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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.5b01992 • Publication Date (Web): 15 Oct 2015

Copper-Catalyzed *para*–Selective C–H Amination of Electron-Rich Arenes

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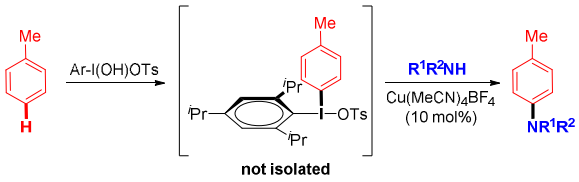


Abstract: A one-pot two-step method for *para*-selective C−H amination of carbocyclic arenes comprises the *in situ* formation of unsymmetrical diaryl-λ^3-iodanes followed by their Cu(I)-catalyzed reaction with a range of *N*-unprotected amines.

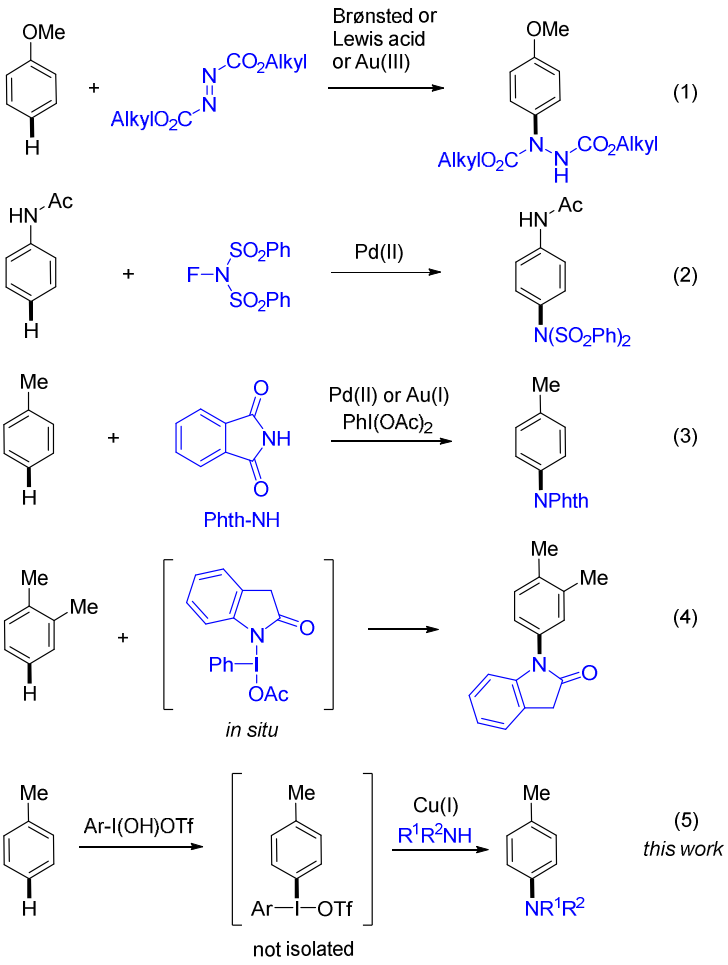
Keywords: hypervalent iodine, diaryliodonium salts, copper, amination, regioselectivity

Introduction

Late-stage modification of pharmaceutically relevant compounds allows for introduction of a structural diversity at final stages of synthesis and provides a rapid and straightforward access to a number of analogues. Therefore the late-stage modification is frequently employed to streamline the lead-optimization process in drug development.[1] Ideally, introduction of structural diversity is to be accomplished without a preactivation of the lead compound. Hence, the most suitable approach to the late-stage modification relies on the functionalization of C–H bonds.

