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Transition-Metal-Free Synthesis of *N*-Aryl Hydroxamic Acids via Insertion of Arynes

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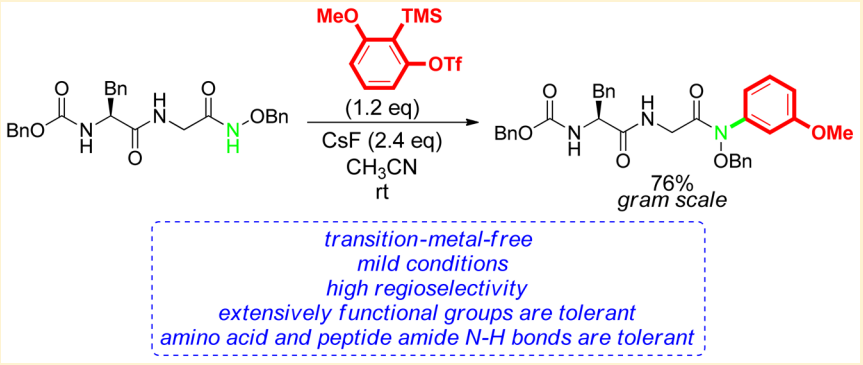
Supporting Information

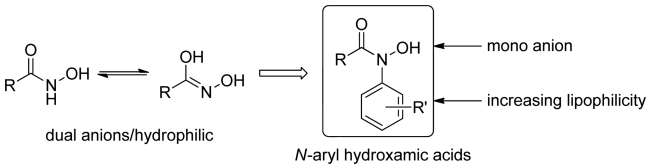


ABSTRACT: An efficient and transition-metal-free *N*-arylation of amides via the insertion of arynes into the N−H bonds in the *N*-alkoxy amides is described. A variety of the reactive functional groups including the reactive aldehyde carbonyl group, furan ring, carbon−carbon double bonds, and free N−H bond of indole are found to be compatible with this process. In particular, the protocol is applicable in the synthesis of structurally diverse *N*-aryl hydroxamates and hydroxamic acids derived from *N*-protecting amino acids and peptides. In the presence of multiple amide N−H bonds, the *N*-arylation reaction can proceed selectively in the N−H bonds of terminal *N*-OBn amides giving rise to the desired *N*-aryl hydroxamates.

INTRODUCTION

The hydroxamic acid moiety (Scheme 1, general formula as −CON(R)OH) is widely spread in naturally occurring secondary metabolites, such as microbial hydroxamate siderophores produced by various bacteria and fungi.[1] They are known as excellent metal-chelating agents and evolved in microbes to function in ingesting iron and other important metals for metabolism from the scarcely natural bioavailability. In addition, they are also associated with other biological properties.[2] The biological significance of hydroxamic acids is further illustrated by the increasing numbers of clinical drugs, for example, Kelatorphan (endogenous enkephalinase inhibitor), Panobinostat, Vorinostat, and Belinostat (histone deacetylase inhibitors, HDAC inhibitors). These chemotherapeutical agents with hydroxamic acid as the key pharmacophore are effective in vitro and in vivo through either binding directly to the active sites of enzymes or acting as a chelator for the metal ions to regulate the activity of intracellular metal-associated proteins.[3]

Scheme 1. Structures of Hydroxamic Acids



To date, a large number of methods have been developed for the synthesis of hydroxamic acids starting from carboxylic acids or their derivatives.[4] These methods overwhelmingly involve reactions of activated forms of carboxylic acids with *O*-benzyl hydroxylamine to produce *O*-Bn hydroxamates, the key precursor of free hydroxamic acids. Some of these methods proved quite efficient for the preparation of *N*-alkyl substituted hydroxamic acids, while the preparation of *N*-aryl substituted hydroxamates, especially for amino acid and peptide substrates, still remains unexplored. This can be, to a large extent, attributed to the difficult accessibility of *N*-aryl hydroxylamines. Recently, *N*-aryl hydroxamates have received increasing interest from the pharmacy and biochemistry communities due to their unusual monoanionic character and relatively lipophilic property (Scheme 1).[5] In 2001, Ursic and co-workers reported an approach to *N*-*p*-chlorophenyl hydroxamic acids by reacting acyl chlorides with nitrosobenzene in the presence of catalytic amounts of HCl, possibly involving addition of an acylnitroso intermediate which underwent nucleophilic attack by a chloride ion at the *para*-position of the phenyl ring.[6] Unfortunately, there are obvious limitations in this method and only *para*-

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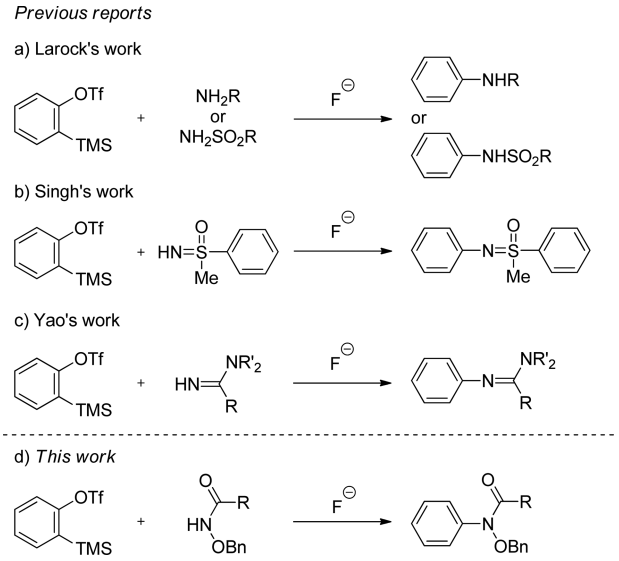
chloride hydroxamic acids can be obtained. Recently, several valuable transition-metal-catalyzed (Cu, Pd) *N*-arylation methods have been developed for the synthesis of *N*-aryl hydroxamate derivatives.[7,8] Despite these significant recent improvements, there still are limitations in the present transition metal-catalyzed *N*-arylation strategies for hydroxamic acid substrates. For example, most reactions are performed under fairly harsh conditions and usually require elevated temperature (>80 °C) as well as the use of a strong base and polar solvents, making these methods not suitable for base- and acid-sensitive substrates, such as amino acids and peptides. Considering the importance of synthesis and functionalization of hydroxamic acids, development of mild methods for the preparation of *N*-arylated hydroxamic acids is of great importance. We herein wish to report a practical and efficient method for the synthesis of *N*-aryl hydroxamic acids by the insertion of arynes into the N−H bond of amides under mild conditions (Scheme 2d).

Scheme 2. *N*-Arylation via Insertion of Arynes into the N−H Bonds

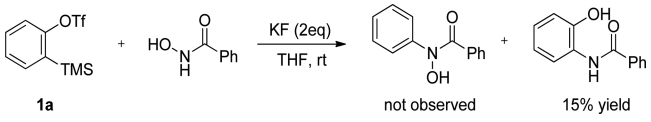


As the highly reactive intermediates, arynes have been used as the versatile synthons and widely applied in organic synthesis.[9] The highly electrophilic character of arynes enables them to react with extensive nucleophiles, under mild and transition-metal-free conditions, leading to the formation of carbon−carbon and carbon−heteroatom bonds.[10] In particular, Larock,[11] Garg,[12] Greaney,[13] Singh,[14] Wang,[15] Hosoya,[16] Yao,[17] and others[18] disclosed that the N−H σ-bonds in amines, sulfonamides, amidines, *N*-aryl trifluoroacetamides and trifluoromethylsulfinamides, sulfoximines, sulfilimines, *N*-aryl cyanamides, and *N*-aryl phosphorylamides enable direct addition across the highly strained carbon−carbon triple bonds of arynes to provide the related *N*-arylation products under transition-metal-free conditions (Scheme 2a−c). However, to the best of our knowledge, the insertion of arynes into the N−H bonds in the common primary or *N*-alkyl amides proved unsuccessful to date.[9c,11] Based on the above-mentioned background, we decided to investigate whether the *N*-acyoxyl and -alkoxyl amides, even the free hydroxamic acids, can serve as effective substrates to produce the desired *N*-aryl hydroxamate derivatives through insertion of arynes into the N−H bond of amides under mild conditions.

RESULTS AND DISCUSSION

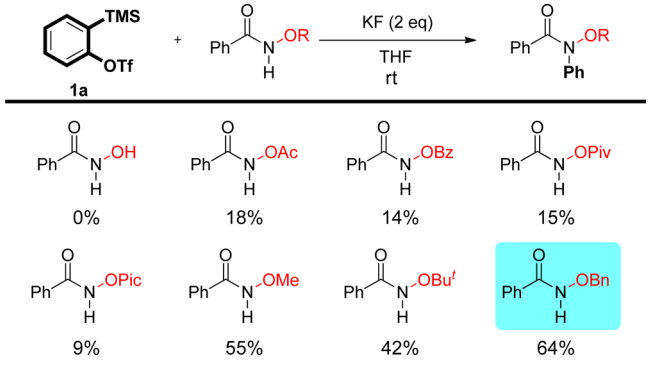
At the outset, given the electron-withdrawing property of the hydroxyl group, we envisioned that the presence of the free OH group in the hydroxamic acids enables the *N*-arylation process via the direct insertion of arynes into the N−H bonds of amides under transition-metal-free conditions. Much to our disappointment, as in the case of the primary amides, insertion of benzyne into the *N*-hydroxybenzamide failed to give the desired *N*-phenyl hydroxamic acid, and an undesired insertion of benzyne into the N−O bond resulting in α-aminophenols is observed (Scheme 3).[19]

Scheme 3. Preliminary Study on *N*-Arylation of Hydroxamic Acid



Therefore, various readily removable *O*-acyl and -alkyl groups are incorporated further and the resulting hydroxamates subjected to insertion reactions of benzyne **1a** (Scheme 4).

