hexanes = 1:4); yield 93% (67 mg); mp 163−165 °C; IR (KBr) 3293, 2364, 1413, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 8.01 (d, 1H, J = 7.4 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.44−7.37 (m, 3H), 7.09 (dd, 2H, J_1 = 9.6 Hz, J_2 = 1.9 Hz), 6.97 (dd, 2H, J_1 = 8.2 Hz, J_2 = 1.9 Hz), 4.10−3.97 (m, 3H), 3.38 (dd, 1H, J_1 = 21.7 Hz, J_2 = 10.6 Hz), 2.76−2.69 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.2, 159.0 (d, J_{C-F} = 250.0 Hz), 154.6, 147.5, 141.8 (d, J_{C-F} = 6.4 Hz), 133.2, 130.9, 128.9, 123.8 (d, J_{C-F} = 3.4 Hz), 116.0, 115.3 (d, J_{C-F} = 22.1 Hz), 115.1, 106.8 (d, J_{C-F} = 20.8 Hz), 54.0, 38.2, 29.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{23}H_{16}Br_2F_2N_3OS$ 577.9349, found 577.9314.

(1S,2R*,4S*)-N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,4-bis(3-formylphenyl)cyclobutanecarboxamide (**5n**).* Following the general procedure C, **5n** was obtained from the carboxamide **1k** after purification by column chromatography on silica gel (EtOAc/hexanes = 1:4) as a brown solid: R_f = 0.52 (EtOAc/hexanes = 1:4); yield 35% (20 mg); mp 132−134 °C; IR (DCM) 3054, 2987, 1697, 1265, 741; cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.94 (s, 2H), 8.20 (br s, 1H), 7.88 (d, 1H, J = 7.8 Hz), 7.85 (s, 2H), 7.64−7.60 (m, 4H), 7.52 (d, 1H, J = 8.8 Hz), 7.41 (t, 2H, J = 7.6 Hz), 7.31 (t, 1H, J = 7.9 Hz), 4.21−4.15 (m, 3H), 3.65−3.58 (m, 1H), 2.87−2.80 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 192.4, 168.5, 154.5, 147.4, 141.1, 136.3, 133.0, 130.8, 129.0, 128.9, 128.2, 128.0, 115.8, 115.0, 54.2, 38.6, 29.5; HRMS (ESI) calcd for $C_{25}H_{20}N_3O_3S$ [M + H]$^+$ 442.1225, found 442.1208.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-methylbenzamide (**6a**).* Following the general procedure H, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **6a** as a pale yellow solid: R_f = 0.68 (EtOAc/hexanes = 1:4); yield 60% (326 mg); mp 147−149 °C; IR (DCM) 3054, 2305, 1265, 895, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (br s, 1H), 8.68 (d, 1H, J = 7.2 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.70−7.66 (m, 2H), 7.46 (t, 1H, J = 7.1 Hz), 7.37−7.34 (m, 2H), 2.61.(s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 168.2, 154.8, 147.9, 136.9, 135.6, 131.6, 131.2, 130.9, 130.1, 127.1, 126.2, 116.0, 115.0, 20.2; HRMS (ESI) calcd for $C_{14}H_{12}N_3OS$ [M + H]$^+$ 270.0701, found 270.0708.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,3-dimethylbenzamide (**6b**).* Following the general procedure H, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **6b** as a yellow solid: R_f = 0.70 (EtOAc/hexanes = 1:4); yield 35% (100 mg); mp 147−149 °C; IR (DCM) 3054, 2986, 1421, 895, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (br s, 1H), 8.79 (d, 1H, J = 7.3 Hz), 7.75 (dd, 1H, J_1 = 8.8, J_2 = 0.8 Hz), 7.69 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.45 (d, 1H, J = 7.4 Hz), 7.33 (d, 1H, J = 7.4 Hz), 7.24 (t, 1H, J = 7.6 Hz), 2.46 (s, 3H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 169.0, 154.8, 147.9, 138.5, 136.6, 134.8, 132.1, 131.2, 130.1, 125.9, 124.6, 116.0, 115.1, 204, 16.5; HRMS (ESI) calcd for $C_{15}H_{14}N_3OS$ [M + H]$^+$ 284.0858, found 284.0862.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-methoxybenzamide (**6c**).* Following the general procedure H, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **6c** as a yellow solid: R_f = 0.54 (EtOAc/hexanes = 1:4); yield 25% (100 mg); mp 144−146 °C; IR (DCM) 3054, 2986, 1550, 895, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.50 (br s, 1H), 8.71 (dd, 1H, J_1 = 7.1, J_2 = 1.2 Hz), 8.35 (dd, 1H, J_1 = 7.8, J_2 = 1.8 Hz), 7.69 (dd, 1H, J_1 = 8.8, J_2 = 1.2 Hz), 7.66−7.62 (m, 1H), 7.57−7.53 (m, 1H), 7.19−7.15 (m, 1H), 7.10 (d, 1H, J = 8.3 Hz), 4.22 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 163.7, 157.7, 154.9, 148.5, 133.7, 132.5, 131.4,