Among a variety of C–H functionalization methods, the intermolecular C–H amination has become a focus of increasing research during the last years. Notwithstanding remarkable advances in the field of transition metal-catalyzed Csp^2–H amination,[2,3] the majority of the developed methods require the presence of a metal-coordinating substituent[4] which facilitates the cleavage of an *ortho*-C–H bond by transition metal. Therefore most of the reported catalytic C–H to C–N transformations in arenes are directed to the *ortho*-position.[5] Recently, auxiliary substituents capable of directing the C-H activation to the *meta*-position have been designed,[6] however the directed *meta*-C–H amination has not been reported thus far. Likewise, a complementary *para*-selective Csp^2–H amination methodology is considerably less developed compared to the directed *ortho*-C–H amination. Thus, there are a handful of *para*-selective Csp^2–H amination examples in the literature. Early reports describe electrophilic aromatic substitution of electron-rich arenes with azodicarboxylates in the presence of Lewis acids[7] or Brønsted acids,[8] and more recently, in a Au(III)-catalyzed process (eq 1).[9] Zhang has reported an amide-directed Pd-catalyzed *para*-C–H imidation with *N*-fluorobenzenesulfonimide (NFBS) as a source of nitrogen (eq 2).[10] High *para*-selectivity levels of Csp^2–N bond formation in arenes have been achieved by using hypervalent iodine(III) reagents. Thus, $PhI(OAc)_2$-mediated oxidative transfer of phthalimide moiety to arene rings proceeded with reasonable *para*-selectivity in the presence of Au(I) catalyst (eq 3).[11] Relevant to our work is a transition metal-free *para*-C−H amidation of arenes in the presence of $PhI(OAc)_2$ (eq 4), which presumably involves formation of a phenyl-λ^3-iodane intermediate possessing an iodine−nitrogen bond.[12] A single example of metal-free *para*-C−H imidation using *bis*-tosylimido-λ^3-iodane has recently been reported by Muñiz.[13] Importantly, in all of the above-mentioned examples, additional synthetic steps are

required to elaborate the C–H amination products into *N*-unsubstituted anilines. These post-amination transformations reduce the synthetic advantages of the direct C–H to C–N transformation, so a method compatible with *N*-unprotected amines as the source of nitrogen would substantially increase the synthetic value of the *para*-selective Csp^2–H amination methodology.



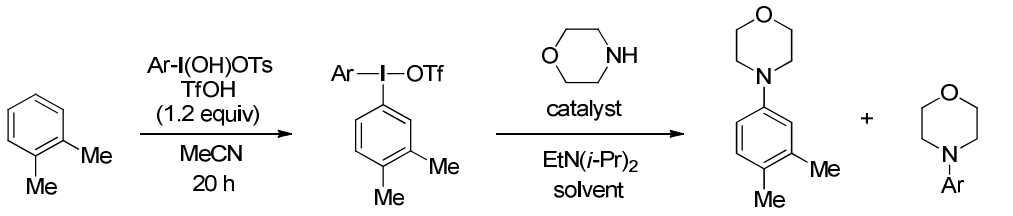
In our continuing efforts to develop a synthetic method for the late-stage functionalization of pharmaceutically relevant heterocycles we recently disclosed a Cu(I)–catalyzed Csp^2–H amination of heteroarenes with *N*-unprotected amines.[14] The one-pot two-step method comprised the reaction between arene and hypervalent iodonium reagent ArI(OH)OTs to form unsymmetrical diaryl-λ^3-iodanes, which reacted *in situ* with a range of *N*-unprotected amines in the presence of Cu(I) catalyst to afford heteroarylamines. The developed method was suitable also for C–H amination of certain electron-rich carbocyclic arenes in moderate yields. Importantly, C–N bond formation in arenes proceeded in *para*-position with respect to electron-releasing substituents. Unfortunately, moderate yields and narrow scope of suitable

arenes compromised the synthetic advantage of the developed *para*-Csp^2–H amination approach. Herein, we report a further development of the Cu(I)–catalyzed *para*–Csp^2–H amination methodology (eq 5) which addresses the above-mentioned drawbacks. Key to the success was the increase of steric hindrance in iodonium reagent ArI(OH)OTs and the use of strong acid additives as described below. The new conditions feature improved yields and are compatible with substantially increased scope of arenes.

Results and Discussion

Ortho-xylene (**1d**) was selected as a substrate for the method development studies because it was unreactive under the published C–H amination conditions which involved an initial treatment of the arene **1d** with MesI(OH)OTs (1.1 equiv) in anhydrous CH_2Cl_2 at room temperature to form an unsymmetrical diaryl-λ^3-iodane **2d**, followed by addition of catalytic amounts of $Cu(MeCN)_4BF_4$, morpholine, DIPEA and DMSO.[14] We reasoned that the lack of reactivity for **1d** may be attributed to slow formation of an intermediate unsymmetrical diaryl-λ^3-iodane **2d** in the reaction of **1d** with MesI(OH)OTs reagent. It has been shown that strong acids such as TsOH and TfOH facilitate the formation of diaryl-λ^3-iodanes from arenes.[15] Indeed, addition of TfOH (1.2 equiv) to a mixture of *ortho*-xylene (**1d**) and MesI(OH)OTs in acetonitrile resulted in the formation of diaryl-λ^3-iodane **2d** in 83% yield. The latter was isolated in pure form and was subsequently used for optimization of Cu(I)-catalyzed reaction with morpholine as shown in Table 1.