Scheme 4. *O*-Substituent Effect of Hydroxamates on Insertion of Benzyne[a,b]



[a]Reaction conditions: hydroxamamate (0.1 mmol), **1a** (0.12 mmol, 1.2 equiv), KF (0.2 mmol, 2.0 equiv), THF (2 mL), rt, 10 h. [b]Isolated yield. Pic, 2-picolinoyl.

Gratifyingly, reactions of *O*-acyl hydroxamates with benzyne precursor **1a** with KF as a [F$^-$] source affords the corresponding *N*-phenyl products, albeit in poor yields, whereas reactions of benzyne with *O*-alkyl hydroxamates deliver the target *N*-phenyl products in increasing yields. Among them, insertion of benzyne into the N−H bond in *O*-benzyl hydroxamate gives the highest yield (64%).

Subsequently, using benzyne precursor **1a** and *O*-benzyl hydroxamte **2a** as the model substrates, extensive reaction parameters such as fluoride source, solvent, and additive are screened for the optimal conditions (Table 1). Among the alkali metal fluorides screened, cesium fluoride shows the highest reactivity (Table 1, entry 4). TBAF[20] and TBAT[13a,21] are also effective for this reaction albeit in lower yields (Table 1, entries 5 and 6). In addition, a combination of KF/18-crown-6[22] gives a slightly higher yield related to that of KF (Table 1, entry 7). It is found that the presence of molecular sieves does

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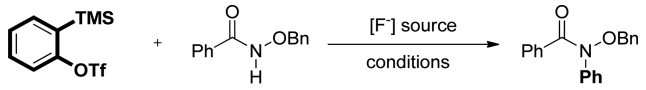
Table 1. Optimization for Insertion of Aryne[a,b]



1a 2a 3a

entry	[F⁻] source	additive	solvent	yield (%)
1	LiF	–	THF	44
2	NaF	–	THF	56
3	KF	–	THF	64
4	CsF	–	THF	78
5	TBAF	–	THF	37
6	TBAT	–	THF	63
7	KF	18-crown-6	THF	67
8	CsF	4 Å M.S.	THF	75
9	CsF	–	toluene	trace
10	CsF	–	DCM	trace
11	CsF	–	DME	65
12	CsF	–	1,4-dioxane	59
13	CsF	–	CH_3CN	99

[a]Reaction conditions: *O*-benzyl hydroxamate **2a** (0.1 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.12 mmol, 1.2 equiv), [F⁻] source (0.2 mmol, 2.0 equiv), additive (2.0 equiv, for 4 Å molecular sieves, 100 mg), solvent (2 mL), rt, 20 h. [b]Isolated yield. M.S., molecular sieves. TBAF, tetrabutylammonium fluoride. TBAT, tetrabutylammonium difluorotriphenylsilicate.

not furnish an improved yield in this reaction (Table 1, entry 8). Notably, the solvent is shown to play a crucial role in the *N*-arylation process. Acetonitrile proves to be the solvent of choice. With CsF as the base, reactions performed in the low-polarity solvents such as toluene and dichloromethane only supply a trace amount of products (Table 1, entries 9 and 10), while near-quantitative yield is achieved when an insertion reaction is performed in the acetonitrile (Table 1, entry 13).

With the optimized reaction conditions in hand, a variety of *O*-benzyl hydroxamates are thus prepared and subjected to the *N*-arylation reaction with benzyne precursor **1a**. As exemplified in Table 2, both electron-donating and -withdrawing groups in the phenyl rings are compatible with this insertion reaction. Commonly, aromatic hydroxamates **2e** and **2k**−**m** incorporating the electron-withdrawing groups give rise to the declined yields (Table 2, entries 5, 11−13). Notably, the carbonyl group in the aromatic aldehyde and furan ring, which are prone to undergo [2 + 2][23] and [4 + 2][24] cycloaddition reactions with benzyne, is tolerant in the insertion process (Table 2, entries 12 and 15). The free N−H bonds in the indole rings also survive in the *N*-arylation of amides (Table 2, entries 17 and 19). In addition, *O*-benzyl hydroxamates **2t**−**2x** derived from *α*,*β*-unsaturated carboxylic acids and aliphatic carboxylic acids all prove to be suitable substrates for this transformation (Table 2, entries 20−24).

Next, the reactivity of various arynes in the *N*-arylation of *O*-benzyl hydroxamtes is examined (Table 3). For unsymmetrical 3-methoxy benzyne and 1,2-naphthyl-based aryne, only single regioisomer **4a**/**4b** are obtained in 72% and 87% yields (Table 3, entries 1 and 2), respectively. In contrast, almost equivalent amount of *para*-/*meta*-regioisomers are produced when unsymmetrical 4-methoxy and 4-methyl benzynes are used (Table 3, entries 4 and 5). Further, symmetrical and electron-deficient 3,4-difluorobenzyne also affords the *N*-aryl hydroxamate in a reasonable yield (Table 3, entry 3).

In view of the predominant biological potential of hydroxamaic acids derived from amino acids and peptides, we also envisioned that, in the presence of multiple amide N−H bonds, the *N*-arylation reaction can proceed selectively in the N−H bonds of terminal *N*-OBn amides to give rise to the desired *N*-aryl hydroxamates. Therefore, a variety of *O*-benzyl hydroxamates derived from *N*-protected amino acids are allowed to react with the aryne precursors in the presence of CsF (Table 4). Encouragingly, all hydroxamates prepared from *N*-Ac Phe, *N*-Cbz Phe, *N*-Boc Val, and *N*-Boc *tert*-Ile are arylated exclusively in the N−H bonds of *N*-OBn amides in good yields (Table 4, entries 1, 2, 4, and 5). It is noteworthy that *p*-toluenesulfonamide, which is known to undergo *N*-arylation with silylaryl triflate,[11a,c] is tolerant under the reaction conditions (Table 4, entry 3). *N*-Arylation proceeds cleanly in the N−H bond of *N*-OBn amide.[25] When a 4-methoxy- or 4-methyl-substituted aryne precursor is employed with hydroxamate from *N*-Boc Phe, *para*-/*meta*-isomers were obtained in almost equal amounts (Table 4, entries 6 and 7). Meanwhile, ratios of *para*-/*meta*-isomers for *N*-Boc *tert*-Ile are 3.5:1 and 6:1, respectively (Table 4, entries 8 and 9). In a similar manner to the common aromatic hydroxamates, *N*-arylation of hydroxamate derived from *N*-Boc Phe with 3-methoxy-, 3,4-difluoro-, and 1,2-naphthyl-based arynes cleanly generates a single regioisomer (Table 4, entries 10−12).

To shed some light on the reaction pathway, the control experiment with CD_3CN as solvent is performed to check for any proton incorporation from the solvent. As observed in the *N*-arylation of anilines by Greaney and co-workers,[13c] no *ortho* deuterated products are detected based on analysis of ^1H NMR and LC-MS. Moreover, when using CH_3OD as an additive (1.0 equiv) or the reaction solvent, the insertion reaction is suppressed completely and the starting *N*-OBn amide recovered quantitatively, indicating that the nucleophilic attack of the deprotonated amide anion to aryne initiates the *N*-arylation procedure. Therefore, a putative reaction pathway is concluded (Scheme 5). The unusual regioselectivity of *N*-arylation on protected amino acid substrates can be attributed to the presence of the *N*-OBn group, which induces a smaller pK_a value on the related amide N−H bond.

To demonstrate the versatility of the present protocol for *N*-arylation, an insertion reaction of *O*-benzyl hydroxamate **7** prepared from dipeptide Cbz-Phe-Gly-OH with silylaryl triflate **1b** proceeds smoothly to give the *N*-arylated product **8** at gram-scale level with a satisfactory yield (Scheme 6). Finally, the target hydroxamic acids are produced smoothly in good yields by removal of the *O*-benzyl protecting groups via Pd/C catalytic hydrogenolysis (Scheme 7). Additionally, the reductive cleavage of the N−O bonds mediated by SmI_2 also delivers the corresponding *N*-arylated amide derivatives.[26]

■ CONCLUSION

In conclusion, we have developed an efficient, mild, and transition-metal-free method for the synthesis of *N*-aryl hydroxamic aicds by the insertion of an aryne into the N−H *σ*-bonds. The process tolerates a variety of reactive functional groups, such as the aldehyde carbonyl group, furan ring, C═C double bond, sulfonamide, carbamate, etc. In particular, the present protocol is applicable in the synthesis of *N*-aryl hydroxamic acid derivatives of *N*-protecting amino acids and peptides. In the presence of multiple amide N−H bonds, the *N*-arylation reaction can proceed selectively in the N−H bonds of terminal *N*-OBn amides giving rise to the desired *N*-aryl

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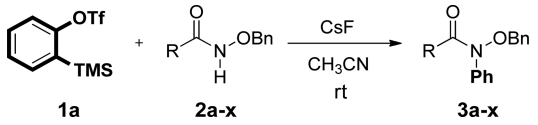
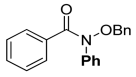
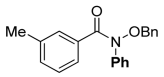
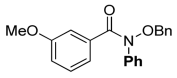
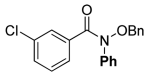
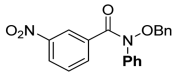
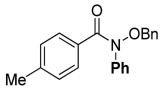
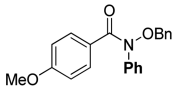
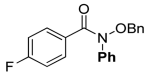
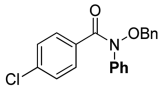
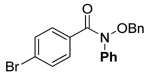
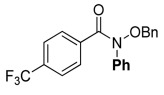
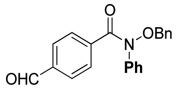
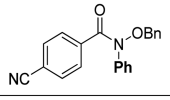
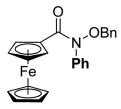
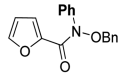
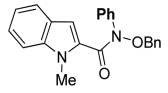
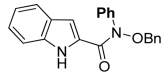
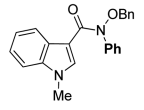
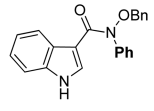
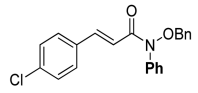
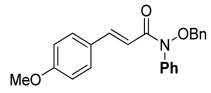
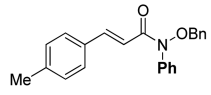
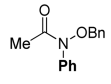
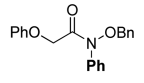
Table 2. *N*-Arylation of *O*-Benzyl Hydroxamates with Benzyne[a,b]



entry	*O*-benzyl hydroxamate	product		yield (%)
1	**2a**		**3a**	99
2	**2b**		**3b**	84
3	**2c**		**3c**	81
4	**2d**		**3d**	80
5	**2e**		**3e**	65
6	**2f**		**3f**	88
7	**2g**		**3g**	98
8	**2h**		**3h**	83
9	**2i**		**3i**	86
10	**2j**		**3j**	86
11	**2k**		**3k**	71
12	**2l**		**3l**	52
13	**2m**		**3m**	74
14	**2n**		**3n**	93
15	**2o**		**3o**	53
16	**2p**		**3p**	89
17	**2q**		**3q**	85
18	**2r**		**3r**	91
19	**2s**		**3s**	89
20	**2t**		**3t**	89
21	**2u**		**3u**	91
22	**2v**		**3v**	88
23	**2w**		**3w**	83
24	**2x**		**3x**	75