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

130.9, 121.6, 121.2, 115.4, 115.3, 111.7, 56.3; HRMS (ESI) calcd for $C_{14}H_{12}N_3O_2S$ $[M + H]^+$ 286.0650, found 286.0659.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-chlorobenzamide (**6d**).* Following the general procedure G, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **6d** as a yellow solid: R_f = 0.60 (EtOAc/hexanes = 1:4); yield 86% (250 mg); mp 141−143 °C; IR (DCM); 3053, 1699, 1456, 895, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.42 (br s, 1H), 8.69 (d, 1H, J = 7.3 Hz), 7.90 (dd, 1H, J_1 = 7.4 J_2 = 1.9 Hz), 7.76 (dd, 1H, J_1 = 8.8 J_2 = 0.8 Hz), 7.70−7.66 (m, 1H), 7.55−7.43 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 164.6, 154.8, 147.9, 134.4, 132.2, 131.1, 131.0, 130.7, 130.7, 129.8, 127.4, 116.4, 115.5; HRMS (ESI) calcd for $C_{13}H_9ClN_3OS$ $[M + H]^+$ 290.0155, found 290.0150.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-methylbenzamide (**6e**).* Following the general procedure H, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **6e** as a pale yellow solid: yield 51% (274 mg); R_f = 0.68 (EtOAc/hexanes = 1:4); mp 145−147 °C; IR (DCM) 3054, 1653, 1411, 1265, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.26 (br s, 1H), 8.67 (d, 1H, J = 7.2 Hz), 7.84 (br s, 1H), 7.82 (d, 1H, J = 6.7 Hz), 7.74 (d, 1H, J = 8.8 Hz), 7.70−7.66 (m, 1H), 7.48−7.49 (m, 2H), 2.50 (s, 3H) $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.8, 154.8, 148.1, 139.0, 134.2, 133.2, 131.2, 130.1, 128.9, 127.9, 124.2, 115.9, 115.0, 21.5, HRMS (ESI) calcd for $C_{14}H_{12}N_3OS$ $[M + H]^+$ 270.0701, found 270.0689.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4-methylbenzamide (**8a**).* Following the general procedure G, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **8a** as a pale yellow solid: R_f = 0.68 (EtOAc/hexanes = 1:4); yield 94% (255 mg); mp 118−120 °C; IR (DCM) 3053, 2986, 1548, 895, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.27 (br s, 1H), 8.67 (dd, 1H, J_1 = 7.2, J_2 = 1.0 Hz), 7.94 (d, 2H, J = 8.2 Hz), 7.74 (dd, 1H, J_1 = 8.8, J_2 = 1.1 Hz), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.38 (d, 2H, J = 7.9 Hz), 2.49 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.6, 154.8, 148.1, 143.1, 131.3, 130.2, 129.7, 129.2, 127.2, 115.8, 115.0, 21.6; HRMS (ESI) calcd for $C_{14}H_{12}N_3OS$ $[M + H]^+$ 270.0701, found 270.0711.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4-chlorobenzamide (**8b**).* Following the general procedure G, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **8b** as a pale yellow solid: R_f = 0.60 (EtOAc/hexanes = 1:4); yield 60% (174 mg); mp 151−153 °C; IR (DCM) 3054, 2986, 1548, 1265, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.21 (br s, 1H), 8.64 (dd, 1H, J_1 = 7.3, J_2 = 0.8 Hz), 7.97 (d, 2H, J = 8.7 Hz), 7.75 (dd, 1H, J_1 = 8.8, J_2 = 1.0 Hz), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.55 (d, 2H, J = 8.7 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 164.5, 154.8, 148.0, 138.8, 132.5, 131.2, 129.8, 129.3, 128.6, 116.2, 115.2; HRMS (ESI) calcd for $C_{13}H_9ClN_3OS$ $[M + H]^+$ 290.0155, found 290.0161.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4-methoxybenzamide (**8c**).* Following the general procedure H, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **8c** as a pale yellow solid: R_f = 0.54 (EtOAc/hexanes = 1:4); yield 35% (100 mg); mp 150−152 °C; IR (DCM) 3054, 2986, 2305, 895, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (br s, 1H), 8.65 (dd, 1H, J_1 = 7.2, J_2 = 1.0 Hz), 8.01 (d, 2H, J = 8.8 Hz), 7.72 (dd, 1H, J_1 = 8.8, J_2 = 1.1 Hz), 7.67 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.06 (d, 2H, J = 8.8 Hz), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.1, 162.9, 154.8, 148.1, 131.3, 129.2, 126.4, 115.7, 114.8, 114.2, 55.6; HRMS (ESI) calcd for $C_{14}H_{12}N_3O_2S$ $[M + H]^+$ 286.0650, found 286.0644.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)benzamide (**8d**).* Following the general procedure G, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **8d** as a pale yellow solid: R_f = 0.70 (EtOAc/hexanes = 1:4); yield 70% (177 mg); mp 124−126 °C; IR (DCM) 3054, 2986, 1681, 895, 747, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.27 (br s, 1H), 8.66 (dd, 1H, J_1 = 7.2, J_2 = 0.6 Hz), 8.03 (d, 2H, J = 7.0 Hz), 7.73 (dd, 1H, J_1 = 8.8, J_2 = 0.9 Hz), 7.67 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.62 (d, 1H, J = 7.2 Hz), 7.57 (t, 1H, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.6, 154.8, 148.0, 134.2, 132.4, 131.2, 130.0, 129.0, 127.2, 116.0, 115.1; HRMS (ESI) calcd for $C_{13}H_{10}N_3OS$ $[M + H]^+$ 256.0545, found 256.0547.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4′-ethyl-3-methyl[1,1′-biphenyl]-2-carboxamide (**7a**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7a** as a pale yellow semisolid: R_f = 0.72 (EtOAc/hexanes = 1:4); yield 70% (21 mg); IR (DCM) 3054, 2986, 1421, 1265, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.50 (dd, 1H, J_1 = 7.2, J_2 = 0.8 Hz), 8.26 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 0.9 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.46 (d, 1H, J = 7.6 Hz), 7.41 (d, 2H, J = 8.3 Hz), 7.32 (t, J = 2H, 7.5 Hz), 7.06 (d, 2H, J = 8.0 Hz), 2.55 (s, 3H), 2.46 (q, 2H, J = 7.6 Hz), 0.98 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.6, 154.6, 147.6, 143.6, 139.8, 137.4, 136.2, 135.7, 131.0, 129.9, 129.7, 129.5, 128.5, 127.9, 127.6, 115.8, 114.8, 28.3, 19.8, 15.3; HRMS (ESI) calcd for $C_{22}H_{20}N_3OS$ $[M + H]^+$ 374.1327, found 374.1319.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4′-methoxy-3-methyl[1,1′-biphenyl]-2-carboxamide (**7b**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7b** as a pale yellow solid: R_f = 0.46 (EtOAc/hexanes = 1:4); yield 58% (25 mg); mp 112−114 °C; IR (DCM) 3054, 2987, 2305, 1683, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, 1H J = 7.3 Hz), 8.30 (br s, 1H), 7.66 (d, 1H, J = 8.8 Hz), 7.60 (dd, 1H J_1 = 8.8, J_2 = 7.3 Hz), 7.45 (d, 2H, J = 8.6 Hz), 7.46−7.42 (m, 1H), 7.31 (d, 1H, J = 7.6 Hz), 7.29 (d, 1H, J = 7.6 Hz), 6.80 (d, 2H, J = 8.6 Hz), 3.68 (s, 3H), 2.54 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.7, 159.1, 154.6, 147.6, 139.3, 136.1, 135.8, 132.5, 131.0, 129.8, 129.7, 129.3, 127.6, 115.9, 114.9, 113.9, 55.1, 19.8; HRMS (ESI) calcd for $C_{21}H_{18}N_3O_2S$ $[M + H]^+$ 376.1120, found 376.1130.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-methyl[1,1′-biphenyl]-2-carboxamide (**7c**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7c** as a pale yellow solid: R_f = 0.52 (EtOAc/hexanes = 1:4); yield 55% (22 mg); mp 154−156 °C; IR (DCM) 2987, 2306, 1422, 1265, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.36 (d, 1H, J = 7.5 Hz), 8.31 (d, 1H, J = 8.2 Hz), 8.22 (d, 1H, J = 8.9 Hz), 7.85 (dd, 1H, J_1 = 8.8, J_2 = 7.0 Hz), 7.72−7.69 (m, 2H), 7.44 (d, 1H, J = 7.4 Hz), 7.30−7.21 (m, 3H), 6.49 (d, 1H, J = 8.1 Hz), 2.92 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.5, 156.3, 152.1, 143.3, 138.6, 135.9, 132.3, 132.0, 131.0, 130.5, 129.6, 129.2, 123.8, 122.8, 122.6, 120.3, 119.5, 115.9, 24.5; HRMS (ESI) calcd for $C_{20}H_{16}N_3OS$ $[M + H]^+$ 346.1014, found 346.1015. The NH proton was detected in the ^1H NMR spectrum.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-methyl-3′-nitro[1,1′-biphenyl]-2-carboxamide (**7d**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7d** as a pale yellow solid: R_f = 0.40 (EtOAc/hexanes = 1:4); yield 65% (30 mg); mp 133−135 °C; IR (DCM) 3055, 2987, 2305, 1422, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.46 (d, 1H, J = 7.4 Hz), 8.42 (br s, 1H), 8.34 (br s, 1H), 8.03 (dd, 1H, J_1 = 8.2, J_2 = 0.9 Hz), 7.85 (d, 1H, J = 7.7 Hz), 7.69 (d, 1H, J = 8.9 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.52 (t, 1H, J = 7.6 Hz), 7.43 (t, 2H, J = 7.8 Hz), 7.36 (d, 1H, J = 7.6 Hz), 2.57 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.7, 154.6, 148.2, 147.5, 141.7, 137.1, 136.4, 135.9, 134.6, 130.9, 130.8, 130.1, 129.4, 129.2, 127.5, 123.6, 122.5, 116.5, 115.4, 19.7; HRMS (ESI) calcd for $C_{20}H_{15}N_4O_3S$ $[M + H]^+$ 391.0865, found 391.0857.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3,3′,5′-trimethyl[1,1′-biphenyl]-2-carboxamide (**7e**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7e** as a pale yellow solid: R_f = 0.64 (EtOAc/hexanes = 1:4); yield 58% (26 mg); mp 118−120 °C; IR (DCM) 3055, 2987, 2305, 1422, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.49 (dd, 1H, J_1 = 7.2, J_2 = 0.9 Hz), 8.26 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 1.1 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.32 (d, 1H, J = 7.7 Hz), 7.31 (d, 1H, J = 7.7 Hz), 7.10 (br s, 2H), 6.69 (br s, 1H), 2.55 (s, 3H), 2.15 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.6, 154.6, 147.6, 140.1, 140.0, 137.9, 136.2, 135.7, 131.0, 130.0, 129.7, 129.5, 129.0, 127.5, 126.4, 115.7, 114.6, 21.1, 19.9; HRMS (ESI) calcd for $C_{22}H_{20}N_3OS$ $[M + H]^+$ 374.1327, found 374.1322.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-(2,3-dihydrobenzo[b][1,4]-dioxin-6-yl)-6-methylbenzamide (**7f**).* Following the general proce-