Table 1. Reaction of λ^3-iodanes **2d** and **3d** with morpholine.



entry	λ^3-iodane	catalyst, mol%	solvent	time, temp	**4d**,%[a,b]	**5**,%[b]	**6**,%[b]
1	**2d**	$Cu(MeCN)_4BF_4$, 10	CH_2Cl_2–DMSO 4:1	8 days, rt	40	14	-
2	**2d**	$Cu(MeCN)_4BF_4$, 10	MeCN–DMSO 1:4	8 days, rt	49	18	-

3	**3d**	$Cu(MeCN)_4BF_4$, 10	CH_2Cl_2–DMSO 4:1	8 days, rt	39	-	<1
4	**3d**	$Cu(MeCN)_4BF_4$, 10	MeCN–DMSO 1:4	12 h, 40 °C	80	-	<1
5	**3d**	$Cu(MeCN)_4BF_4$, 10	DMSO	12 h, 40 °C	83	-	<1
6	**3d**	$Cu(MeCN)_4BF_4$, 5	MeCN–DMSO 1:4	40 h, 40 °C	84	-	<1
7	**3d**	$Cu(MeCN)_4BF_4$, 2	MeCN–DMSO 1:4	48 h, 40 °C	75[c]	-	<1
8	**3d**	$Cu(MeCN)_4BF_4$, 0.5	MeCN–DMSO 1:4	48 h, 40 °C	47[d]	-	<1
9	**3d**	CuI, 10	MeCN–DMSO 1:4	24 h, 40 °C	75	-	<1
10	**3d**	$CuBr\text{-}SMe_2$, 10	MeCN–DMSO 1:4	130 h, 40 °C	37	-	<1
11	**3d**	CuOTf, 10	MeCN–DMSO 1:4	130 h, 40 °C	26	-	<1
12	**3d**	$Cu(OTf)_2$, 10	MeCN–DMSO 1:4	40 h, 40 °C	74[e]	-	<1
13	**3d**	$Cu(BF_4)_2 \bullet 6H_2O$, 10	MeCN–DMSO 1:4	60 h, 40 °C	31	-	<1
14[f]	**3d**	$Cu(MeCN)_4BF_4$, 10	MeCN–DMSO 1:4	40 h, 40 °C	68	-	<1
15[g]	**3d**	$Cu(MeCN)_4BF_4$, 10	MeCN–DMSO 1:4	40 h, 40 °C	67	-	<1
16	**3d**	none	MeCN–DMSO 1:4	40 h, 40 °C	<1[h]	-	<1

[a] 99% conversion of **2d** or **3d**. [b] Isolated yield of >95% pure product (NMR assay). [c] 90% conversion of **3d**. [d] 50% conversion of **3d**. [e] 49% conversion of **3d** after 12 h at 40 °C. [f] In the presence of water (10 equiv). [g] Performed under air. [h] 20% conversion of **3d**.

The reaction of **2d** with morpholine turned out to be very slow and the desired product **4d** was formed in only 40% yield after 8 days at room temperature (entry 1). Furthermore, a concomitant formation of the undesired *N*-mesityl morpholine **5d** was also observed (3:1 ratio of **4d**:**5d**). Simple change of solvents did not alter the **4d**:**5d** ratio (entry 2). Apparently, insufficient electronic and steric differences between the nontransferable mesityl ligand and xylyl moiety were responsible for the poor regioselectivity of the Cu–catalyzed reaction between the diaryl-λ^3-iodane **2d** and morpholine. We hypothesized that increase of the steric demand of the nontransferable aryl ligand in the diaryl-λ^3-iodane **2d** could solve the selectivity issue.[16] To this end, unsymmetrical diaryl-λ^3-iodane **3d** possessing bulky 2,4,6-triisopropylphenyl (TIPP) group was synthesized from *ortho*-xylene (**1d**) and TIPP-I(OH)OTs[17] in the presence of TfOH (48% yield of recrystallized material). The structure of **3d** was confirmed by X-ray crystallographic analysis (Figure 1).