[a]Reaction conditions: *O*-benzyl hydroxamamate (0.5 mmol), **1a** (0.6 mmol, 1.2 equiv), CsF (1.2 mmol, 2.4 equiv), CH_3CN (2 mL), rt, 10 h. [b]Isolated yield.

hydroxamates. We have also shown that *p*-toluenesulfonamide, which is reactive in the insertion of an aryne into the N−H bond, readily tolerates the reaction conditions. Given its simplicity, efficiency, and high regioselectivity, we believe that this method can serve as a powerful tool for the synthesis of structurally diverse *N*-aryl hydroxamates and hydroxamic acids.

EXPERIMENTAL SECTION

Unless otherwise stated, all reactions were carried out under an air atmosphere, and all commercially available reagents were used without further purification. Acetonitrile was purified by distillation under air from P_2O_5 immediately prior to use. ^1H NMR spectra were recorded on a Bruker AV-400 instrument (400 MHz). Unless indicated, chemical shifts were quoted in parts per million (ppm) referenced to 0.00 ppm for tetramethylsilane. ^{13}C NMR spectra were recorded on a Bruker AV-400 instrument (100 MHz) and were fully decoupled by broad-band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. Infrared spectroscopic data are reported in wavenumbers (cm^{-1}) with only select peaks shown. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF. Known compounds **2a**,[27] **2b**,[28] **2c**,[29] **2d** and **2u**,[30] **2e**,[31] **2f**–**2i** and **2o**,[32] **2j**,[33] **2m**,[34] **2q**,[35] **2u**,[36] **2w** and **2x**[37] are prepared according to the general

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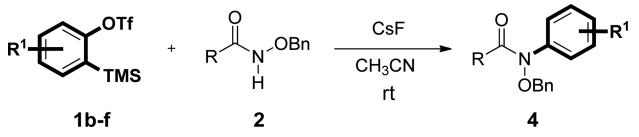
J. Org. Chem. 2016, 81, 3542−3552

Table 3. *N*-Arylation of *O*-Benzyl Hydroxamates with Various Arynes[a,b]



entry	*O*-benzyl hydroxamate	silylaryl triflate	product	yield (%)
1	**2a**	**1b**	**4a**	72
2	**2a**	**1c**	**4b**	87
3	**2a**	**1d**	**4c**	50
4	**2g**	**1e**	**4d**	67[c]
5	**2g**	**1f**	**4e**	91[d]

[a]Reaction conditions: *O*-benzyl hydroxamamate **2** (0.5 mmol), aryne precursor **1b**–**f** (0.6 mmol, 1.2 equiv), CsF (1.2 mmol, 2.4 equiv), CH_3CN (2 mL), rt, 20 h. [b]Isolated yield. [c]The products are isolated as a mixture of *para*- and *meta*-isomers (1:1) based on ^{1}H NMR analysis. [d]The products are isolated as a mixture of *para*- and *meta*-isomers (1.1:1) based on ^{1}H NMR analysis.

procedures, and their analysis data are identical with those in the reported literature.

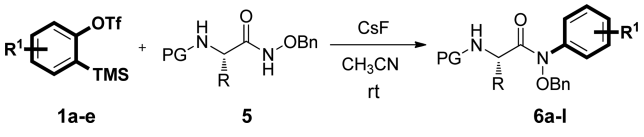
General Procedure for Synthesis of Hydroxamate *O*-Benzyl Esters. To a suspension solution of substituted benzoic acid (5 mmol) in CH_2Cl_2 was added DMF (0.5 mmol) at 0 °C by syringe. Oxalyl chloride (6 mmol) was subsequently added dropwise by syringe. The reaction was allowed to warm to rt gradually and stirred for another 3 h. Then, the reaction mixture was evaporated to afford a clear oil which is used without any further purification. In air, *O*-benzylhydroxylamine hydrochloride (5 mmol) and Na_2CO_3 (10 mmol) were weighed into a flask equipped with a stir bar. CH_2Cl_2 and distilled H_2O (v/v 4:1) were successively added, and the flask was cooled in an ice bath. The above-mentioned benzoyl chloride in CH_2Cl_2 was added in one portion by syringe, and the reaction mixture was stirred for 2 h at 0 °C. Then, the reaction mixture was poured into saturated aq. $NaHCO_3$ and the resulting solution was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuum to afford the crude product, which was purified by flash chromatography with a mixture of EtOAc and hexane as an eluent to afford the desired amide.

*N-(Benzyloxy)-4-(trifluoromethyl)benzamide (**2k**).* Colorless solid; 1.34 g, 91% yield; mp 179–181 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.0 (br, 1H), 7.95 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 6.8 Hz, 2H), 7.44–7.35 (m, 3H), 4.97 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 163.3, 136.4 (d, J_{CF} = 26 Hz), 131.8 (q, J_{CF} = 32 Hz), 129.4, 128.8, 128.4, 128.3, 125.9 (d, J_{CF} = 3.0 Hz), 125.6, 122.9, 120.2, 77.4; FTIR (thin film), cm^{-1} 2928, 1661, 1342, 1210, 1198, 1003, 699; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{12}F_3NO_2$ 296.0893; found 296.0892.

*N-(Benzyloxy)-4-formylbenzamide (**2l**).* Colorless solid; 0.87 g, 68% yield; mp 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 9.93 (br, 1H), 7.83 (s, 4H), 7.37 (m, 2H), 7.32 (m, 3H), 4.99 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5, 138.3, 137.0, 134.9, 129.6, 129.2, 128.8, 128.5, 127.8, 78.3; FTIR (thin film), cm^{-1} 2919, 1712, 1674, 1499, 1322, 810, 721, 698; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{13}NO_3$ 256.0968; found 256.0967.

*N-Benzyloxy Ferrocenylformamide (**2n**).* Yellow solid; 1.91 g, 93% yield; mp 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.8 (br, 1H), 7.48–7.40 (m, 2H), 7.40–7.35 (m, 3H), 5.01 (s, 2H), 4.71 (s, 2H), 4.33 (s, 2H), 4.16 (s, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 135.4, 129.1, 128.6, 128.5, 78.2, 72.7, 70.6, 69.8, 68.2; FTIR (thin film) cm^{-1} 2918, 1666, 1450, 1357, 1299, 778, 692; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{17}FeNO_2$ 336.0681; found 336.0690.

Table 4. *N*-Arylation of *O*-Benzyl Hydroxamates Derived from *N*-Protected Amino Acids[a,b]



entry	*O*-benzyl hydroxamate	silylaryl triflate	product	yield (%)
1	**5a**	**1a**	**6a**	81
2	**5b**	**1a**	**6b**	85
3	**5c**	**1a**	**6c**	83
4	**5d**	**1a**	**6d**	83
5	**5e**	**1a**	**6e**	86
6	**5f**	**1e**	**6f**	90[c]
7	**5f**	**1f**	**6g**	82[c]
8	**5e**	**1e**	**6h**	53[d]
9	**5e**	**1f**	**6i**	61[e]
10	**5f**	**1d**	**6j**	35
11	**5f**	**1b**	**6k**	68
12	**5f**	**1c**	**6l**	61

[a]Reaction conditions: *O*-benzyl hydroxamamate (0.5 mmol), aryne precursor (0.6 mmol, 1.2 equiv), CsF (1.2 mmol, 2.4 equiv), CH_3CN (2 mL), rt, 20 h. [b]Isolated yield. [c]The products are isolated as a mixture of *para*- and *meta*-isomers (1:1) based on ^{1}H NMR analysis. [d]The products are isolated as a mixture of *para*- and *meta*-isomers (3.5:1) based on ^{1}H NMR analysis. [e]The products are isolated as a mixture of *para*- and *meta*-isomers (6:1) based on ^{1}H NMR analysis.

*N-(Benzyloxy)-1-methyl-1H-indole-2-carboxamide (**2p**).* Colorless solid; 1.15 g, 82% yield; mp 141–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (br, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.44–7.28 (m, 7H), 7.13 (t, J = 8.0 Hz, 1H), 6.71 (s, 1H), 5.02 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 139.1, 135.1, 129.3, 128.8, 128.6, 128.4, 125.8, 124.4, 121.9, 120.6, 110.1, 104.5, 78.5, 31.3; FTIR (thin film) cm^{-1} 2921, 1655, 1506, 1474, 1325, 751, 696; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{16}N_2O_2$ 281.1285; found 281.1282.