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

dure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7f** as a pale yellow solid: R_f = 0.45 (EtOAc/hexanes = 1:4); yield 77% (37 mg); mp 159−161 °C; IR (DCM) 3055, 2987, 2305, 1422, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.52 (dd, 1H, J_1 = 7.2, J_2 = 0.8 Hz), 8.32 (br s, 1H), 7.67 (dd, 1H, J_1 = 8.8, J_2 = 1.0 Hz), 7.61 (dd, 1H, J_1 = 8.8, J_2 = 7.3 Hz), 7.42 (dd, 1H, J_1 = 8.0, J_2 = 7.8 Hz), 7.29 (d, 2H, J = 7.0 Hz), 7.04 (d, 1H, J = 2.2 Hz), 6.97 (dd, 1H, J_1 = 8.4, J_2 = 2.2 Hz), 6.71 (d, 1H, J = 8.3 Hz), 4.13−4.10 (m, 4H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.5, 154.7, 147.7, 143.4, 139.1, 136.1, 135.7, 133.5, 131.1, 129.9, 129.7, 129.4, 127.6, 121.8, 117.5, 117.2, 115.9, 115.0, 64.3, 64.2, 19.8; HRMS (ESI) calcd for $C_{22}H_{18}N_3O_3S$ $[M + H]^+$ 404.1069, found 404.1065.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4′-ethyl-3,4-dimethyl[1,1′-biphenyl]-2-carboxamide (**7g**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7g** as a pale yellow semisolid: R_f = 0.65 (EtOAc/hexanes = 1:4); yield 58% (27 mg); IR (DCM) 3054, 2987, 2686, 1547, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.51 (dd, 1H, J_1 = 7.2, J_2 = 1.0 Hz), 8.31 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.9, J_2 = 1.0 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 7.2 Hz), 7.40 (d, 2H, J = 8.2 Hz), 7.34 (d, 1H, J = 7.8 Hz), 7.24 (d, 1H, J = 7.8 Hz), 7.05 (d, 2H, J = 8.2 Hz), 2.46 (q, 2H, J = 7.6 Hz), 2.43 (s, 3H), 2.40 (s, 3H), 0.99 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 169.2, 154.6, 147.6, 143.3, 137.5, 137.4, 136.6, 136.2, 134.2, 131.1, 131.0, 129.9, 128.5, 127.8, 127.4, 115.8, 114.9, 28.3, 20.2, 16.7, 15.3; HRMS (ESI) calcd for $C_{23}H_{22}N_3OS$ $[M + H]^+$ 388.1484, found 388.1484.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4′-ethyl-3-methoxy[1,1′-biphenyl]-2-carboxamide (**7h**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7h** as a pale yellow solid: R_f = 0.64 (EtOAc/hexanes = 1:4); yield 50% (21 mg); mp 152−154 °C; IR (DCM) 3054, 2986, 1421, 895, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.63 (br s, 1H), 8.53 (d, 1H, J = 7.3 Hz), 7.66 (d, 1H, J = 8.8 Hz), 7.59 (dd, 1H, J_1 = 8.6, J_2 = 7.6 Hz), 7.49 (t, 1H, J = 8.0 Hz), 7.42 (d, 2H, J = 7.9 Hz), 7.13−7.08 (m, 3H), 7.03 (d, 1H, J = 8.4 Hz), 3.93 (s, 3H), 2.54 (q, 2H, J = 7.6 Hz), 1.10 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.2, 156.8, 154.7, 147.7, 143.7, 141.9, 137.0, 131.2, 130.9, 130.1, 128.4, 127.9, 125.2, 122.7, 115.6, 115.0, 109.9, 56.1, 28.4, 15.3; HRMS (ESI) calcd for $C_{22}H_{19}N_3NaO_2S$ $[M + Na]^+$ 412.1096, found 412.1087.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-chloro-4′-methoxy[1,1′-biphenyl]-2-carboxamide (**7i**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7i** as a green semisolid: R_f = 0.48 (EtOAc/hexanes = 1:4); yield 70% (33 mg); IR (DCM) 3054, 2987, 1689, 1422, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, 1H, J = 7.3 Hz), 8.45 (br s, 1H), 7.70 (d, 1H, J = 8.8 Hz), 7.61 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.50−7.44 (m, 4H), 7.38 (dd, 1H, J_1 = 6.0, J_2 = 6.0 Hz), 6.84 (d, 2H, J = 8.7 Hz), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.5, 159.5, 154.7, 147.6, 141.5, 135.1, 131.8, 131.1, 131.0, 130.7, 129.7, 129.5, 128.7, 128.4, 116.3, 115.4, 114.0, 55.2; HRMS (ESI) calcd for $C_{20}H_{15}ClN_3O_2S$ $[M + H]^+$ 396.0574, found 396.0554.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-chloro-3′-nitro[1,1′-biphenyl]-2-carboxamide (**7j**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7j** as a pale yellow solid: R_f = 0.39 (EtOAc/hexanes = 1:4); yield 53% (26 mg); mp 198−200 °C; IR (DCM) 3055, 2987, 1422, 1265, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.57 (br s, 1H), 8.44 (d, 1H J = 7.4 Hz), 8.41 (br s, 1H), 8.12 (d, 1H, J = 8.2 Hz), 7.87 (d, 1H, J = 7.6 Hz), 7.71 (d, 1H, J = 8.8 Hz), 7.61−7.54 (m, 3H), 7.49 (t, 1H, J = 8.0 Hz), 7.43 (d, 1H, J = 7.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 164.5, 154.6, 148.2, 147.5, 140.4, 139.4, 135.3, 134.6, 132.1, 131.2, 130.9, 130.0, 129.6, 129.0, 128.6, 123.6, 123.1, 116.8, 115.8; HRMS (ESI) calcd for $C_{19}H_{12}ClN_4O_3S$ $[M + H]^+$ 411.0319, found 411.0311.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-chloro-4′-ethyl[1,1′-biphenyl]-2-carboxamide (**7k**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7k** as a greenish yellow semisolid: R_f = 0.64 (EtOAc/hexanes = 1:4); yield 65% (30 mg); IR (DCM) 3054, 2305, 1422, 896, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, 1H, J = 7.3 Hz), 8.44 (br s, 1H), 7.68 (d, 1H, J = 8.8 Hz), 7.60 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.50−7.46 (m, 2H), 7.43 (d, 2H, J = 8.1 Hz), 7.41−7.39 (m, 1H), 7.12 (d, 2H, J = 8.1 Hz), 2.53 (q, 2H, J = 7.6 Hz), 1.07 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.4, 154.6, 147.6, 144.3, 141.9, 136.1, 135.1, 131.8, 131.0, 130.7, 129.5, 128.7, 128.6, 128.4, 128.1, 116.2, 115.3, 28.4, 15.2; HRMS (ESI) calcd for $C_{21}H_{17}ClN_3OS$ $[M + H]^+$ 394.0781, found 394.0783.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-chloro[1,1′-biphenyl]-2-carboxamide (**7l**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7l** as a pale yellow semisolid: R_f = 0.59 (EtOAc/hexanes = 1:4); yield 60% (26 mg); IR (DCM) 3384, 2923, 1688, 1547, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.51 (dd, 1H, J_1 = 7.4, J_2 = 0.6 Hz), 8.45 (br s, 1H), 7.69 (dd, 1H, J_1 = 8.9, J_2 = 0.9 Hz), 7.60 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.54−7.48 (m, 4H), 7.41 (dd, 1H, J_1 = 6.9, J_2 = 6.9 Hz), 7.31 (t, 2H, J = 7.4 Hz), 7.25−7.20 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.2, 154.6, 147.6, 141.9, 138.8, 135.2, 131.8, 131.0, 130.8, 129.4, 128.8, 128.7, 128.6, 128.5, 128.1, 116.3, 115.3; HRMS (ESI) calcd for $C_{19}H_{13}ClN_3OS$ $[M + H]^+$ 366.0468, found 366.0454.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-chloro-6-(2,3-dihydrobenzo-[b][1,4]dioxin-6-yl)benzamide (**7m**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7m** as a greenish yellow semisolid: R_f = 0.48 (EtOAc/hexanes = 1:4); yield 59% (30 mg); mp 98−100 °C; IR (DCM) 2987, 2305, 1422, 896, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, 1H, J = 7.3 Hz), 8.48 (br s, 1H), 7.70 (d, 1H, J = 8.8 Hz), 7.62 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.49−7.44 (m, 2H), 7.36 (dd, 1H, J_1 = 6.8, J_2 = 6.8 Hz), 7.03 (d, 1H, J = 2.0 Hz), 6.99 (dd, 1H, J_1 = 8.3, J_2 = 2.0 Hz), 6.76 (d, 1H, J = 8.3 Hz), 4.16 (s, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.4, 154.7, 147.7, 143.6, 143.5, 141.3, 135.0, 132.1, 131.8, 131.1, 130.7, 129.6, 128.6, 128.5, 121.7, 117.6, 117.4, 116.2, 115.4, 64.3, 64.2; HRMS (ESI) calcd for $C_{21}H_{15}ClN_3O_3S$ $[M + H]^+$ 424.0523, found 424.0529.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-chloro-3′,5′-dimethyl[1,1′-biphenyl]-2-carboxamide (**7n**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **7n** as a pale yellow solid: R_f = 0.65 (EtOAc/hexanes = 1:4); yield 75% (35 mg); mp 116−118 °C; IR (DCM) 3054, 2986, 1421, 895, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.49 (dd, 1H, J_1 = 7.3, J_2 = 0.6 Hz), 8.43 (br s, 1H), 7.69 (dd, 1H, J_1 = 8.9, J_2 = 0.9 Hz), 7.61 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.51−7.45 (m, 2H), 7.39 (dd, 1H, J_1 = 7.1, J_2 = 7.1 Hz), 7.11 (s, 2H), 6.80 (s, 1H), 2.19 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.3, 154.6, 147.6, 142.2, 138.7, 138.1, 135.1, 131.8, 131.0, 130.7, 129.7, 129.6, 128.6, 128.6, 126.3, 116.1, 115.2, 21.2; HRMS (ESI) calcd for $C_{21}H_{17}ClN_3OS$ $[M + H]^+$ 394.0781, found 394.0770.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4′-methoxy-4-methyl[1,1′-biphenyl]-2-carboxamide (**7o**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **7o** as a pale yellow viscous liquid: yield 44% (20 mg); R_f = 0.52 (EtOAc/hexanes = 1:4); IR (DCM) 3385, 3057, 1545, 1265, 744, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, 1H, J = 7.1 Hz), 8.43 (br s, 1H), 7.72 (br s, 1H), 7.65 (dd, 1H, J_1 = 8.8, J_2= 1.0 Hz), 7.60 (dd, 1H, J_1 = 8.8, J_2= 7.2 Hz), 7.42 (d, 2H, J = 8.6 Hz), 7.39−7.36 (m, 2H), 6.85 (d, 2H, J = 8.6 Hz), 3.71 (s, 3H) 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.2, 159.5, 154.6, 147.5, 137.4, 137.0, 134.6, 131.9, 131.8, 131.1, 130.6, 130.1, 130.0, 115.7, 114.5, 114.3, 55.2, 21.0; HRMS (ESI) calcd for $C_{21}H_{18}N_3O_2S$ $[M + H]^+$ 376.1120, found 376.1106.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″-dimethoxy-4′-methyl-[1,1′:3′,1″-terphenyl]-2′-carboxamide (**7o′**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **7o′** as a pale yellow viscous liquid: yield < 10% (6 mg); R_f = 0.45 (EtOAc/hexanes = 1:4); IR (DCM) 3385, 3057, 1545, 1265, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25 (br s, 1H), 8.17 (d, 1H, J = 7.4 Hz), 7.58 (d, 1H, J = 8.8