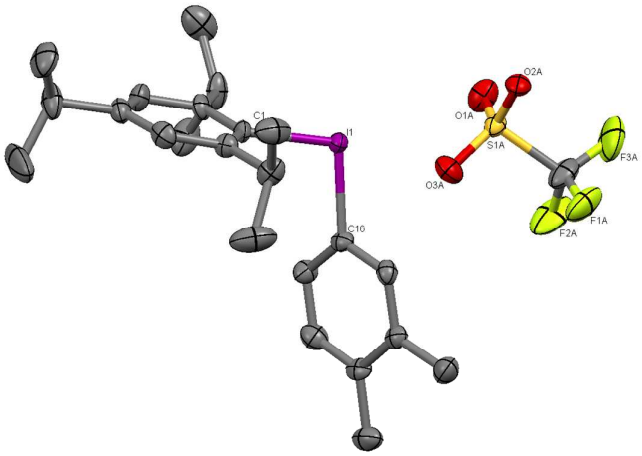


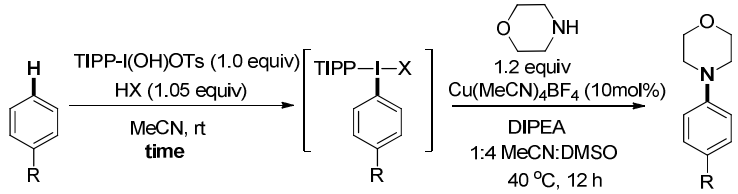
Figure 1. X-ray crystal structure of λ^3-iodane **3d** (ellipsoids at 50% probability) with hydrogen atoms omitted for clarity. Selected bond distances (Å) and angles (deg): I1−C1, 2.131(5); I1−C16, 2.118(6); I1−O1A, 3.359(4); I−O3A, 3.513(4); C1−I1−C16, 100.1(2). See the Supporting Information for details.

We were pleased to see that the reaction of diaryl-λ^3-iodane **3d** with morpholine in the presence of $Cu(MeCN)_4BF_4$ catalyst[18] proceeded with excellent selectivity and formation of the undesired **6** was not observed (Table 1, entry 3). Furthermore, the long reaction time (8 days) could be decreased to merely 12 hours by simple increase of temperature to 40 ^oC (entry 4). The desired C–H amination product **4d** was isolated in 80% yield. The reaction readily proceeded also in pure DMSO (entry 5). Twofold decrease of the catalyst loading resulted in slower reaction and required longer time to go to completion (entry 6). Further lowering of the catalyst amount (entries 7 and 8) resulted in incomplete conversion of **3d**. Among various Cu(I) sources tested, only CuI was efficient as a catalyst (entry 9). Other Cu(I) salts were less efficient (entries 10,11). $Cu(OTf)_2$ could also be used as a catalyst (entry 12), however the Cu(II)-catalyzed reaction between λ^3-iodane **3d** and morpholine required longer time to go to completion compared to the best Cu(I) source (entry 12 vs. entry 4). Interestingly, $Cu(BF_4)_2$ hexahydrate was far less efficient as a catalyst compared to $Cu(MeCN)_4BF_4$ or copper (II) triflate (entry 13 vs. entries 4 and 12, respectively). Poor catalytic efficiency of $Cu(BF_4)_2$ hexahydrate could be attributed to the presence of water (0.6 equiv) in the Cu(II) catalyst, because diminished yields of the product **4d** were also observed if C-H amination under the best conditions (with $Cu(MeCN)_4BF_4$ as the catalyst) was performed in the presence of water (10 equiv; entry 14 vs. entry 4). On the other hand, the C-H amination reaction mixture always contains water (1 equiv)

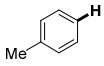
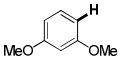
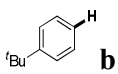
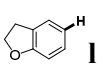
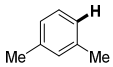
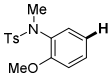
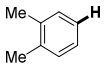
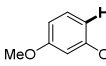
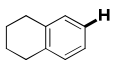
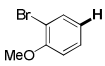
which forms during the λ^3-iodane **3d** formation from the starting arene **1d** and TIPP-I(OH)OTs, so the presence of water is likely not responsible for the poor catalytic efficiency of $Cu(BF_4)_2$ hexahydrate. The oxygen-free conditions are important to achieve high yields of the C-H amination product **4d** (compare entries 15 and 4). Finally, the reaction of λ^3-iodane **3d** with morpholine in the absence of the Cu(I) catalyst resulted in slow formation of iodo-xylene and the formation of the desired **4d** was not observed (entry 16). It should be noted, that the addition of the radical scavenger TEMPO considerably decelerated the formation of iodo-xylene, so the noncatalyzed reaction of the diaryl-λ^3-iodane **3d** with morpholine presumably proceeds through a radical chain pathway.[14]