*N-(Benzyloxy)-1-methyl-1H-indole-3-carboxamide (**2r**).* Colorless solid; 1.19 g, 85% yield; mp 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (br, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.51–7.32 (m, 7H),

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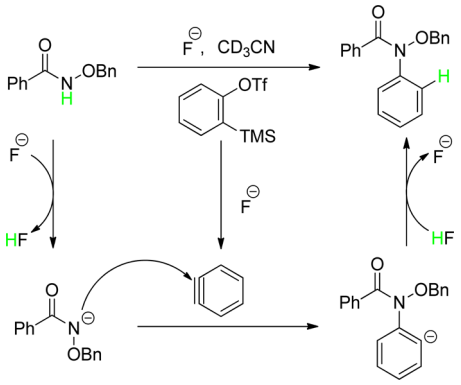
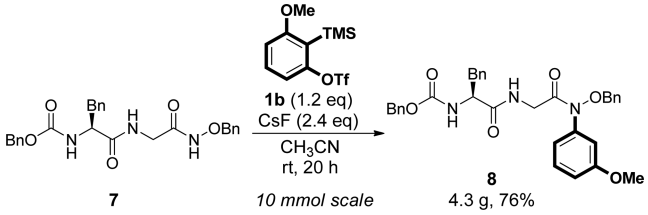
J. Org. Chem. 2016, 81, 3542–3552

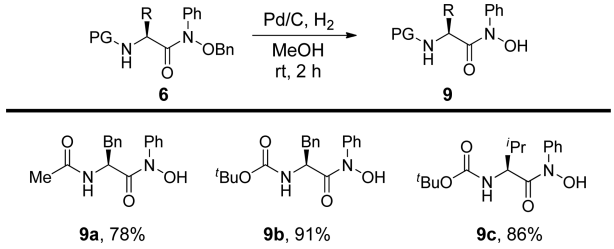
Scheme 5. Plausible Reaction Pathway



Scheme 6. *N*-Arylation of *O*-Benzyl Hydroxamate Derived from Dipeptide



Scheme 7. Synthesis of *N*-Aryl Hydroxamic Acids via Catalytic Hydrogenolysis



7.17 (t, J = 8.0 Hz, 1H), 6.76 (s, 1H), 5.06 (s, 2H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 139.0, 135.0, 129.3, 128.7, 128.5, 128.4, 125.8, 124.3, 121.8, 120.5, 110.0, 104.5, 78.5, 31.2; FTIR (thin film) cm^{-1} 2912, 1661, 1521, 1444, 742; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{16}N_2O_2$ 281.1285; found 281.1281.

N-(Benzyloxy)-1H-indole-3-carboxamide (**2s**). Colorless solid; 1.02 g, 77% yield; mp 204−206 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.6 (br, 1H), 11.1 (br, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 4.0 Hz, 1H), 7.52−7.30 (m, 6H), 7.25−7.16 (m, 2H), 4.95 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 163.9, 136.3, 135.9, 128.7, 128.2, 128.1, 120.7, 120.5, 111.9, 107.3, 77.1; FTIR (thin film) cm^{-1} 2925, 2289, 1658, 1534, 1191, 696; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{14}N_2O_2$ 267.1128; found 267.1130.

(E)-N-(Benzyloxy)-3-(4-chlorophenyl)acrylamide (**2t**). Colorless solid; 1.22 g, 85% yield; mp 184−185 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.40 (br, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.63−7.36 (m, 8H), 6.51 (d, J = 15.8 Hz, 1H), 4.95 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 163.1, 138.7, 136.4, 134.6, 134.0, 129.8, 129.4, 129.2, 128.8, 128.7, 119.8, 77.4; FTIR (thin film) cm^{-1} 2885, 1666, 1580, 1313, 1055, 740, 692; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{14}ClNO_2$ 288.0786; found 288.0783.

(E)-N-(Benzyloxy)-3-(p-tolyl)acrylamide (**2v**). Colorless solid; 1.28 g, 96% yield; mp 123−124 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.27 (br, 1H), 7.75−7.41 (m, 8H), 7.31 (d, J = 7.0 Hz, 2H), 6.39 (d, J = 16.0 Hz, 1H), 4.88 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.3, 141.7, 138.2, 134.0, 131.7, 131.0, 130.7, 130.6, 130.5, 129.8, 119.6, 79.2, 23.1; FTIR (thin film) cm^{-1} 2910, 1671, 1643, 1488, 1344, 799, 685; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{17}NO_2$ 268.1332; found 268.1335.

General Procedure for *N*-arylation of *N*-OBn Hydroxamates with Benzyne. To a solution of *N*-OBn amide **2** (0.5 mmol) and CsF 1.2 mmol) in dry MeCN (5 mL) was added (trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (0.6 mmol) by syringe at rt. The reaction mixture was then allowed to stir overnight at room temperature. Afterward, the starting materials were consumed completely monitored by TLC. The reaction solvent was removed under vacuum, and the resulting residue was purified by flash chromatography column on silica gel, with the mixture of hexane/ethyl acetate as the eluent, to afford the desired *N*-arylation product. The compounds **3i** and **3w** are known, and their analysis data are identical with those reported in the literature.[38]

N-(Benzyloxy)-N-phenylbenzamide (**3a**). Pale yellow oil, 150 mg, 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.59 (m, 2H), 7.52−7.24 (m, 11H), 7.20−7.10 (m, 2H), 4.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 139.6, 134.8, 134.0, 130.5, 129.5, 128.9, 128.8, 128.5, 128.4, 127.9, 126.8, 124.0, 76.3; FTIR (thin film) cm^{-1} 2920, 2865, 1654, 1344, 756, 699; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{17}NO_2$ 304.1332; found 304.1336.

N-(Benzyloxy)-3-methyl-N-phenylbenzamide (**3b**). Pale yellow oil, 133 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.50 (m, 2H), 7.48−7.26 (m, 11H), 7.19−7.13 (m, 2H), 4.85 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 139.7, 137.6, 134.7, 134.1, 131.2, 129.6, 129.1, 128.9, 128.7, 128.4, 127.7, 126.7, 125.6, 124.0, 76.3, 21.2; FTIR (thin film) cm^{-1} 2921, 2849, 1649, 1489, 1348, 1305, 750, 694; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}NO_2$ 318.1489; found 318.1488.

N-(Benzyloxy)-3-methoxy-N-phenylbenzamide (**3c**). Pale yellow oil, 135 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.50 (m, 2H), 7.49−7.10 (m, 11H), 6.99−6.95 (m, 1H), 4.85 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 159.0, 139.7, 135.9, 134.0, 129.5, 129.0, 128.7, 128.4, 126.9, 124.2, 120.9, 116.8, 113.4, 76.3, 55.2; FTIR (thin film) cm^{-1} 2921, 1604, 1530, 1454, 1038, 730, 693; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}NO_3$ 334.1438; found 334.1444.

N-(Benzyloxy)-3-chloro-N-phenylbenzamide (**3d**). Pale yellow oil, 135 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.55 (m, 3H), 7.52−7.39 (m, 4H), 7.40−7.24 (m, 5H), 7.12 (d, J = 7.0 Hz, 2H), 4.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 139.0, 136.4, 133.9, 133.6, 130.5, 129.7, 129.1, 129.0, 128.9, 128.7, 128.5, 127.1, 126.7, 123.9, 76.4; FTIR (thin film) cm^{-1} 2898, 1671, 1489, 1354, 1307, 758, 742, 691; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{16}ClNO_2$ 338.0942; found 338.0941.

N-(Benzyloxy)-3-nitro-N-phenylbenzamide (**3e**). Pale yellow oil, 113 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38−8.35 (m, 1H), 8.28−8.23 (m, 1H), 7.87−7.83 (d, J = 7.7 Hz, 1H), 7.66−7.60 (m, 2H), 7.53−7.42 (m, 3H), 7.36−7.19 (m, 4H), 7.08−6.97 (d, J = 7.2 Hz, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 147.5, 138.3, 136.2, 134.4, 133.2, 129.7, 129.2, 129.1, 128.7, 128.5, 127.4, 124.9, 123.9, 123.8, 76.4; FTIR (thin film) cm^{-1} 1667, 1530, 1348, 751, 698; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{16}N_2O_4$ 349.1183; found 349.1180.

N-(Benzyloxy)-4-methyl-N-phenylbenzamide (**3f**). Pale yellow oil, 140 mg, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.10 (m, 14H), 4.85 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 140.9, 140.0, 134.2, 131.7, 129.5, 128.9, 128.8, 128.5, 128.4, 126.8, 124.3, 76.3, 21.4; FTIR (thin film) cm^{-1} 2921, 2850, 1661, 1489, 1349, 748, 695; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}NO_2$ 318.1489; found 318.1486.

N-(Benzyloxy)-4-methoxy-N-phenylbenzamide (**3g**). Pale yellow oil, 163 mg, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.36−7.32 (m, 3H), 7.30−7.21 (m, 3H), 6.83 (d, J = 8.9 Hz, 2H), 4.86 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 161.5, 140.3, 134.3, 131.0, 129.6, 128.9, 128.8, 128.4, 126.7, 124.3, 113.2, 76.3, 55.3; FTIR (thin film) cm^{-1} 2955, 2849, 1650, 1604, 1254, 1175, 1028, 752, 694; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}NO_3$ 334.1438; found 334.1437.

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J. Org. Chem. 2016, 81, 3542−3552

*N-(Benzyloxy)-4-fluoro-N-phenylbenzamide (**3h**).* Pale yellow oil, 133 mg, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.60 (m, 2H), 7.55−7.46 (m, 2H), 7.38−7.29 (m, 2H), 7.27−7.19 (m, 4H), 7.14−7.06 (m, 2H), 7.03−6.92 (m, 2H), 4.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 163.8 (d, J_{CF} = 252.5 Hz), 139.4, 133.8, 131.1 (d, J_{CF} = 9.0 Hz), 130.7 (d, J_{CF} = 3.0 Hz), 129.5, 128.9, 128.8, 128.4, 126.9, 124.0, 114.9 (d, J_{CF} = 21.0 Hz), 76.3; FTIR (thin film) cm^{-1} 1665, 1601, 1506, 1352, 1230, 844, 749, 694; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{16}FNO_2$ 322.1238; found 322.1235.