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

Hz), 7.47−7.43 (m, 4H), 7.36 (d, 1H, J = 7.8 Hz), 7.26 (d, 2H, J = 7.4 Hz), 6.81 (d, 4H, J = 8.6 Hz), 3.71 (s, 3H), 3.70 (s, 3H), 2.21 (s, 3H); HRMS (ESI) calcd for $C_{28}H_{24}N_3O_3S$ $[M + H]^+$ 482.1538, found 482.1521. This compound contains residual grease impurity, and the purity of this compound is about 90−95%. For this compound, only a representable proton NMR was recorded.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4-methyl-3′-nitro[1,1′-biphenyl]-2-carboxamide (**7p**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **7p** as a pale yellow solid: yield < 10% (6 mg); R_f = 0.42 (EtOAc/hexanes = 1:4); mp 161−163 °C; IR (DCM) 3054, 2987, 1526, 1265, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.48 (br s, 1H), 8.48 (d, 1H, J = 6.9 Hz), 8.42 (br s, 1H), 8.10 (d, 1H, J = 8.7 Hz), 7.77 (d, 1H, J = 8.6 Hz), 7.72 (br s, 1H), 7.68 (d, 1H, J = 8.8 Hz), 7.60 (dd, 1H, J_1 = 7.8, J_2= 7.6 Hz), 7.49−7.42 (m, 3H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.2, 154.6, 148.5, 147.5, 141.6, 139.2, 135.1, 135.0, 132.1, 131.0, 130.7, 129.6, 129.5, 129.5, 123.6, 122.5, 116.2, 115.0, 21.2; HRMS (ESI) calcd for $C_{20}H_{15}N_4O_3S$ $[M + H]^+$ 391.0865, found 391.0852. This compound contains residual grease impurity, and the purity of this compound is about 95%.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4′-methyl-3,3″-dinitro-[1,1′:3′,1″-terphenyl]-2′-carboxamide (**7p′**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **7p′**as a pale yellow solid: yield < 20% (13 mg); R_f = 0.36 (EtOAc/hexanes = 1:4); mp 159−161 °C; IR (DCM) 3054, 2987, 1526, 1265, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.45 (br s, 1H), 8.32 (br s, 1H), 8.24 (br s, 1H), 8.09 (d, 2H, J = 8.1 Hz), 8.00 (d, 1H, J = 7.4 Hz), 7.86 (d, 1H, J = 7.8 Hz), 7.71 (d, 1H, J = 7.6 Hz), 7.62−7.58 (m, 2H), 7.53−7.49 (m, 2H), 7.46 (d, 1H, J = 7.5 Hz), 7.42 (d, 1H, J = 8.6 Hz), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.3, 154.4, 148.3, 148.1, 147.2, 141.2, 139.9, 137.7, 137.3, 136.2, 135.4, 134.6, 132.2, 130.7, 130.1, 129.6, 129.5, 128.6, 124.3, 123.6, 122.8, 122.7, 116.6 115.3, 20.7 HRMS (ESI) calcd for $C_{26}H_{18}N_5O_5S$ $[M + H]^+$ 512.1029, found 512.1015. This compound contains residual grease impurity and purity of this compound is about 90−95%.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″-diethyl-5′-methyl-[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9a**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9a** as a pale yellow solid: R_f = 0.75 (EtOAc/hexanes = 1:4); yield 75% (33 mg); mp 145−147 °C; IR (DCM) 3055, 2987, 2306, 1265, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.29 (br s, 1H), 8.27 (br s, 1H), 7.58 (d, 1H, J = 8.4 Hz), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.43 (d, 4H, J = 8.0 Hz), 7.29 (s, 2H), 7.11 (d, 4H, J = 8.0 Hz), 2.53 (q, 4H, J = 7.6 Hz), 2.50 (s, 3H), 1.07 (t, 6H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.1, 154.5, 147.5, 143.5, 140.8, 139.8, 137.6, 132.5, 131.1, 130.0, 130.0, 128.5, 127.9, 115.4, 114.4, 28.4, 21.4, 15.3; HRMS (ESI) calcd for $C_{30}H_{28}N_3OS$ $[M + H]^+$ 478.1953, found 478.1944.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″-dimethoxy-5′-methyl-[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9b**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9b** as a pale yellow solid: R_f = 0.48 (EtOAc/hexanes = 1:4); yield 65% (39 mg); mp 145−147 °C; IR (DCM) 3054, 2987, 1609, 1422, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.32 (br s, 1H), 8.31 (d, 1H, J = 6.7 Hz), 7.60 (d, 1H, J = 8.8 Hz), 7.51 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.45 (d, 4H, J = 8.7 Hz), 7.26 (s, 2H), 6.83(d, 4H, J = 8.7 Hz), 3.72 (s, 6H), 2.50 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.2, 159.0, 154.6, 147.5, 140.3, 139.7, 132.7, 132.5, 131.1, 129.9, 129.7, 115.6, 114.6, 113.8, 55.2, 21.4; HRMS (ESI) calcd for $C_{28}H_{23}N_3NaO_3S$ $[M + Na]^+$ 504.1358, found 504.1370.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-5′-methyl-3,3″-dinitro-[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9c**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9c** as a pale yellow solid: R_f = 0.35 (EtOAc/hexanes = 1:4); yield 42% (25 mg); mp 225−227 °C; IR (DCM) 2918, 1647, 1529, 1351, 805 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.45 (br s, 2H), 8.28 (br s, 1H), 8.15 (d, 1H, J = 7.4 Hz), 8.10 (dd, 2H, J_1 = 8.2, J_2 = 1.2 Hz), 7.85 (d, 2H, J = 7.7 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.50−7.45 (m, 3H), 7.41 (s, 2H), 2.58 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.5, 154.5, 148.2, 147.3, 141.4, 141.0, 138.5, 134.7, 132.7, 131.0, 130.7, 129.4, 128.8, 123.7, 122.7, 116.6, 115.4, 21.47; HRMS (ESI) calcd for $C_{26}H_{18}N_5O_5S$ $[M + H]^+$ 512.1029, found 512.1008.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″,5′-trimethyl[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9d**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9d** as a pale yellow solid: R_f = 0.72 (EtOAc/hexanes = 1:4); yield 70% (37 mg); mp 139−141 °C; IR (DCM) 3055, 2987, 2306, 1422, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30 (br s, 1H), 8.29 (d, 1H, J = 7.5 Hz), 7.59 (dd, 1H, J_1 = 8.8, J_2 = 0.8 Hz), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.41 (d, 4H, J = 8.0 Hz), 7.27 (s, 2H), 7.09 (d, 4H, J = 8.0 Hz), 2.50 (s, 3H), 2.24 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.1, 154.6, 147.5, 140.8, 139.7, 137.4, 137.2, 132.5, 131.1, 130.0, 129.9, 129.1, 128.4, 115.5, 114.6, 21.4, 21.1; HRMS (ESI) calcd for $C_{28}H_{24}N_3OS$ $[M + H]^+$ 450.1640, found 450.1644.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,6-bis(2,3-dihydrobenzo[b]-[1,4]dioxin-6-yl)-4-methylbenzamide (**9e**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9e** as a yellow semisolid: R_f = 0.43 (EtOAc/hexanes = 1:4); yield 60% (40 mg); IR (DCM) 2986, 2305, 1421, 895, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.33 (br s, 1H), 8.31 (br s, 1H), 7.62 (d, 1H, J = 8.7 Hz), 7.53 (dd, 1H, J_1 = 8.7, J_2 = 7.3 Hz), 7.23 (s, 2H), 7.04 (d, 2H, J = 2.0 Hz), 6.96 (dd, 2H, J_1 = 8.3, J_2 = 2.1 Hz), 6.73 (d, 2H, J = 8.3 Hz), 4.16 (s, 8H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 169.9, 148.2, 144.8, 143.8, 141.0, 138.2, 136.3, 134.4, 131.7, 131.1, 130.3, 130.0, 129.7, 129.4, 128.1, 127.8, 127.3, 127.2, 126.2, 122.9, 122.2, 121.6, 116.5, 58.9, 53.9, 45.0, 30.1, 22.3; HRMS (ESI) calcd for $C_{30}H_{23}N_3NaO_5S$ $[M + Na]^+$ 560.1256, found 560.1276.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,6-bis(2,3-dihydrobenzo[b]-[1,4]dioxin-6-yl)benzamide (**9f**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9f** as a pale yellow solid: R_f = 0.45 (EtOAc/hexanes = 1:4); yield 50% (31 mg); mp 178−180 °C; IR (DCM) 3054, 2986, 2305, 1687, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (br s, 1H), 8.32 (d, 1H, J = 7.3 Hz), 7.63 (dd, 1H, J_1 = 8.8, J_2 = 0.7 Hz), 7.56−7.51 (m, 2H), 7.42 (d, 2H, J = 7.6 Hz), 7.05 (d, 2H, J = 2.1 Hz), 6.98 (dd, 2H, J_1 = 8.4, J_2 = 2.2 Hz), 6.74 (d, 2H, J = 8.3 Hz), 4.16 (s, 8H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.8, 154.6, 147.6, 143.3, 143.2, 140.1, 134.9, 133.5, 131.1, 129.9, 129.7, 129.2, 121.8, 117.6, 117.2, 115.6, 114.8, 64.3, 64.2; HRMS (ESI) calcd for $C_{29}H_{22}N_3O_5S$ $[M + H]^+$ 524.1280, found 524.1282.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″,5′-trimethoxy[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9g**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9g** as a pale yellow solid: R_f = 0.38 (EtOAc/hexanes = 1:4); yield 60% (35 mg); mp 68−70 °C; IR (DCM) 2987, 2686, 2305, 896, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30 (br s, 1H), 8.28 (br s, 1H), 7.60 (d, 1H, J = 8.8 Hz), 7.50 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.45 (d, 4H, J = 8.7 Hz), 6.94 (s, 2H), 6.83 (d, 4H, J = 8.7 Hz), 3.93 (s, 3H), 3.71 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.0, 159.9, 159.2, 154.6, 147.5, 142.2, 132.6, 131.1, 129.9, 129.6, 128.2, 115.5, 114.5, 113.8, 55.6, 55.2; HRMS (ESI) calcd for $C_{28}H_{24}N_3O_4S$ $[M + H]^+$ 498.1488, found 498.1497.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″-diethyl-5′-methoxy-[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9h**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9h** as a yellow solid: R_f = 0.52 (EtOAc/hexanes = 1:4); yield 61% (36 mg); mp 105−107 °C; IR (DCM) 2987, 2411, 2306, 1422, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, 1H, J_1 = 7.3 Hz), 8.24 (br s, 1H), 7.58 (d, 1H, J = 8.6 Hz), 7.49 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.44 (d, 4H, J = 8.0 Hz), 7.11 (d, 4H, J = 8.0 Hz), 6.99 (s, 2H), 3.93 (s, 3H), 2.53 (q, 4H, J = 7.6 Hz), 1.06 (t, 6H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.9, 159.9, 154.5, 147.4, 143.8, 142.7, 137.6, 131.1, 130.1, 128.4,