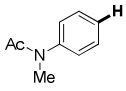
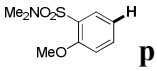
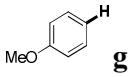
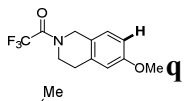
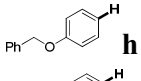
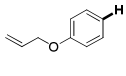
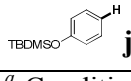
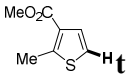
The *N*-xylyl-morpholine **4d** could also be synthesized in a sequential one-pot mode without isolation of the diaryl-λ^3-iodane **3d**. This required careful control of **3d** formation and the addition of $Cu(MeCN)_4BF_4$, morpholine, $EtN(i\text{-}Pr)_2$ and DMSO to the reaction mixture immediately after the conversion of xylene **1d** to the intermediate **3d** was completed. The sequential one-pot two-step C–H amination avoided the isolation and handling of potentially unstable intermediate diaryl-λ^3-iodane **3d** and hence is superior compared to the stepwise approach.

Table 2. Sequential C–H amination of arenes **1a–t**.[a]



TIPP = 2,4,6,-triisopropylphenyl

entry	arene **1**	HX	time (h)	yield **4** (%)[b]	entry	arene **1**	HX	time (h)	yield **4** (%)[b]
1	 **a**	TfOH[c]	3	25	11	 **k**	TsOH	0.2	80(61)[d]
2	 **b**	TfOH[c]	3	35	12	 **l**	TsOH	2	72(49)[d]
3	 **c**	TfOH[c]	2	62	13	 **m**	TsOH	0.2	74
4	 **d**	TfOH[c]	3	62	14[f]	 **n**	TfOH	3	50[g]
5	 **e**	TfOH	3	56(41)[d]	15	 **o**	TfOH	1	70

6	 **f**	TfOH	18	49	16	 **p**	TfOH	12	82
7	 **g**	TsOH	2	80(52)[d]	17	 **q**	TfOH[h]	1	44
8	 **h**	TsOH	0.3	66	18	 **r**	TsOH	0.5	49
9	 **i**	TsOH	0.5	71	19	 **s**	TsOH	0.5	44
10	 **j**	none[e]	0.2	55	20	 **t**	TfOH	0.5	62

[a] Conditions: Arene **1** (1.2 equiv); acid (1.05 equiv) and TIPP-I(OH)OTs (1.0 equiv) in MeCN (0.5 M) at room temperature; then $Cu(MeCN)_4BF_4$ (10 mol%), morpholine (1.2 equiv) and DIPEA (2.0 equiv) in 1:4 MeCN:DMSO (0.1 M) at 40 °C for 12 h. [b] Average yield of two runs. [c] λ^3-Iodane did not form with TsOH as an additive. [d] In parenthesis yields from ref. 14. [e] Performed in CF_3CH_2OH as a solvent without the acid additive. [f] With 1 equivalent of $Cu(MeCN)_4BF_4$. [g] Isomeric product **4n'** possessing the morpholine moiety in *para*-position to OCF_3 group was isolated in 15% yield. [h] At 0 °C with 3 equiv of TfOH and 4 equiv of DIPEA.

A series of carbocyclic arenes was subsequently subjected to the one-pot sequential C–H amination to demonstrate the scope of the developed methodology (Table 2). Yields of the two-step sequential C–H amination depended on the ease of the formation of unsymmetrical diaryl-λ^3-iodane intermediates as well as on their stability. The formation of the iodonium salt intermediates **3a-u** was found to be sensitive to the electronic properties of arene **1**.[19] Toluene (entry 1) represents a reactivity borderline: less electron-rich arenes than toluene did not react with TIPP-I(OH)OTs even in the presence of TfOH or TsOH as an additive. *Tert*-butylbenzene was slightly more reactive than toluene (entry 2 vs. 1), a result that is consistent with better electron-releasing ability of *tert*-butyl group (σ_p= –0.20) compared to that of the methyl group (σ_p= –0.17).[20] Not surprisingly, arenes possessing two alkyl substituents were readily transformed into diaryl-λ^3-iodane intermediates and, hence, afforded the C–H amination products in 56-62% yields (entries 3–5). It should be noted that all the tested alkyl-substituted arenes (entries 1–5) required TfOH as an additive to afford the unsymmetrical diaryl-λ^3-iodane intermediates. Moderate C–H amination yields for *N*-acetanilide (entry 6) presumably could be attributed to partial acid hydrolysis of the amide moiety.[21] Electron-rich alkoxy-substituted arenes (entries 7–12) readily reacted with TIPP-I(OH)OTs in the presence of TsOH as an additive.[22] Importantly, the strong electron-donating effect of methoxy group (σ_p= –0.27)[20] compensated for the presence of deactivating electron-withdrawing substituents such