*N-(Benzyloxy)-4-chloro-N-phenylbenzamide (**3i**).* Pale yellow oil, 145 mg, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.48 (m, 4H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.35−7.25 (m, 6H), 7.14 (d, *J* = 6.5 Hz, 2H), 4.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 139.3, 136.7, 133.8, 133.0, 130.2, 129.6, 129.0, 128.9, 128.5, 128.1, 127.1, 124.1, 76.4; FTIR (thin film) cm^{-1} 2921, 1661, 1591, 1350, 1089, 841, 741, 696; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{16}ClNO_2$ 338.0942; found 338.0940.

*N-(Benzyloxy)-4-bromo-N-phenylbenzamide (**3j**).* Pale yellow oil, 163 mg, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.35−7.23 (m, 4H), 7.17 (d, *J* = 6.2 Hz, 2H), 7.01 (t, *J* = 8.0 Hz, 2H), 4.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 139.3, 133.8, 133.5, 131.1, 130.3, 129.6, 129.0, 128.9, 128.5, 127.1, 125.1, 124.1, 76.4; FTIR (thin film) cm^{-1} 1664, 1588, 1535, 1010, 848, 755, 741, 696; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{16}BrNO_2$ 382.0437; found 382.0433.

*N-(Benzyloxy)-N-phenyl-4-(trifluoromethyl)benzamide (**3k**).* Pale yellow oil, 131 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.63−7.52 (m, 4H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.35−7.21 (m, 4H), 7.03 (d, *J* = 8.0 Hz, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 138.8, 138.2, 133.5, 132.0 (q, J_{CF} = 32 Hz), 129.6, 129.1, 128.9, 128.8, 128.4, 127.2, 124.8 (q, J_{CF} = 4.0 Hz), 124.6 (q, J_{CF} = 157 Hz), 123.9, 76.4; FTIR (thin film) cm^{-1} 1665, 1323, 1168, 1127, 1048, 694; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{16}F_3NO_2$ 372.1206; found 372.1202.

*N-(Benzyloxy)-4-formyl-N-phenylbenzamide (**3l**).* Pale yellow oil, 86 mg, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.54 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.33−7.21 (m, 4H), 7.06 (d, *J* = 8.0 Hz, 2H), 4.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 167.2, 140.3, 138.7, 137.1, 133.5, 129.5, 129.1, 128.9, 128.4, 127.2, 123.9, 76.4; FTIR (thin film) cm^{-1} 1702, 1665, 1489, 1357, 1305, 1205, 839, 749, 669; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{17}NO_3$ 332.1281; found 332.1285.

*N-(Benzyloxy)-4-cyano-N-phenylbenzamide (**3m**).* Pale yellow oil, 121 mg, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 4H), 7.58−7.52 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.35−7.22 (m, 4H), 7.03 (d, *J* = 6.7 Hz, 2H), 4.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.9, 138.4, 133.3, 131.5, 129.6, 129.1, 129.0, 129.0, 128.5, 127.3, 123.8, 118.1, 113.7, 76.4; FTIR (thin film) cm^{-1} 2229, 1663, 1490, 1359, 751, 695; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{16}N_2O_2$ 329.1285; found 329.1282.

*N-(Benzyloxy)-N-phenyl-ferrocenamide (**3n**).* Brown solid, mp 101−102 °C; 191 mg, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.48−7.35 (m, 7H), 7.29 (t, *J* = 7.4 Hz, 1H), 4.92 (s, 2H), 4.79 (s, 2H), 4.39−4.31 (m, 2H), 4.20 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 139.9, 134.3, 129.3, 128.8, 128.7, 128.5, 126.8, 124.4, 76.2, 74.2, 71.6, 70.7, 69.8; FTIR (thin film) cm^{-1} 1643, 1489, 1440, 1379, 1338, 1301, 759, 710; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{24}H_{21}FeNO_2$ 412.0994; found 412.0996.

*N-(Benzyloxy)-N-phenylfuran-2-carboxamide (**3o**).* Pale yellow oil, 77 mg, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.58 (m, 3H), 7.47−7.42 (m, 2H), 7.40−7.24 (m, 7H), 7.12 (d, *J* = 3.3 Hz, 1H), 6.48 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.93 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 145.8, 145.4, 138.6, 133.7, 129.3, 128.9, 128.8, 128.5, 128.4, 126.9, 126.8, 123.6, 118.2, 111.5, 76.6; FTIR (thin film) cm^{-1} 1721, 1656, 1490, 1468, 1391, 1358, 755, 695; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{18}H_{15}NO_3$ 294.1125; found 294.1128.

*N-(Benzyloxy)-1-methyl-N-phenyl-1H-indole-2-carboxamide (**3p**).* Pale yellow oil, 158 mg, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.56 (m, 3H), 7.43−7.36 (m, 2H), 7.36−7.16 (m, 8H), 7.12 (ddd, *J* = 7.9, 6.6, 1.3 Hz, 1H), 6.91 (s, 1H), 4.90 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 139.6, 138.3, 134.0, 130.4, 129.7, 128.9, 128.8, 128.3, 127.0, 126.1, 124.2, 124.0, 122.1, 120.1, 109.8, 108.2, 76.5, 31.6; FTIR (thin film) cm^{-1} 1648, 1515, 1487, 1464, 1391, 1320, 746, 695; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{23}H_{20}N_2O_2$ 357.1598; found 357.1595.

*N-(Benzyloxy)-N-phenyl-1H-indole-2-carboxamide (**3q**).* Pale yellow oil, 145 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.76−7.71 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.54−7.46 (m, 2H), 7.45−7.26 (m, 7H), 7.17 (br, 1H), 7.14−7.08 (m, 1H), 5.01 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 138.9, 136.0, 133.7, 129.5, 129.1, 129.0, 128.7, 128.2, 128.0, 127.2, 125.0, 124.0, 122.5, 120.4, 111.8, 109.2, 76.8; FTIR (thin film) cm^{-1} 2925, 1654, 1497, 1390, 745, 694; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{18}N_2O_2$ 343.1441; found 343.1440.

*N-(Benzyloxy)-1-methyl-N-phenyl-1H-indole-3-carboxamide (**3r**).* Pale yellow oil, 162 mg, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.77 (s, 1H), 7.74−7.70 (m, 2H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.41−7.24 (m, 9H), 4.93 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 140.1, 136.3, 134.6, 134.4, 129.4, 128.9, 128.7, 128.6, 126.1, 123.6, 122.8, 122.7, 121.7, 109.2, 107.5, 76.5, 33.2; FTIR (thin film) cm^{-1} 2920, 2849, 1644, 1533, 1439, 747; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{23}H_{20}N_2O_2$ 357.1598; found 357.1602.

*N-(Benzyloxy)-N-phenyl-1H-indole-3-carboxamide (**3s**).* Pale yellow oil, 152 mg, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.43−8.38 (m, 1H), 7.71 (d, *J* = 3.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.34−7.16 (m, 10H), 4.88 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 139.9, 135.3, 134.2, 130.5, 129.3, 128.8, 128.5, 127.6, 126.5, 124.1, 122.9, 122.1, 121.7, 111.3, 108.6, 76.3; FTIR (thin film) cm^{-1} 2950, 1666, 1540, 1412, 738, 692; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{18}N_2O_2$ 343.1441; found 343.1445.

*(E)-N-(Benzyloxy)-3-(4-chlorophenyl)-N-phenylacrylamide (**3t**).* Pale yellow oil, 161 mg, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.58 (m, 3H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.43−7.27 (m, 10H), 6.95 (br, 1H), 4.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 142.1, 138.5, 135.6, 134.0, 133.5, 129.5, 129.1, 129.0, 128.9, 128.7, 126.6, 123.3, 117.8, 76.9; FTIR (thin film) cm^{-1} 2920, 2849, 1644, 1533, 1439, 747; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{18}ClNO_2$ 364.1099; found 364.1101.

*(E)-N-(Benzyloxy)-3-(4-methoxyphenyl)-N-phenylacrylamide (**3u**).* Pale yellow oil, 163 mg, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 15.7 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.46−7.35 (m, 9H), 7.26 (t, *J* = 8.0 Hz, 1H), 6.98−6.82 (m, 3H), 4.91 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 161.0, 143.3, 138.8, 134.1, 129.6, 129.4, 128.9, 128.7, 128.6, 127.7, 126.3, 123.1, 114.6, 114.1, 76.8, 55.2; FTIR (thin film) cm^{-1} 1600, 1511, 1355, 1252, 1172, 825, 758, 698; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{23}H_{21}NO_3$ 360.1594; found 360.1597.

*(E)-N-(Benzyloxy)-3-(4-methylphenyl)-N-phenylacrylamide (**3v**).* Pale yellow oil, 151 mg, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 15.8 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.49−7.34 (m, 9H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.06−6.90 (br, 1H), 4.92 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 143.7, 140.2, 138.8, 134.1, 132.3, 129.5, 129.4, 129.0, 128.8, 128.6, 128.0, 126.4, 123.2, 116.1, 76.9, 21.4; FTIR (thin film) cm^{-1} 1663, 1620, 1490, 1354, 809, 757, 698; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{23}H_{21}NO_2$ 344.1645; found 344.1646.

*N-(Benzyloxy)-2-phenoxy-N-phenylacetamide (**3x**).* Brown oil, 125 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 2H), 7.48−7.34 (m, 7H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.18−7.13 (m, 2H), 6.66−6.58 (m, 2H), 4.84 (s, 2H), 4.68 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 156.7, 137.3, 133.5, 130.0, 129.5, 129.2, 129.0, 128.9, 126.8, 126.2, 122.5, 115.9, 76.1, 66.3; FTIR (thin film) cm^{-1} 1705, 1546, 1324, 748, 693; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{19}NO_3$ 334.1438; found 334.1435.