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

128.2, 127.9, 115.3, 114.7, 114.3, 55.6, 28.4, 15.3; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_2S$ $[M + H]^+$ 494.1902, found 494.1890.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″-dimethoxy[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9i**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9i** as a pale yellow solid: R_f = 0.41 (EtOAc/hexanes = 1:4); yield 60% (33 mg); mp 148−150 °C; IR (DCM) 3055, 2987, 2306, 1547, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.33 (br s, 1H), 8.31 (d, 1H J = 7.5 Hz), 7.61 (d, 1H, J = 8.8 Hz), 7.59−7.49 (m, 2H), 7.46 (d, 4H J = 8.8 Hz), 7.45−7.43 (m, 2H), 6.84 (d, 4H, J = 8.8 Hz), 3.72 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.0, 159.1, 154.6, 147.5, 140.2, 135.1, 132.5, 131.0, 129.8, 129.8, 129.7, 129.2, 115.7, 114.8, 113.9, 55.2; HRMS (ESI) calcd for $C_{27}H_{22}N_3O_3S$ $[M + H]^+$ 468.1382, found 468.1370.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3,3″-dinitro[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9j**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9j** as a pale yellow solid: R_f = 0.33 (EtOAc/hexanes = 1:4); yield 50% (30 mg); mp 227−229 °C; IR (DCM) 3055, 2308, 1422, 1265, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.46 (br s, 2H), 8.32 (br s, 1H), 8.15−8.11 (m, 3H), 7.87 (d, 2H, J = 7.7 Hz), 7.75 (t, 1H, J = 7.7 Hz), 7.65−7.60 (m, 3H), 7.51−7.47 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.2, 154.5, 148.3, 147.3, 141.2, 138.5, 135.3, 134.7, 130.7, 130.7, 130.4, 129.5, 128.7, 123.7, 122.9, 116.7, 115.5; HRMS (ESI) calcd for $C_{25}H_{16}N_5O_5S$ $[M + H]^+$ 498.0872, found 498.0855.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″-dimethyl[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9k**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9k** as a pale yellow solid: R_f = 0.68 (EtOAc/hexanes = 1:4); yield 75% (39 mg); mp 189−191 °C; IR (DCM) 3055, 2987, 2306, 1422, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.22 (br s, 1H), 8.18 (dd, 1H, J_1 = 7.4, J_2 = 0.7 Hz), 7.51−7.45 (m, 2H), 7.40 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.35 (d, 2H, J = 7.4 Hz), 7.31 (d, 4H, J = 8.0 Hz), 7.00 (d, 4H, J = 8.0 Hz), 2.14 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.9, 154.6, 147.5, 140.6, 137.3, 137.2, 135.1, 131.1, 129.8, 129.7, 129.4, 129.1, 128.5, 115.6, 114.8, 21.1; HRMS (ESI) calcd for $C_{27}H_{22}N_3OS$ $[M + H]^+$ 436.1484, found 436.1506.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4,4″-diethyl[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9l**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9l** as a pale yellow solid: R_f = 0.69 (EtOAc/hexanes = 1:4); yield 74% (41 mg); mp 152−154 °C; IR (DCM) 3055, 2987, 2305, 1546, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (br s, 1H), 8.26 (br s, 1H), 7.61−7.57 (m, 2H), 7.52−7.46 (m, 3H), 7.44 (d, 4H, J = 8.0 Hz), 7.11 (d, 4H, J = 8.0 Hz), 2.53 (q, 4H, J = 7.6 Hz), 1.07 (t, 6H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.0, 154.5, 147.5, 143.6, 140.7, 137.5, 135.1, 131.1, 129.9, 129.8, 129.3, 128.6, 127.9, 115.5, 114.6, 28.4, 15.3; HRMS (ESI) calcd for $C_{29}H_{26}N_3OS$ $[M + H]^+$ 464.1797, found 464.1784.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)[1,1′:3′,1″-terphenyl]-2′-carboxamide (**9m**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **9m** as a pale yellow solid: R_f = 0.61 (EtOAc/hexanes = 1:4); yield 50% (24 mg); mp 175−177 °C; IR (DCM) 3054, 2685, 2305, 895, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30 (br s, 1H), 8.26 (dd, 1H, J_1 = 7.4, J_2 = 0.4 Hz), 7.64−7.58 (m, 2H), 7.55−7.47 (m, 7H), 7.31 (t, 4H, J = 7.3 Hz), 7.24−7.20 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.6, 154.5, 147.4, 140.7, 140.1, 135.2, 131.0, 129.8, 129.6, 129.5, 128.6, 128.4, 127.6, 115.7, 114.7; HRMS (ESI) calcd for $C_{25}H_{18}N_3OS$ $[M + H]^+$ 408.1171, found 408.1166.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-methoxy-6-(4-nitrobenzyl)-benzamide (**11a**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **11a** as a yellow solid: R_f = 0.38 (EtOAc/hexanes = 1:4); yield 47% (23 mg); mp 157−159 °C; IR (DCM) 3054, 2986, 2305, 895, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.92 (br s, 1H), 8.61 (d, 1H, J = 7.3 Hz), 7.98 (d, 2H, J = 8.6 Hz), 7.73 (d, 1H, J = 8.8 Hz), 7.66 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.36 (d, 2H, J = 8.6 Hz), 6.98 (d, 1H, J = 8.4 Hz), 6.91 (d, 1H, J = 7.7 Hz), 4.29 (s, 2H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.7, 156.8, 154.8, 148.3, 147.7, 146.3, 139.7, 131.4, 131.1, 129.8, 129.8, 125.4, 123.6, 123.3, 116.1, 115.1, 110.0, 56.0, 39.2; HRMS (ESI) calcd for $C_{21}H_{17}N_4O_4S$ $[M + H]^+$ 421.0971, found 421.0963.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-methyl-6-(4-nitrobenzyl)-benzamide (**11b**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **11b** as a pale yellow solid: R_f = 0.35 (EtOAc/hexanes = 1:4); yield 50% (24 mg); mp 179−181 °C; IR (DCM) 2987, 2306, 1422, 1265, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.64 (d, 1H, J = 7.3 Hz), 8.37 (br s, 1H), 7.94 (d, 2H, J = 8.4 Hz), 7.76 (d, 1H, J = 8.8 Hz), 7.67 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.37 (t, 1H J = 7.6 Hz), 7.31 (d, 2H, J = 8.4 Hz), 7.25 (d, 1H J = 7.6 Hz), 7.15 (d, 1H J = 7.6 Hz), 4.19 (s, 2H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.3, 154.7, 148.0, 147.4, 146.4, 137.1, 136.1, 135.2, 130.9, 130.0, 129.6, 129.3 128.0, 123.6, 116.6, 115.3, 39.3, 19.5; HRMS (ESI) calcd for $C_{21}H_{17}N_4O_3S$ $[M + H]^+$ 405.1021, found 405.1019.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-chloro-6-(4-nitrobenzyl)-benzamide (**11c**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **11c** as a pale yellow solid: R_f = 0.38 (EtOAc/hexanes = 1:4); yield 65% (33 mg); mp 172−174 °C; IR (DCM) 3055, 2987, 2307, 896, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.62 (dd, 1H, J_1 = 7.4, J_2 = 0.6 Hz), 8.45 (br s, 1H), 7.96 (d, 2H, J = 8.8 Hz), 7.78 (dd, 1H, J_1 = 8.9, J_2 = 0.9 Hz), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.45−7.39 (m, 2H), 7.33 (d, 2H, J = 8.8 Hz), 7.23 (dd, 1H, J_1 = 6.8, J_2 = 2.0 Hz), 4.22 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.1, 154.7, 147.4, 147.0, 146.5, 139.1, 136.1, 131.5, 131.1, 130.9, 129.8, 129.1, 129.0, 128.5, 123.7, 116.8, 115.6, 39.2; HRMS (ESI) calcd for $C_{20}H_{14}ClN_4O_3S$ $[M + H]^+$ 425.0475, found 425.0471.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4-methyl-2,6-bis(4-nitrobenzyl)benzamide (**12a**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **12a** as a pale yellow solid: R_f = 0.31 (EtOAc/hexanes = 1:4); yield 55% (35 mg); mp 165−167 °C; IR (DCM) 3055, 2987, 1422, 1265, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, 1H, J = 7.4 Hz), 8.13 (br s, 1H), 7.97 (d, 4H, J = 8.5 Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.65 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.30 (d, 4H, J = 8.5 Hz), 7.03 (s, 2H), 4.16 (s, 4H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.9, 154.6, 147.6, 147.1, 146.5, 140.6, 136.7, 134.6, 130.8, 129.9, 129.6, 129.0, 123.7, 116.8, 115.2, 39.5, 21.4; HRMS (ESI) calcd for $C_{28}H_{20}N_5O_5S$ $[M - H]^-$ 538.1185, found 538.1163.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-4-methoxy-2,6-bis(4-nitrobenzyl)benzamide (**12b**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **12b** as a pale yellow solid: R_f = 0.30 (EtOAc/hexanes = 1:4); yield 52% (24 mg); mp 240−242 °C; IR (DCM) 3054, 2987, 1422, 896, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.53 (dd, 1H, J_1 = 7.4, J_2 = 0.6 Hz), 8.14 (br s, 1H), 7.98 (d, 4H, J = 8.8 Hz), 7.75 (dd, 1H, J_1 = 8.8, J_2 = 0.8 Hz), 7.64 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.31 (d, 4H, J = 8.7 Hz), 6.72 (s, 2H), 4.18 (s, 4H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.7, 160.6, 154.5, 147.3, 146.5, 138.6, 130.8, 130.1, 129.6, 129.0, 123.8, 116.7, 115.1, 114.6, 55.5, 39.5; HRMS (ESI) calcd for $C_{28}H_{22}N_5O_6S$ $[M + H]^+$ 556.1291, found 556.1298.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2,6-bis(4-nitrobenzyl)-benzamide (**12c**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **12c** as a yellow solid: R_f = 0.33 (EtOAc/hexanes = 1:4); yield 58% (36 mg); mp 188−190 °C; IR (DCM) 3055, 2306, 1348, 1265, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.56 (d, 1H J = 7.3 Hz), 8.15 (br s, 1H), 7.96 (d, 4H, J = 8.6 Hz), 7.76 (d, 1H, J = 8.8 Hz), 7.66 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.45 (t, 1H, J = 7.7 Hz), 7.30 (d, 4H, J = 8.6 Hz), 7.24 (d, 2H, J = 7.7 Hz), 4.20 (s, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.6, 154.5, 147.5, 147.1, 146.5, 137.2, 136.7, 130.8, 130.4, 129.6, 129.3, 128.9, 123.8, 116.9,