as OCF_3 group (σ_p= +0.35; entry 14) and bromine (σ_p= +0.23, entry 15)[23] and even sulfonamide moiety (σ_p= +0.65; entry 16). In the latter case, the reaction with TIPP-I(OH)OTs required addition of TfOH and prolonged time to afford the unsymmetrical diaryl-λ^3-iodane intermediate. Noteworthy, TIPP-I(OH)OTs–based conditions afforded C–H amination products in higher yields than the previously published method[14] (see yields in entries 5,7,11 and 12). Finally, substituted thiophenes also appeared to be suitable substrates for the developed C-H amination reaction (entries 18–20).

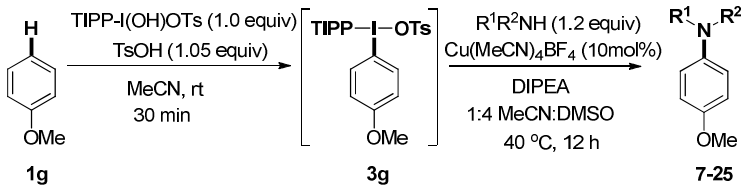
The regioselectivity of the C−H amination is controlled during the formation of the unsymmetrical diaryl-λ^3-iodane intermediates. Notably, all monosubstituted arenes underwent highly regioselective *para*-C–H amination and the formation of isomeric *ortho*-substituted products generally was not observed.[24] The C–H amination in multiply substituted arenes proceeded selectively at the *para*-position to the strongest electron-releasing substituent (entries 11–16). For example, 2,3-dihydrobenzofuran (entry 12) and *N*-tosyl anisidine (entry 13) afforded C–H amination product in *para*-position to the alkoxy group. In tetrahydroisoquinoline (entry 17) the *para*-position with respect to the strongest electron-releasing substituent (MeO group) is blocked, and the reaction took place regioselectively at the sterically less hindered *ortho*-position.[25] The regioselective C–H amination of 6-MeO-tetrahydroisoquinoline is noteworthy, because this substrate usually affords a mixture of 5– and 7–substituted products in electrophilic halogenation[26] and nitration[27] reactions. 3-Substituted thiophenes underwent C–H amination at position 2 (entries 18–20).

The C−H amination conditions were compatible with the presence of *O*-benzyl (entry 8, Table 2), *O*-allyl (entry 9) and *O*-TBDMS (entry 10) protecting groups as well as *O*-Me ester moiety (entry 20) and bromide (entry 15). *N*-Trifluoroacetyl (entry 17, Table 2) and *N*-Ts (entry 13) protecting groups were also tolerated. A variety of aliphatic primary amines (entries 1−7, Table 3), aliphatic secondary amines (entries 8 −13), aromatic, heteroaromatic amines (entries 14−16) and imidazole (entry 17) could be employed. Azoles possessing a relatively acidic *N*-H bonds such as tetrazole (entry 18) and 1,2,4-triazole (entry 19) also reacted in the presence of DIPEA as the base. Less acidic *N*−H heterocycles such as indoles did not react under the standard conditions. The reaction of ammonium trifluoroacetate (1.2 equiv) with diaryl-λ^3-

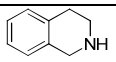
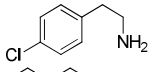
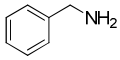
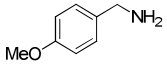
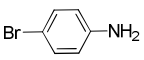
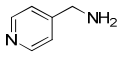
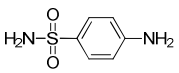
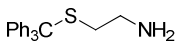
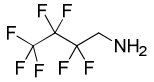
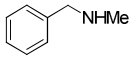
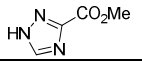
iodane **3g** afforded bis(4-methoxyphenyl)amine **26** as the major product (entry 20). Disappointingly, poor conversion (<5%) of the diaryl-λ^3-iodane **3g** was observed when aqueous saturated ammonia (10 equiv) or 2M solution of NH_3 in methanol (5 equiv) were used as a source of ammonia. Possibly, a complex formation with the excess of NH_3 inhibited the Cu(I) catalyst. Nevertheless, an introduction of NH_2 functional group is possible *via* the *para*-C-H amination using *N*-allyl (entry 1) or *N*-benzyl amines (entries 3,4), followed by *N*-deprotection of the corresponding anilines **7**, **9** and **10**, respectively (Table 3).