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J. Org. Chem. 2016, 81, 3542−3552

General Procedure for *N*-Arylation of *O*-Benzyl Hydroxamates with Various Arynes. To a solution of *N*-OBn amide **2** (0.5 mmol) and CsF (1.2 mmol) in dry MeCN (5 mL) was added the aryne precursor **1b−f** (0.6 mmol) by syringe at rt. The reaction mixture was then allowed to stir overnight at room temperature. Afterward, the starting materials were consumed completely monitored by TLC. The reaction solvent was removed under vacuum, and the resulting residue was purified by flash chromatography column on silica gel, with the mixture of hexane/ethyl acetate as the eluent, to afford the desired *N*-arylation product **4a−e**.

*N-(Benzyloxy)-N-(3-methoxyphenyl)benzamide (**4a**).* Pale yellow oil, 120 mg, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.57 (m, 2H), 7.46−7.39 (m, 1H), 7.38−7.23 (m, 6H), 7.15−7.05 (m, 4H), 6.82−6.76 (m, 1H), 4.82 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 159.9, 140.7, 134.8, 133.9, 130.5, 129.6, 129.5, 128.8, 128.4, 127.8, 116.2, 112.7, 109.3, 76.3, 55.3; FTIR (thin film) cm^{-1} 2922, 1604, 1539, 1030, 744, 694; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{19}NO_3$ 334.1438; found 334.1435.

*N-(Benzyloxy)-N-(naphthalene-2-yl)benzamide (**4b**).* Red-brown oil, 153 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.88−7.74 (m, 3H), 7.64 (m, 3H), 7.53−7.45 (m, 2H), 7.45−7.40 (m, 1H), 7.36−7.25 (m, 5H), 7.13 (d, *J* = 6.5 Hz, 2H), 4.86 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 137.0, 134.7, 134.0, 133.2, 131.9, 130.5, 129.6, 128.9, 128.8, 128.5, 128.4, 128.0, 127.9, 127.6, 126.6, 126.3, 122.5, 76.4; FTIR (thin film) cm^{-1} 2950, 2865, 1652, 1466, 1301, 758, 699; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{24}H_{19}NO_2$ 354.1489; found 354.1486.

*N-(Benzyloxy)-N-(3,4-difluorophenyl)benzamide (**4c**).* Pale yellow oil, 84 mg, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.61 (m, 2H), 7.53−7.47 (m, 2H), 7.42−7.36 (m, 2H), 7.35−7.24 (m, 4H), 7.20−7.12 (m, 1H), 7.06−6.98 (d, *J* = 6.9 Hz, 2H), 4.74 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 150.4 (dd, J_{CF} = 154.5, 13.1 Hz), 147.9 (dd, J_{CF} = 140.4, 13.0 Hz), 136.0 (dd, J_{CF} = 8.0, 4.0 Hz), 134.1, 133.3, 130.8, 129.6, 129.0, 128.52, 128.5, 127.9, 119.2 (dd, J_{CF} = 5.0, 4.0 Hz), 117.2 (d, J_{CF} = 16 Hz), 112.8 (d, J_{CF} = 21 Hz), 76.8; FTIR (thin film) cm^{-1} 1669, 1589, 1511, 1360, 1209, 852, 750, 694; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{15}F_2NO_2$ 340.1144; found 340.1141.

*N-(Benzyloxy)-4-methoxy-N-(4-methoxyphenyl)benzamide and N-(Benzyloxy)-4-methoxy-N-(3-methoxyphenyl)benzamide (**4d**).* Products are isolated as a *para*-/*meta*- mixture of *approx.* 1:1 based on the analysis of ^{1}H NMR spectra, which cannot be isolated as the single isomer by conventional column chromatography. Pale yellow oil, 121 mg, 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.44 (m, 4H), 7.23−7.15 (m, 6H), 7.14−7.05 (m, 6H), 6.95−6.86 (m, 4H), 6.75−6.62 (m, 6H), 4.75 (s, 2H), 4.72 (s, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.45, 167.43, 161.07, 161.05, 159.47, 159.45, 140.81, 139.79, 133.75, 133.73, 130.37, 130.36, 129.1, 128.3, 127.9, 126.13, 126.10, 116.0, 112.70, 112.69, 112.1, 109.2, 75.7, 54.8. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{21}NO_4$ 364.1543; found 364.1541.

*N-(Benzyloxy)-4-methoxy-N-(4-methylphenyl)benzamide and N-(Benzyloxy)-4-methoxy-N-(3-methylphenyl)benzamide (**4e**).* Products are isolated as a *para*-/*meta*- mixture of *approx.* 1.1:1 based on the analysis of ^{1}H NMR spectra, which cannot be isolated as the single isomer by conventional column chromatography. Pale yellow oil, 151 mg, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.58 (m, 4H), 7.35−7.28 (m, 8H), 7.26−7.21 (m, 6H), 7.19−7.14 (m, 2H), 7.10−7.03 (m, 1H), 6.87−6.78 (m, 4H), 4.90 (s, 2H), 4.88 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.78, 167.68, 161.28, 161.24, 139.9, 138.7, 137.5, 136.8, 134.2, 134.1, 130.7, 129.4, 128.57, 128.55, 128.2, 127.5, 126.49, 126.46, 124.9, 124.7, 121.4, 112.9, 75.9, 75.7, 55.11, 55.09, 21.2, 20.8. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{21}NO_3$ 348.1594; found 348.1592.

General Procedure for Synthesis of *O*-Benzyl Hydroxamates (5a−f) of *N*-Protected Amino Acids. To a cooled (0 °C) solution of *N*-protected amino acid (10 mmol) and *O*-benzylhydroxylamine hydrochloride (12 mmol) in $CHCl_3$ was added successively trimethylamine (12 mmol). After the reaction mixture was stirred for 30 min at 0 °C, 1-hydroxybenzotriazole (HOBt) (10 mmol) in THF (20 mL) and *N*,*N*-dicyclohexylvcarbiimide (DCC) (11 mmol) in $CHCl_3$ (15 mL) were added into the mixture in turn. Therefore, the mixture was allowed to warm to room temperature and stirred overnight. Once the starting materials were consumed completely monitored by TLC, the reaction mixture was filtrated via a short pad of Celite to remove off the resulting dicyclohexylurea (DCU). After removal of solvent under vacuum, the residue was redissolved in EtOAc (50 mL) and washed successively with water (30 mL), 10% aq. citric acid (2 × 30 mL), water (30 mL), saturated aq. $NaHCO_3$, (2 × 30 mL), water (30 mL), and saturated aq. NaCl (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude amide product was purified by silica gel chromatography column with the mixture of hexane/ethyl acetate as the eluent to give the pure *N*-OBn amides **5**.

*(S)-2-Acetamido-N-(benzyloxy)-3-phenylpropanamide (**5a**).* Colorless solid, mp 185−187 °C; 2.65 g, 85% yield. $[\alpha]^{25.8}_{589}$ −34.7 (*c* 0.144, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (br, 1H), 7.35−7.14 (m, 10H), 6.96 (d, *J* = 7.2 Hz, 1H), 4.75−4.55 (m, 3H), 3.15−2.95 (m, 2H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.5, 136.3, 135.0, 129.3, 129.1, 128.57, 128.52, 128.3, 126.9, 78.1, 51.9, 38.3, 22.7; FTIR (thin film) cm^{-1} 3280, 1710, 1669, 1521, 1259, 1278, 750, 698; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{18}H_{20}N_2O_3$ 313.1547; found 313.1544.

*(S)-Benzyl (1-((Benzyloxy)amino)-1-oxo-3-phenylpropan-2-yl)-carbamate (**5b**).* Colorless solid, mp 143−145 °C; 3.27 g, 81% yield. $[\alpha]^{25.8}_{589}$ −7.2 (*c* 0.110, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br, 1H), 7.48−7.05 (m, 16H), 5.58−5.44 (m, 1H), 5.05−4.88 (m, 2H), 4.81−4.71 (m, 1H), 4.69−4.60 (m, 1H), 4.35−4.20 (m, 1H), 3.10−2.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 155.9, 136.0, 135.8, 134.8, 129.3, 129.2, 128.6, 128.5, 128.4, 128.2, 127.9, 127.0, 78.2, 67.1, 53.9, 38.2; FTIR (thin film) cm^{-1} 3320, 1703, 1656, 1491, 1239, 750, 696; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{24}H_{24}N_2O_4$ 405.1809; found 405.1806.

*(S)-N-(Benzyloxy)-2-(4-methylphenylsulfonamido)-3-phenylpropanamide (**5c**).* Colorless solid, mp 139−141 °C; 3.77 g, 89% yield. $[\alpha]^{25.8}_{589}$ −22.4 (*c* 0.262, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (br, 1H), 7.53 (d, *J* = 6.8 Hz, 2H), 7.48−7.24 (m, 5H), 7.23−7.20 (m, 5H), 6.95−6.90 (m, 2H), 5.245.18 (m, 1H), 4.72−4.68 (m, 2H), 3.90−3.80 (m, 1H), 2.93−2.88 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 143.8, 135.8, 134.9, 134.7, 129.7, 129.2, 128.8, 128.7, 128.5, 127.2, 127.0, 78.4, 56.3, 38.3, 21.4; FTIR (thin film) cm^{-1} 3289, 1674, 1472, 1357, 1029, 886, 752, 696; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{23}H_{24}N_2O_4S$ 425.1530; found 425.1531.

*(S)-tert-Butyl (1-((Benzyloxy)amino)-3-methyl-1-oxobutan-2-yl)-carbamate (**5d**).* Colorless solid, mp 133−134 °C; 2.42 g, 75% yield. $[\alpha]^{25.8}_{589}$ 11.5 (*c* 0.104, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (br, 1H), 7.48−7.30 (m, 5H), 5.33−5.26 (m, 1H), 4.89 (s, 2H), 3.82−3.74 (m, 1H), 2.06−1.96 (m, 1H), 1.42 (s, 9H), 0.93 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 155.9, 135.0, 129.1, 128.6, 128.4, 80.0, 78.2, 57.6, 30.7, 28.2, 19.0, 18.2; FTIR (thin film) cm^{-1} 3320, 1726, 1670, 1456, 1170, 740, 698; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{17}H_{26}N_2O_4$ 323.1965; found 323.1963.