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

115.3, 39.2; HRMS (ESI) calcd for $C_{27}H_{20}N_5O_5S$ $[M + H]^+$ 526.1185, found 526.1197.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-3-methyl-2,6-bis(4-nitrobenzyl)benzamide (**12d′**).* Following the general procedure I, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **12d′** as a pale yellow solid: yield 30% (19 mg); R_f = 0.33 (EtOAc/hexanes = 1:4); mp 144−146 °C; IR (DCM) 3054, 2987, 1421, 1265, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, 1H, J = 7.4 Hz), 8.16 (br s, 1H), 8.01 (d, 2H, J = 8.6 Hz), 7.96 (d, 2H, J = 8.6 Hz), 7.72 (d, 1H, J = 8.8 Hz), 7.61 (dd, 1H, J_1 = 8.7, J_2 = 7.6 Hz), 7.35 (d, 1H, J = 7.9 Hz), 7.32 (d, 2H, J = 8.6 Hz), 7.23 (d, 2H, J = 8.6 Hz), 7.19 (d, 1H, J = 7.8 Hz), 4.19 (s, 4H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.2, 154.5, 147.8, 147.1, 147.1, 146.4, 138.2, 136.9, 134.1, 134.1, 132.4, 130.8, 129.6, 129.5, 128.9, 128.9, 123.8, 123.7, 116.8, 115.2, 39.1, 36.4, 19.9; HRMS (ESI) calcd for $C_{28}H_{22}N_5O_5S$ $[M + H]^+$ 540.1342, found 540.1360.

*N-(2-(Methylthio)phenyl)-3-(3-nitrophenyl)propanamide (**21c**).* Following the general procedure B, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **21c** as a brown semisolid: R_f = 0.40 (EtOAc/hexanes = 1:4); yield 30% (24 mg); IR (DCM) 3333, 2923, 1682, 1530, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, 1H, J = 8.2 Hz), 8.24 (br s, 1H), 8.16 (br s, 1H), 8.09 (d, 1H, J = 8.2 Hz), 7.63 (d, 1H, J = 7.6 Hz), 7.48 (t, 2H, J = 8.0 Hz), 7.31 (d, 1H, J = 7.5 Hz), 7.09 (t, 1H, J = 7.4 Hz), 3.21 (t, 2H, J = 7.4 Hz), 2.82 (t, 2H, J = 7.4 Hz), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 169.4, 148.4, 142.6, 137.8, 135.0, 132.7, 129.5, 128.8, 125.4, 124.7, 123.2, 121.6, 120.8, 38.7, 30.8, 18.9; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3S$ $[M + H]^+$ 317.0960, found 317.0946.

*3-(3-Nitrophenyl)-N-(quinolin-8-yl)propanamide (**21d**).*[20c] Following the general procedure B, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **21d** as a pale gray solid: R_f = 0.43 (EtOAc/hexanes = 1:4); yield 21% (17 mg); mp 148−150 °C; IR (DCM) 3347, 2987, 1687, 1525, 737; cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.81 (br s, 1H), 8.79−8.76 (m, 2H), 8.20−8.17 (m, 2H), 8.18 (d, 1H, J = 8.3 Hz), 8.08 (d, 1H, J = 8.2 Hz), 7.67 (d, 1H, J = 7.6 Hz), 7.57−7.51 (m, 2H), 7.47 (t, 2H, J = 7.8 Hz), 3.27 (t, 2H, J = 7.5 Hz), 2.97 (t, 2H, J = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 169.7, 148.2, 142.8, 138.2, 136.4, 135.0, 134.2, 129.5, 127.9, 127.4, 123.3, 121.7, 121.7, 121.5, 116.6, 38.8, 30.9; HRMS (ESI) calcd for $C_{18}H_{16}N_3O_3$ $[M + H]^+$ 322.1192, found 322.1178.

*3,3-Bis(3-nitrophenyl)-N-(quinolin-8-yl)propanamide (**21d′**).* Following the general procedure B, resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **21d′** as a pale gray solid: R_f = 0.29 (EtOAc/hexanes = 1:4); yield 18% (20 mg); mp 201−203 °C; IR (DCM) 3347, 2987, 1527, 1265, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.86 (br s, 1H), 8.78 (d, 1H, J = 4.2 Hz), 8.65 (dd, 1H, J_1 = 6.0, J_2 = 2.6 Hz), 8.23 (br s, 2H), 8.17 (d, 1H, J = 8.2 Hz), 8.11 (d, 1H, J = 8.2 Hz), 8.72 (d, 2H, J = 7.5 Hz), 7.72 (d, 2H, J = 7.7 Hz), 7.56−7.50 (m, 4H), 7.47 (dd, 1H, J_1 = 8.0, J_2 = 3.4 Hz), 5.07 (t, 1H, J = 7.6 Hz), 3.45 (d, 2H, J = 7.7 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.8, 148.6, 148.3, 144.5, 138.1, 136.4, 134.2, 133.8, 130.0, 127.9, 127.3, 122.5, 122.4, 122.0, 121.8, 116.6, 46.2, 43.3; HRMS (ESI) calcd for $C_{24}H_{19}N_4O_5$ $[M + H]^+$ 443.1355, found 443.1337.

*Methyl 4-(3-Oxo-3-(quinolin-8-ylamino)propyl)benzoate (**21e**).* Following the general procedure B, **21e** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 25:75) as a colorless viscous liquid: R_f = 0.44 (EtOAc/hexanes = 1:4); yield 40% (17 mg); IR (DCM) 3350, 1720, 1526, 1282, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.80 (br s, 1H), 8.79−8.78 (m, 2H), 8.18 (d, 1H, J = 8.2 Hz), 7.99 (d, 2H, J = 8.0 Hz), 7.58−7.51 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.39 (d, 2H, J = 8.0 Hz), 3.91 (s, 3H), 3.22 (t, 2H, J = 7.6 Hz), 2.93 (t, 2H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 170.3, 167.1, 148.1, 146.3, 138.3, 136.4, 134.3, 129.9, 128.5, 128.2, 127.9, 127.4, 121.6, 121.6, 116.5, 52.0, 39.1, 31.4; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_3$ $[M + H]^+$ 335.1396, found 335.1381.

*Dimethyl 4,4′-(3-Oxo-3-(quinolin-8-ylamino)propane-1,1-diyl)-dibenzoate (**21e′**).* Following the general procedure B, **21e′** was obtained after purification by column chromatography on silica gel (EtOAc/hexanes = 1:3) as a colorless viscous liquid: R_f = 0.30 (EtOAc/hexanes = 1:4); yield 17% (10 mg); IR (DCM) 3054, 1721, 1526, 1265, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.79 (br s, 1H), 8.77 (d, 1H, J = 4.1 Hz), 8.68 (t, 1H, J = 4.4 Hz), 8.16 (d, 1H, J = 8.2 Hz), 7.98 (d, 4H, J = 8.1 Hz), 7.50 (d, 2H, J = 4.6 Hz), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.42 (d, 4H, J = 8.1 Hz), 4.93 (t, 1H, J = 7.7 Hz), 3.91 (s, 6H), 3.37 (d, 2H, J = 7.7 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.6, 166.8, 148.1, 138.2, 136.4, 134.0, 130.1, 128.7, 127.9, 127.9, 127.3, 121.7, 121.6, 116.6, 52.1, 47.0, 43.7; HRMS (ESI) calcd for $C_{28}H_{25}N_2O_5$ $[M + H]^+$ 469.1763, found 469.1745.