Importantly, the C-H amination reaction conditions are compatible with alkene moiety in the amine (entry 1) and *S*-trityl (entry 6) protecting group. Various functional groups such as ethers (entry 4), esters (entry 19) and a bromide (entry 14) are all tolerated. Amines react chemoselectively in the presence of unprotected amide (entry 13) and sulfonamide moieties (entry 15). Monoamination with piperazine is also possible (entry 12).

Table 3. Scope of amines.[a]



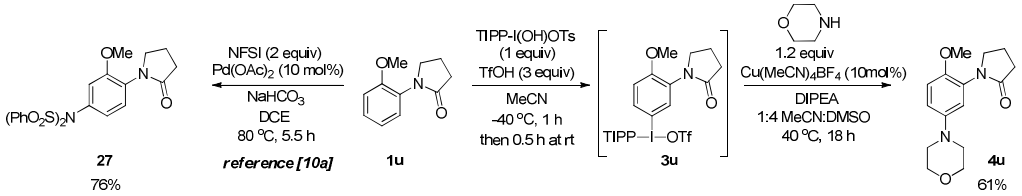
TIPP = 2,4,6,-triisopropylphenyl

entry	amine	product, yield (%)[b]	entry	amine	product, yield (%)[b]
1		**7**, 77	11		**17**, 56
2		**8**, 70	12[d]		**18**, 50[e]
3		**9**, 73	13		**19**, 61
4		**10**, 77	14		**20**, 74
5		**11**, 44	15		**21**, 49
6[c]		**12**, 42	16		**22**, 20
7		**13**, 72	17[c]		**23**, 76
8		**14**, 63	18[f]		**24**, 79[g]
9		**15**, 78	19[c]		**25**, 39

10		**16**, 80	20	$NH_4^{\oplus}\,^{\ominus}OCOCF_3$	**26**, 33[h]

[a] Conditions: Anisole **1g** (1.2 equiv); TsOH*H_2O (1.05 equiv) and TIPP-I(OH)OTs (1.0 equiv) in MeCN (0.5 M) at room temperature for 30 min; then $Cu(MeCN)_4BF_4$ (10 mol%), amine (1.2 equiv) and DIPEA (2.0 equiv) in MeCN/DMSO =1:4 (0.1 M) at 40 °C for 12h. [b] Average yield of two runs. [c] The reaction of **3g** with amine proceeded within 30 h at 40 °C. [d] DIPEA was not added; piperazine (3.5 equiv) was used both as the nucleophile and as the base. [e] Accompanied with 18% of 1,4-bis(4-methoxyphenyl)piperazine. [f] The reaction of **3g** with amine required 40 h at 50 °C and 2.5 equiv of DIPEA. [g] A mixture of 1-aryltetrazole **24a** (35%) and 2-aryltetrazole **24b** (44%). [h] Yield of *bis*(4-methoxyphenyl)amine **26**; the reaction of **3g** with NH_4-$OCOCF_3$ required 30 h at 40 °C and 3.5 equiv of DIPEA.