*(S)-tert-Butyl (1-((Benzyloxy)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**5e**).* Colorless solid, mp 129−130 °C; 2.42 g, 72% yield. $[\alpha]^{25.8}_{589}$ −1.2 (*c* 0.288, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br, 1H), 7.40−7.30 (m, 5H), 5.38−5.32 (m, 1H), 4.90 (s, 2H), 3.82−3.76 (m, 1H), 1.42 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 155.9, 135.0, 129.1, 128.6, 128.4, 80.0, 78.2, 59.3, 34.4, 28.3, 26.3; FTIR (thin film) cm^{-1} 3350, 1718, 1690, 1468, 1215, 755, 702; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{18}H_{28}N_2O_4$ 337.2122; found 337.2129.

*(S)-tert-Butyl (1-((Benzyloxy)amino)-1-oxo-3-phenylpropan-2-yl)-carbamate (**5f**).* Colorless solid, mp 137−138 °C; 3.26 g, 88% yield. $[\alpha]^{25.8}_{589}$ −17.8 (*c* 0.112, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (br, 1H), 7.33−7.15 (m, 10H), 5.21 (br, 1H), 4.20−4.62 (m, 2H), 4.21 (br, 1H), 3.10−2.95 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 155.5, 136.3, 134.9, 129.4, 129.2, 128.6, 128.5, 127.0, 80.4, 78.3, 53.6, 49.18, 38.3, 28.2; FTIR (thin film) cm^{-1} 3426, 1715,

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1692, 1500, 1198, 748, 696; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{26}N_2O_4$ 371.1965; found 371.1963.

General Procedure for *N*-Arylation of *O*-Benzyl Hydroxamates of *N*-Protected Amino Acids. To a solution of *N*-OBn amino acid amide **5** (0.5 mmol) and CsF (1.2 mmol) in dry MeCN (5 mL) was added the aryne precusor **1** (0.6 mmol) by syringe at room temperature. The reaction mixture was then allowed to stir overnight at room temperature. Afterward, the starting materials were consumed completely monitored by TLC. The reaction solvent was removed under vacuum, and the resulting residue was purified by flash chromatography column on silica gel, with the mixture of hexane/ethyl acetate as the eluent, to afford the desired *N*-arylation product **6a**–**l**.

*(S)-2-Acetamido-N-(benzyloxy)-N,3-diphenylpropanamide (**6a**).* Pale yellow oil, 157 mg, 81% yield. $[\alpha]^{25.8}_{589}$ 73.6 (c 0.190, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–6.95 (m, 15H), 6.62–6.56 (m, 1H), 5.53 (br, 1H), 5.02–4.96 (m, 1H), 4.80–4.74 (m, 1H), 3.16–3.10 (m, 1H), 2.98–2.90 (m, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 169.9, 137.6, 136.2, 133.4, 129.6, 129.3, 129.0, 128.8, 128.6, 128.3, 126.7, 122.8, 77.0, 51.6, 38.1, 23.0; FTIR (thin film) cm^{-1} 3321, 1675, 1654, 1539, 1490, 1385, 1287, 759, 698; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{24}N_2O_3$ 389.1860; found 389.1867.

*(S)-Benzyl (1-((Benzyloxy)(phenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**6b**).* Pale yellow oil, 204 mg, 85% yield. $[\alpha]^{25.8}_{589}$ 70.4 (c 0.176, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–6.95 (m, 20H), 5.63–5.55 (m, 1H), 5.27 (br, 1H), 5.16–5.06 (m, 2H), 4.97–4.88 (m, 1H), 4.80–4.75 (m, 1H), 3.14–3.09 (m, 1H), 2.93–2.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 155.9, 137.6, 136.3, 133.4, 129.5, 129.4, 129.1, 128.9, 128.7, 128.4, 128.3, 128.0, 127.9, 126.8, 122.7, 77.0, 66.7, 53.5, 38.6; FTIR (thin film) cm^{-1} 1717, 1672, 1493, 1391, 1249, 754, 697; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{30}H_{28}N_2O_4$ 481.2122; found 481.2132.

*(S)-N-(Benzyloxy)-2-(4-methylphenylsulfonamido)-N,3-diphenylpropanamide (**6c**).* Pale yellow oil, 207 mg, 83% yield. $[\alpha]^{25.8}_{589}$ 13.0 (c 0.478, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.0 Hz, 2H), 7.42–7.34 (m, 5H), 7.32–7.21 (m, 5H), 7.18–7.10 (m, 6H), 7.03–6.97 (m, 2H), 5.85–5.77 (m, 1H), 4.80–4.70 (m, 1H), 4.60–4.48 (m, 2H), 3.10–3.00 (m, 1H), 2.90–2.78 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.2, 137.24, 137.0, 136.8, 135.7, 133.1, 129.5, 129.3, 129.2, 129.1, 128.77, 128.70, 128.2, 127.2, 126.8, 126.7, 122.6, 76.6, 55.4, 39.2, 21.3; FTIR (thin film) cm^{-1} 3250, 1668, 1492, 1375, 1159, 1092, 814, 761, 692; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{28}N_2O_4S$ 501.1843; found 501.1840.

*(S)-tert-Butyl (1-((Benzyloxy)(phenyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**6d**).* Pale yellow oil, 165 mg, 83% yield. $[\alpha]^{25.8}_{589}$ − 75.5 (c 0.196, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.15 (m, 10H), 5.18 (s, 1H), 4.94–4.78 (m, 3H), 2.10–2.00 (m, 1H), 1.40 (s, 9H), 0.90 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 155.8, 137.9, 133.5, 129.5, 128.9, 128.8, 128.6, 126.5, 122.7, 79.3, 76.8, 56.2, 53.3, 31.1, 28.3, 19.5, 17.0; FTIR (thin film) cm^{-1} 3343, 1711, 1674, 1491, 1368, 1169, 760, 706; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{30}N_2O_4$ 399.2278; found 399.2276.

*(S)-tert-Butyl (1-((Benzyloxy)(phenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**6e**).* Pale yellow oil, 177 mg, 86% yield. $[\alpha]^{25.8}_{589}$ 58.3 (c 0.288, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.30 (m, 10H), 5.34–5.30 (m, 1H), 5.12–5.00 (m, 2H), 4.83–4.77 (m, 1H), 1.49 (s, 9H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.8, 137.9, 133.8, 129.8, 128.9, 128.8, 128.7, 126.6, 123.0, 79.5, 77.0, 57.2, 35.7, 28.4, 26.3; FTIR (thin film) cm^{-1} 3359, 1712, 1675, 1488, 1196, 759, 700; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{32}N_2O_4$ 413.2435; found 413.2432.

*(S)-tert-Butyl (1-((Benzyloxy)(4-methoxyphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate and (S)-tert-Butyl (1-((Benzyloxy)(3-methoxyphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**6f**).* Products are isolated as a *para*-/*meta*-isomer mixture of *approx.* 1:1 based on the analysis of ^{1}H NMR spectra, which cannot be isolated as the single isomer by conventional column chromatography. Pale yellow oil, 214 mg, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.10 (m, 13H), 6.90–6.85 (m, 1H), 5.30–5.18 (m, 2H), 5.00–4.93 (m, 1H), 4.86–4.79 (m, 1H), 3.85 (s, 3H), 3.22–3.14 (m, 1H), 3.00–2.93 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.16, 171.12, 159.9, 155.1, 138.9, 136.4, 133.4, 129.5, 129.4, 129.0, 128.6, 128.2, 126.6, 114.9, 112.6, 108.2, 79.5, 76.9, 55.3, 53.0, 38.8, 28.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}N_2O_5$ 477.2384; found 477.2381.

*(S)-tert-Butyl (1-((Benzyloxy)(4-methylphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate and (S)-tert-Butyl (1-((Benzyloxy)(3-methylphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**6g**).* Products are isolated as a *para*-/*meta*-isomer mixture of *approx.* 1:1 based on the analysis of ^{1}H NMR spectra, which cannot be isolated as the single isomer by conventional column chromatography. Pale yellow oil, 188 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.06 (m, 15H), 5.30–5.16 (m, 2H), 4.93–4.86 (m, 1H), 4.75–4.69 (m, 1H), 3.7–3.08 (m, 1H), 2.93–2.87 (m, 1H), 2.36 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.9, 155.1, 138.7, 137.6, 136.7, 136.4, 135.1, 133.5, 129.4, 128.9, 128.6, 128.2, 127.5, 126.6, 123.7, 123.1, 119.9, 79.4, 76.6, 52.9, 38.8, 28.2, 21.3, 21.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}N_2O_4$ 461.2435; found 461.2434.

*(S)-tert-Butyl (1-((Benzyloxy)(4-methoxyphenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate and (S)-tert-Butyl (1-((Benzyloxy)(3-methoxyphenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**6h**).* Products are isolated as a *para*-/*meta*-isomer mixture of *approx.* 3.5:1 based on the analysis of ^{1}H NMR spectra, which cannot be isolated as the single isomer by conventional column chromatography. Pale yellow oil, 117 mg, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.25 (m, 9.77H), 6.97 (d, J = 8.0 Hz, 2.68H), 5.40–5.30 (m, 1H), 5.30–5.25 (m, 0.31H), 5.12–5.06 (m, 1H), 5.05–5.00 (m, 0.32H), 4.99–4.90 (m, 0.35H), 4.85–4.78 (m, 1H), 3.86 (s, 3.86H), 1.52 (s, 9H), 1.29 (s, 2.48H), 1.05 (s, 9H), 0.89 (s, 2.53H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 158.3, 155.7, 133.9, 130.6, 129.7, 129.5, 128.8, 128.6, 128.3, 125.5, 114.4, 114.0, 79.3, 76.5, 56.9, 55.4, 35.7, 28.3, 26.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{34}N_2O_5$ 443.2540; found 443.2544.