*4′-Ethyl-3-(4-ethylbenzyl)-N-(quinolin-8-yl)[1,1′-biphenyl]-2-carboxamide (**22a**).* Following the general procedure B, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **22a** as a colorless solid: R_f = 0.53 (EtOAc/hexanes = 1:4); yield 53% (30 mg); mp 138−140 °C; IR (DCM) 3054, 2928, 1422, 1265, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.50 (br s, 1H), 8.77 (d, 1H, J = 7.6 Hz), 8.55 (d, 1H, J = 4.1 Hz), 8.07 (d, 1H, J = 8.4 Hz), 7.54−7.41 (m, 5H), 7.35 (d, 2H, J = 7.8 Hz), 7.26 (d, 1H, J = 8.0 Hz), 7.16 (d, 2H, J = 7.5 Hz), 7.05 (d, 2H, J = 7.6 Hz), 6.95 (d, 2H, J = 7.5 Hz), 4.22 (s, 2H), 2.44 (q, 4H, J = 7.6 Hz), 1.07 (t, 3H, J = 7.6 Hz), 0.99 (t, 3H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.3, 147.8, 143.2, 141.8, 139.8, 139.5, 137.6, 136.7, 135.9, 134.4, 129.3, 129.1, 129.0, 128.6, 128.6, 128.1, 127.8, 127.7, 127.7, 127.2, 121.5, 121.3, 116.5, 38.8, 28.3, 28.3, 15.5, 15.2; HRMS (ESI) calcd for $C_{33}H_{31}N_2O$ $[M + H]^+$ 471.2436, found 471.2422

Typical Procedure for the β-Acetoxylation of 6c,d (Procedure K). An appropriate amide **6c** or **6d** (0.11 mmol, 30 mg), $Pd(OAc)_2$ (10 mol %, 2.3 mg), $PhI(OAc)_2$ (0.22 mmol, 70 mg), glacial AcOH (7 mg), and AC_2O (13 mg) in anhydrous toluene (3 mL) was heated at 110 °C for 24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuo, and purification of the resulting reaction mixture through column chromatography furnished the corresponding acetoxylated amides **25a,b**.

*2-(Benzo[c][1,2,5]thiadiazol-4-ylcarbamoyl)-3-chlorophenyl Acetate (**25a**).* Following the general procedure K, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **25a** as a pale yellow solid; R_f = 0.50 (EtOAc/hexanes = 1:4); yield 86% (33 mg); mp 129−131 °C; IR (DCM) 3314, 1771, 1692, 1548, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.83 (br s, 1H), 8.64 (d, 1H, J = 7.3 Hz), 7.77 (d, 1H, J = 8.8 Hz), 7.67 (dd, 1H, J_1 = 8.7, J_2 = 7.4 Hz), 7.46 (t, 1H, J = 7.3 Hz), 7.41 (dd, 1H, J_1 = 8.1, J_2 = 1.0 Hz), 7.17 (dd, 1H, J_1 = 8.0, J_2 = 1.1 Hz), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 169.4, 162.0, 154.8, 148.5, 147.7, 132.1, 131.4, 130.9, 129.8, 129.3, 127.7, 121.9, 116.7, 115.8, 20.8; HRMS (ESI) calcd for $C_{15}H_{10}ClNaN_3O_3S$ $[M + Na]^+$ 370.0029, found 370.0014.

*2-(Benzo[c][1,2,5]thiadiazol-4-ylcarbamoyl)-3-methoxyphenyl Acetate (**25b**).* Following the general procedure K, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **25b** as a yellow solid: R_f = 0.52 (EtOAc/hexanes = 1:4); yield 89% (33 mg); mp 130−132 °C; IR (DCM) 3055, 2987, 1679, 1266, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.67 (br s, 1H), 8.64 (d, 1H, J = 7.2 Hz), 7.72 (d, 1H, J = 8.7 Hz), 7.65 (dd, 1H, J_1 = 8.7, J_2 = 7.4 Hz), 7.49 (t, 1H, J = 8.3 Hz), 6.97 (d, 1H, J = 8.5 Hz), 6.84 (d, 1H, J = 8.2 Hz), 4.01 (s, 3H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 169.8, 162.2, 157.6, 154.8, 150.4, 148.0, 132.0, 131.2, 130.2, 117.9, 116.3, 115.9, 115.3, 109.3, 56.5, 21.1; HRMS (ESI) calcd for $C_{16}H_{13}N_3NaO_4S$ $[M + Na]^+$ 366.0524, found 366.0511.

Typical Procedure for the β-Alkoxylation of 6d,b (Procedure L). An appropriate amide **6b** or **6d** (0.11 mmol, 30 mg), $Pd(OAc)_2$ (10 mol %, 2.3 mg), $PhI(OAc)_2$ (0.22 mmol, 70 mg), MeOH (0.4 mL), and anhydrous toluene (1 mL) was heated at 65 °C for 24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuo, and purification of the resulting reaction mixture through column chromatography furnished the corresponding alkoxylated amides **25c,d**.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-2-chloro-6-methoxybenzamide (**25c**).* Following the general procedure L, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

afford **25c** as a yellow solid: R_f = 0.44 (EtOAc/hexanes = 1:4); yield 71% (25 mg); mp 173−175 °C; IR (DCM) 3054, 2987, 1689, 1574, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.86 (br s, 1H), 8.73 (d, 1H, J = 6.9 Hz), 7.75 (dd, 1H, J_1 = 8.8, J_2 = 0.8 Hz), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 7.4 Hz), 7.35 (t, 1H, J = 8.3 Hz), 7.08 (dd, 1H, J_1 = 8.0, J_2 = 0.5 Hz), 6.90 (d, 1H, J = 8.4 Hz), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.5, 157.5, 154.8, 147.8, 132.4, 131.4, 131.2, 129.9, 125.6, 122.0, 116.2, 115.5, 109.7, 56.2; HRMS (ESI) calcd for $C_{14}H_{11}ClN_3O_2S$ $[M + H]^+$ 320.0261, found 320.0249.

*N-(Benzo[c][1,2,5]thiadiazol-4-yl)-6-methoxy-2,3-dimethylbenzamide (**25d**).* Following the general procedure L, the resultant crude mixture was purified by column chromatography (EtOAc/hexane, 1:4) to afford **25d** as a yellow viscous liquid: R_f = 0.45 (EtOAc/hexanes = 1:4); yield 64% (22 mg); IR (DCM) 2965, 1651, 1587, 1462, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.89 (br s, 1H), 8.74 (dd, 1H, J_1 = 7.2, J_2 = 0.8 Hz), 7.73 (dd, 1H, J_1 = 8.8, J_2 = 1.0 Hz), 7.68 (dd, 1H, J_1 = 8.8, J_2 = 7.2 Hz), 7.20 (d, 1H, J = 8.4 Hz), 6.76 (d, 1H, J = 8.4 Hz), 3.83 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.2, 154.9, 154.5, 147.9, 135.6, 131.6, 131.3, 130.2, 129.7, 126.4, 115.8, 115.1, 108.4, 55.9, 19.4, 16.7; HRMS (ESI) calcd for $C_{16}H_{16}N_3O_2S$ $[M + H]^+$ 314.0963, found 314.0951.

*1-Phenyl-9H-fluoren-9-one (**27**).*[20a] Following the general procedure J, the resultant crude mixture was purified by column chromatography (EtOAc/hexanes = 1:4) to afford **27** as a greenish black semisolid: R_f = 0.80 (EtOAc/hexanes = 1:4); yield 66% (8 mg); IR (DCM) 3054, 1711, 1608, 916, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62−7.59 (m, 2H), 7.57−7.49 (m, 6H), 7.47 (d, 2H, J = 7.5 Hz), 7.31 (t, 1H, J = 7.4 Hz), 7.23 (dd, 1H, J_1 = 7.0, J_2 = 1.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 193.1, 145.5, 143.6, 142.3, 137.4, 134.5, 134.2, 131.6, 129.7, 129.2, 129.2, 129.0, 128.2, 127.9, 127.2, 124.1, 120.0, 119.2; HRMS (ESI) calcd for $C_{19}H_{13}O$ $[M + H]^+$ 257.0966, found 257.0956.

*2-Phenylpropanoic Acid (**28c**).*[19] Following the general procedure F, **28c** was obtained as a pale yellow oil: yield 75% (11 mg); IR (neat) 2968, 1709, 1420, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (m, 5H), 3.32−3.27 (m, 1H), 2.70 (dd, 2H, J_1 = 15.5 Hz, J_2 = 6.8 Hz), 2.61 (dd, 1H, J_1 = 15.5 Hz, J_2 = 8.2 Hz), 1.35 (d, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.5, 145.4, 128.6, 126.7, 126.5, 42.6, 36.2, 21.9; HRMS (ESI) m/z $[M - H]^+$ calcd for $C_{10}H_{11}O_2$ 163.0759, found 163.0756.

*3-(4-Chlorophenyl)butanoic Acid (**28d**).*[19] Following the general procedure F, **28d** was obtained as a colorless solid: yield 88% (17 mg); mp 90−92 °C; IR (KBr) 2963, 1705, 1494, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 2H, J = 8.2 Hz), 7.18 (d, 2H, J = 8.2 Hz), 3.30−3.24 (m, 1H), 2.68−2.56 (m, 2H), 1.32 (d, 3H, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.4, 143.8, 132.2, 128.7, 128.2, 42.5, 35.6, 21.9; HRMS (ESI) m/z $[M - H]^+$ calcd for $C_{10}H_{10}ClO_2$ 197.0369, found 197.0365.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01831.

X-ray structures and brief X-ray structure data for compounds **5g** and **7f**; ^1H and ^{13}C NMR spectra (PDF)

X-ray structure data of the compound **5g** (CIF)

X-ray structure data of the compound **7f** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sababu@iisermohali.ac.in.

ORCID

Srinivasarao Arulananda Babu: 0000-0002-1795-8843

Author Contributions

†C.R., N.B., and R. P. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by IISER-Mohali. We thank the central analytical facilities (NMR, HRMS, and X-ray facilities) of IISER-Mohali and the single-crystal X-ray facility of the Department of Chemical Sciences, IISER-Mohali. We thank Dr. Angshuman Roy Choudhury for help with solving the X-ray structure. C.R. and R.P. thank the CSIR, New Delhi, for providing the SRF fellowships. N.B thanks the UGC, New Delhi, for providing the JRF fellowship. We thank the reviewers for their valuable suggestions.

■ REFERENCES

(1) (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208. (c) Castro, L. C. M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410. (d) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (e) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751. (f) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (g) For a themed issue on C−H activation reactions, see: C−H Functionalisation in organic synthesis. *Chem. Soc. Rev.* **2011**, *40*, 184510.1039/c1cs90011k. (h) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (i) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

(2) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Topczewski, J. T.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (e) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (f) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (g) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

(3) (a) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (b) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Ros, A.; Fernandez, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229. (e) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (f) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450. (g) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (h) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (i) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett.* **2016**, *57*, 819.

(4) (a) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. *Synthesis* **2014**, *46*, 1421. (b) Corbet, M.; De Campo, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896. (c) Zhang, B.; Guan, H.; Liu, B.; Shi, B.-F. *Youji Huaxue* **2014**, *34*, 1487. For selected articles, see: (d) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023. (e) Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244. (f) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842. (g) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (h) Reddy, V. P.; Qiu, R.; Iwasaki, T.; Kambe, N. *Org. Biomol. Chem.* **2015**, *13*, 6803 and references cited therein.

(5) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(6) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(7) For selected articles, see: (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (b) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030. (c) Kanyiva, K. S.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 1968. (d) Feng, R.; Wang, B.; Liu, Y.; Liu, Z.; Zhang, Y. *Eur. J. Org. Chem.* **2015**, *2015*, 142. (e) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.* **2014**, *16*, 4956. (f) Wang, B.; Nack, W. A.; He, G.; Zhang, S.-Y.; Chen, G. *Chem. Sci.* **2014**, *5*, 3952. (g) Chen, K.; Zhang, S.-Q.; Xu, J.-W.; Hu, F.; Shi, B.-F. *Chem. Commun.* **2014**, *50*, 13924 and references cited therein. (h) Rajkumar, V.; Naveen; Babu, S. A. *ChemistrySelect* **2016**, *1*, 1207 and references cited therein.

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168

(8) (a) Zhang, Y.-F.; Zhao, H.-W.; Wang, H.; Wei, J.-B.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2015**, *54*, 13686 and references cited therein. (b) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726. (c) Wang, Z.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 4790. (d) Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, Z.-J.; Zheng, X.-X.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 272. (e) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797. For a recent paper on the Pd(II)-catalyzed C−H acetoxylation of amino acid derivatives, see: (f) Chen, K.; Zhang, S.-Q.; Jiang, H.-Z.; Xu, J.-W.; Shi, B.-F. *Chem. - Eur. J.* **2015**, *21*, 3264.

(9) For selected articles, see: (a) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680.

(10) (a) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7507. (b) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430.

(11) (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634 and references cited therein. (b) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070. (c) Misal Castro, L. C.; Chatani, N. *Chem. - Eur. J.* **2014**, *20*, 4548. (d) Ling, P.-X.; Fang, S.-L.; Yin, X.-S.; Chen, K.; Sun, Z.-B.; Shi, B. F. *Chem. - Eur. J.* **2015**, *21*, 17503. (e) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. (f) Zhang, Q.; Yin, X.-S.; Zhao, S.; Fang, S.-L.; Shi, B.-F. *Chem. Commun.* **2014**, *50*, 8353.

(12) (a) He, G.; Zhang, S. Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124. (b) Rodriguez, N.; Romero-Revilla, J. A.; Fernandez-Ibanez, M. A.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175. (c) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. (d) Fan, M.-Y.; Ma, D.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152. (e) Liu, J.; Xie, Y.; Zeng, W.; Lin, D.; Deng, Y.; Lu, X. *J. Org. Chem.* **2015**, *80*, 4618. (f) Zhang, S.-K.; Yang, X.-Y.; Zhao, X.-M.; Li, P.-X.; Niu, J.-L.; Song, M.-P. *Organometallics* **2015**, *34*, 4331. (g) Hao, X.-Q.; Chen, L.-J.; Ren, B.; Li, L.-Y.; Yang, X.-Y.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Org. Lett.* **2014**, *16*, 1104.

(13) (a) Ye, X. H.; He, Z. R.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Chem. Sci.* **2013**, *4*, 3712. (b) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3868. (c) Rit, R. K.; Yadav, R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724. (d) Han, J.; Liu, P.; Wang, C.; Wang, Q.; Zhang, J.; Zhao, Y.; Shi, D.; Huang, Z.; Zhao, Y. *Org. Lett.* **2014**, *16*, 5682. (e) Miura, M.; Feng, C.-G.; Ma, S.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5258.

(14) (a) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80*, 2339 and references cited therein. (b) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80*, 12379. (c) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911 and references cited therein. (d) The Pd(II)-catalyzed arylation of propionamide **1i**, which was derived from the ABTD directing group, was also performed using an electron-rich aryl iodide, e.g., 1-iodo-4-methoxybenzene. A mixture of **1i** (0.125 mmol), 1-iodo-4-methoxybenzene (0.125 mmol), $Pd(OAc)_2$ (10 mol %), and AgOAc (0.27 mmol) was refluxed in toluene for 24 h. The column chromatographic purification of this reaction mixture gave a mixture of compounds, and none of the compounds could be obtained in pure form for characterization. However, the ^{1}H NMR spectra of many fractions indicated that perhaps the monoarylation product was formed as the major compound (see the SI for the ^{1}H NMR spectra). (e) We also attempted to remove the directing group ABTD using other conditions. For example, a mixture of **5e** (0.1 mmol), TfOH (0.2 mL), and H_2O (0.2 mL) in toluene (1 mL) was heated at 100 °C. A mixture of **3a** (0.125 mmol) and HBr (47% aqueous solution, 5 mL) was heated at 50 °C. These reactions were not fruitful.

(15) For selected articles, see: (a) Hoshiya, N.; Kobayashi, T.; Arisawa, M.; Shuto, S. *Org. Lett.* **2013**, *15*, 6202. (b) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 3944. (c) Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1340. (d) Wu, X.; Zhao, Y.; Ge, H. *Chem. - Eur. J.* **2014**, *20*, 9530. (e) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394. (f) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238.

(16) For selected articles, see: (a) Zhang, S.-K.; Yang, X.-Y.; Zhao, X.-M.; Li, P.-X.; Niu, J.-L.; Song, M.-P. *Organometallics* **2015**, *34*, 4331. (b) Gou, Q.; Zhang, Z.-F.; Liu, Z.-C.; Qin, J. *J. Org. Chem.* **2015**, *80*, 3176. (c) Kim, J.; Sim, M.; Kim, N.; Hong, S. *Chem. Sci.* **2015**, *6*, 3611. (d) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (e) Reaction conditions: **1k** (0.125 mmol), ethyl iodoacetate (3 equiv) $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.2 equiv), $(BnO)_2POH$ (20 mol %), *tert*-amyl alcohol (2 mL), 110 °C, 24 h. (f) Compound **22b** was not obtained in a characterizable amount; however, traces of **22b** were seen in the NMR spectra of isolated **22a** (**22a** and **22b** have same R_f values), and the yield **22b** is proposed as 5−10%.

(17) When compared to the other existing bidentate directing groups (Figure 1), 4-amino-2,1,3-benzothiadiazole (ABTD) has a skeleton similar to the 8-aminoquinoline (AQ) bidentate directing group. Furthermore, 2,1,3-benzothiadiazole substrates are known to exhibit notable biological activities, and the 2,1,3-benzothiadiazole (BTD) skeleton is considered as one of the important moieties in the chemistry of photoluminescent compounds, functional materials, and light technology. For selected articles, see: (a) Neto, B. A. D.; Lapis, A. A. M.; da Silva Júnior, E. N.; Dupont, J. *Eur. J. Org. Chem.* **2013**, *2013*, 228. (b) Watanabe, M.; Goto, K.; Shibahara, M.; Shinmyozu, T. *J. Org. Chem.* **2010**, *75*, 6104.

(18) The observed selective *ortho* C−H arylation/benzylation of benzamides and *β*-C−H arylation of aliphatic/alicyclic carboxamides linked with the directing group ABTD can be depicted in agreement with the generally proposed Pd^{II}−Pd^{IV} catalytic cycle mechanism involving the Pd^{II}/AgOAc catalytic system based C−H activation of carboxamides aided by the bidentate directing groups. For selected papers, see: (a) References 1−6. (b) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188. (c) Arroniz, C.; Denis, J. G.; Ironmonger, A.; Rassias, G.; Larrosa, I. *Chem. Sci.* **2014**, *5*, 3509. (d) Tang, H.; Huang, X.-R.; Yao, J.; Chen, H. *J. Org. Chem.* **2015**, *80*, 4672.

(19) Wang, Y.; Ren, W.; Li, J.; Wang, H.; Shi, Y. *Org. Lett.* **2014**, *16*, 5960.

(20) (a) Tilly, D.; Samanta, S. S.; Castanet, A.-S.; De, A.; Mortier, J. *Eur. J. Org. Chem.* **2006**, *2006*, 174. (b) Nicolas, L.; Angibaud, P.; Stansfield, I.; Meerpoel, L.; Reymond, S.; Cossy, J. *RSC Adv.* **2013**, *3*, 18787. (c) Zhu, Q.; Ji, D.; Liang, T.; Wang, X.; Xu, Y. *Org. Lett.* **2015**, *17*, 3798.

DOI: 10.1021/acs.joc.6b01831
J. Org. Chem. 2016, 81, 12143−12168