*(S)-tert-Butyl (1-((Benzyloxy)(4-methylphenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate and (S)-tert-Butyl (1-((Benzyloxy)(3-methylphenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**6i**).* Products are isolated as a *para*-/*meta*-isomer mixture of *approx.* 6:1 based on the analysis of ^{1}H NMR spectra, which cannot be isolated as the single isomer by conventional column chromatography. Pale yellow oil, 130 mg, 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.05 (m, 11.3H), 5.40–5.25 (m, 1H), 5.20–4.95 (m, 2.64H), 4.85–4.80 (m, 1H), 2.42 (m, 3H), 2.33 (m, 0.49H), 1.53 (s, 9H), 1.46 (s, 1.51H), 1.05 (s, 9H), 1.00 (s, 1.49H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.2, 155.7, 138.7, 137.7, 133.8, 129.7, 129.3, 128.8, 128.6, 128.0, 127.9, 127.5, 123.9, 123.3, 120.1, 79.3, 76.8, 57.0, 35.7, 28.3, 28.2, 26.5, 26.3, 21.4, 21.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{34}N_2O_4$ 427.2591; found 427.2594.

*(S)-tert-Butyl (1-((Benzyloxy)(3,4-difluorophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**6j**).* Pale yellow oil, 84 mg, 35% yield. $[\alpha]^{25.8}_{589}$ 53.8 (c 0.512, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–6.95 (m, 13H), 5.16–5.06 (m, 2H), 4.90–4.80 (m, 1H), 4.71–4.60 (m, 1H), 3.05–2.95 (m, 1H), 2.85–2.75 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 155.1, 149.9 (d, J_{CF} = 250.5 Hz), 149.8 (d, J_{CF} = 250.5 Hz), 136.1, 134.4 (d, J_{CF} = 5.0 Hz), 133.0, 129.5, 129.4, 129.2, 128.7, 128.3, 126.8, 118.4, 117.1 (d, J_{CF} = 18 Hz), 112.0 (d, J_{CF} = 22 Hz), 79.7, 77.3, 52.9, 38.7, 28.2; FTIR (thin film) cm^{-1} 3432, 1710, 1686, 1512, 1368, 1169, 752, 699; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{28}F_2N_2O_4$ 483.2090; found 483.2091.

*(S)-tert-Butyl (1-((Benzyloxy)(3-methoxyphenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**6k**).* Pale yellow oil, 162 mg, 68% yield. $[\alpha]^{25.8}_{589}$ 49.0 (c 0.706, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–6.60 (m, 15H), 5.33–5.22 (m, 2H), 5.02–4.95 (m, 1H), 4.85–4.80 (m, 1H), 3.85 (s, 3H), 3.22–3.15 (m, 1H), 3.00–2.91 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.9, 155.1, 138.8, 136.3, 133.4, 129.5, 129.4, 129.0, 128.6, 128.2, 126.6, 114.8, 112.5, 108.2, 79.4, 76.8, 55.3, 53.0, 38.7, 28.2; FTIR (thin film) cm^{-1} 3328, 1710, 1675, 1490, 1388, 1367, 1169, 752, 699; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}N_2O_5$ 477.2384; found 477.2381.

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J. Org. Chem. 2016, 81, 3542–3552

*(S)-tert-Butyl (1-((Benzyloxy)(naphthalene-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**6l**).* Pale yellow oil, 151 mg, 61% yield. $[\alpha]^{25.8}_{589}$ 54.8 (*c* 0.516, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.10−7.10 (m, 19H), 5.35−5.27 (m, 2H), 5.05−5.00 (m, 1H), 4.90−4.80 (m, 1H), 3.29−3.18 (m, 1H), 3.05−2.96 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 155.2, 136.5, 135.3, 133.5, 133.2, 132.0, 129.67, 129.63, 129.1, 128.7, 128.4, 128.1, 127.7, 126.8, 126.7, 126.3, 121.5, 121.3, 79.6, 77.1, 53.1, 38.9, 28.4; FTIR (thin film) cm^{-1} 3325, 1706, 1665, 1453, 1372, 1160, 755, 694; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{31}H_{33}N_2O_4$ 497.2435; found 497.2433.

Procedure for Selective *N*-Arylation of *O*-Benzyl Hydroxamate (7) Derived from Dipeptide. Dipeptide-derived amide Cbz-Phe-Gly-NHOBn **7** was prepared smoothly in good yield according to the previous method.[39] General procedure for *N*-arylation of *O*-benzyl hydroxamates of *N*-protected amino acids was followed: To a solution of compound **7** (10 mol) and CsF 24 mol) in MeCN (80 mL) was added a solution of aryne precusor **1d** (12 mol) in MeCN (20 mL) by syringe at rt. The reaction mixture was then allowed to stir overnight at room temperature. Afterward, the starting materials were consumed completely monitored by TLC. The reaction solvent was removed under vacuum, and the resulting residue was purified by flash chromatography column on silica gel, with the mixture of hexane/ethyl acetate as the eluent, to afford the desired *N*-arylation product **8** (4.3 g, 76% yield). Colorless solid, mp 101−104 °C, 76% yield. $[\alpha]^{25.8}_{589}$ −11.0 (*c* 0.182, $CDCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.10 (m, 16H), 6.94 (d, *J* = 8 Hz, 2H), 6.68 (br, 1H), 5.40−5.35 (m, 1H), 5.15−4.95 (m, 2H), 4.85−4.75 (m, 2H), 4.26−4.19 (m, 1H), 4.18−3.80 (m, 2H), 3.83 (s, 3H), 3.20−2.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 167.7, 155.8, 136.2, 129.5, 129.2, 128.8, 128.7, 128.6, 128.4, 128.0, 127.9, 126.9, 114.3, 76.0, 66.9, 56.0, 55.4, 41.4, 38.4; FTIR (thin film) cm^{-1} 3369, 3244, 1716, 1677, 1665, 1489, 1394, 1240, 1169, 814, 745, 697; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{33}H_{33}N_3O_6$ 568.2442; found 568.2443.

General Procedure for Synthesis of *N*-Aryl Hydroxamic Acids (9). In a sealable vial, *N*-aryl derivative **6** (0.25 mmol) of *O*-benzyl hydroxamate was dissolved in MeOH (5 mL) and to the resulting solution was thus added 10% Pd/C (5 mol %) successfully. The reaction mixture was then stirred under 1 atm of H_2 (balloon) for 2 h. After filtration via a short pad of Celite, the solvent was removed under vacuum to give the pure *N*-aryl hydroxamic acid **9a**−**c**.

*(S)-2-Acetamido-N-hydroxy-N,3-diphenylpropanamide (**9a**).* White solid, mp 147−148 °C; 58 mg, 78% yield. $[\alpha]^{25.8}_{589}$ −8.9 (*c* 0.090, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (br, 1H), 7.46−7.35 (m, 2H), 7.29−7.17 (m, 7H), 7.10−7.01 (m, 2H), 5.10−5.00 (m, 1H), 3.75−3.45 (m, 1H), 3.22−3.02 (m, 2H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.0, 137.6, 136.5, 129.3, 128.7, 128.5, 126.9, 124.3, 120.0, 55.6, 38.7, 22.9; FTIR (thin film) cm^{-1} 3340, 1674, 1605, 1489, 1120, 759, 696; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{18}N_2O_3$ 299.1390; found 299.1391.

*(S)-tert-Butyl (1-(Hydroxy(phenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**9b**).* White solid, mp 198−199 °C; 81 mg, 91% yield. $[\alpha]^{25.8}_{589}$ −31.7 (*c* 0.082, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (br, 1H), 7.41−7.20 (m, 9H), 7.15−7.05 (m, 1H), 5.27−5.14 (m, 1H), 4.51−4.45 (m, 1H), 3.20−3.10 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 155.8, 141.7, 137.2, 129.3, 128.9, 128.8, 127.0, 124.5, 120.0, 80.6, 54.1, 38.3, 28.2; FTIR (thin film) cm^{-1} 3286, 1664, 1598, 1548, 1496, 1166, 750, 695; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{24}N_2O_4$ 357.1809; found 357.1806.

*(S)-tert-Butyl (1-(Hydroxy(phenyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**9c**).* White solid, mp 176−177 °C; 66 mg, 86% yield. $[\alpha]^{25.8}_{589}$ 40.9 (*c* 0.132, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (br, 1H), 7.51−7.44 (m, 2H), 7.29−7.20 (m, 2H), 7.10−7.05 (m, 1H), 5.35−5.28 (m, 1H), 4.10−4.04 (m, 1H), 2.25−2.16 (m, 1H), 1.44 (s, 9H), 1.10−0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 156.3, 137.5, 128.8, 124.3, 119.9, 80.2, 60.9, 30.6, 28.3, 19.3; FTIR (thin film) cm^{-1} 3260, 1674, 1610, 1483, 1369, 1168, 749, 698; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{24}N_2O_4$ 309.1809; found 309.1808.

Regioselectivity Confirmation of N−H Arylation in *O*-Benzyl Hydroxamates (6c) from *N*-Protected Amino Acids. To a cooled (0 °C) solution of *N*-Ts Phe (2 mmol) in dichloromethane (5 mL) was added dropwise a solution of *O*-benzyl *N*-phenylhydroamine (2.5 mmol) in dichloromethane (5 mL). 1-Hydroxybenzotriazole (2.4 mmol) in dimethylformamide (5 mL) was added followed by 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (3 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature overnight. After the starting materials were consumed monitored by TLC, the reaction mixture was diluted by dichloromethane (10 mL) and washed successively with water (10 mL), 10% aqueous citric acid (10 mL), water (10 mL), 10% aqueous $NaHCO_3$ (10 mL), water (10 mL), and finally brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The obtained crude amide product was purified by silica gel chromatography to give pure **6c** in 83% yield. Its ^1H and ^{13}C NMR data as well as specific rotation are in good agreement with those of the above-mentioned product prepared by insertion of an aryne. The preservation of the stereochemistry for compound **6c** prepared by insertion of the aryne is validated by comparison of the specific rotation based on the polarimetric analysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00111.

Copies of ^1H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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