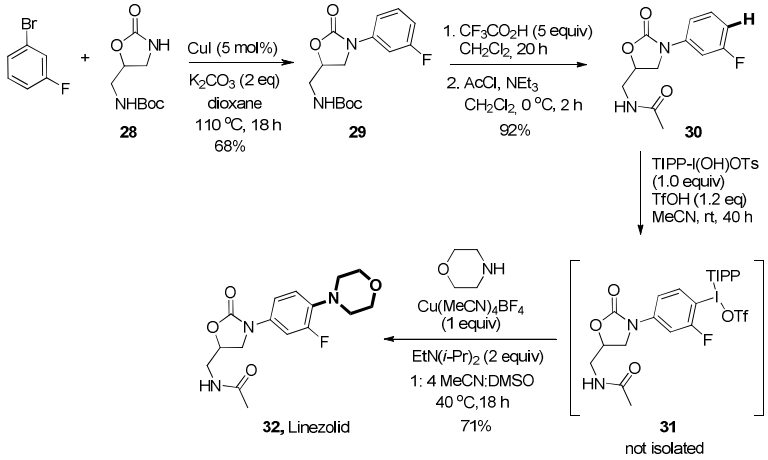
The developed two-step sequential *para*-C–H amination approach provides a complementary regioselectivity to a Pd–catalyzed method reported by Zhang and co-workers (Scheme 1 and eq 2).[10a] Thus, in their work the amide-directed C–H amination of arene **1u** with *N*-fluorobenzenesulfonimide (NFSI) proceeded at the *para*-position to the amide moiety and afforded *para*-phenylenediamine **27**. In contrast, regioselectivity of the reaction between arene **1u** and TIPP-I(OH)OTs was controlled by methoxy group, the strongest electron-releasing substituent in the arene **1u**. Subsequent Cu–catalyzed reaction of the unsymmetrical diaryl-λ^3-iodane **3u** intermediate with morpholine delivered *para*-anisidine **4u** (Scheme 1). Importantly, low temperature (–40 °C) was required in the formation step of intermediate **3u** in order to obtain **4u** in good yield (61%).[28]



Scheme 1. Complementary regioselectivity of different C–H amination methods.

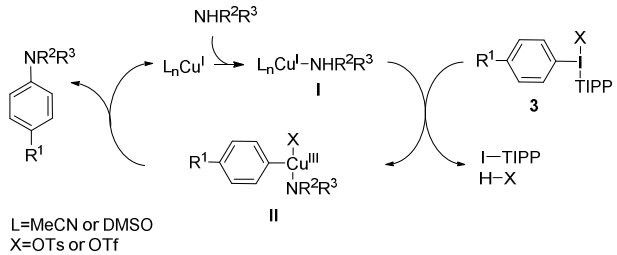
Finally, a synthesis of antibiotic Linezolid **32** was performed to demonstrate the suitability of the developed Cu–catalyzed *para*-C–H amination method for the late-stage functionalization of lead structures (Scheme 2). The synthesis featured installation of the morpholine moiety in a non-prefunctionalized Linezolid core structure **30** in the final synthetic step. Such approach streamlines structural variations of the amine moiety and could provide a rapid and straightforward access to a number of Linezolid analogs. The synthesis commenced with Cu-catalyzed *N*-arylation of commercially available oxazolidinone **28**,[29] followed by cleavage of *N*-Boc protecting

group and subsequent *N*-acetylation to provide the key building block **30** (Scheme 2). The formation of the unsymmetrical diaryl-λ^3-iodane **31** intermediate took prolonged time (40 h) to go to completion. Subsequent *in situ* reaction of **31** with morpholine required presence of stoichiometric amounts[30] of $Cu(MeCN)_4BF_4$ complex[31] to obtain the Linezolid **32** in 71% yield (Scheme 2).



Scheme 2. Synthesis of Linezolide **32** by late-stage C-H amination.

Higher efficiency of $Cu(MeCN)_4BF_4$ complex compared to the representative Cu(II) complex (entry 12 vs. entry 4, Table 1) suggests that Cu(I) salts are the catalytically active species and Cu(II) salts are *in situ* reduced to active Cu(I) catalyst by amine.[32] Such a scenario is consistent with our earlier observation that selective trapping of Cu(I) species with neocuproine (a highly specific chelating agent for Cu(I) ions) resulted in complete inhibition of the C-H amination reaction.[14] Consequently, a Cu^I/Cu^{III} catalytic cycle for the reaction between the unsymmetrical λ^3-iodanes **3** and amines is plausible.[33] It would start with an initial formation of Cu(I)-diamine complex **I**, followed by oxidative addition of the λ^3-iodane **3** to form the Cu(III) intermediate **II** and completed by product forming reductive elimination to afford C-H amination product and regenerate a catalytically active Cu(I) species (Scheme 3).



Scheme 3. Working mechanism for C–H Amination of Arenes.

Unfortunately, the proposed transient Cu(III) complexes could not be detected, presumably because they undergo rapid C−N bond forming reductive elimination.[34] This behavior is expected because related, highly reactive Cu(III) species have only been observed in chelation-stabilized complexes based on stabilizing triazamacrocyclic ligands.[35] Further mechanistic studies are necessary to fully elucidate the mechanism of the developed C−H amination approach.

Conclusions

In summary, the use of bulky 2,4,6-triisopropylphenyl (TIPP) group-containing iodonium reagent TIPP-I(OH)OTs together with strong acid additives such as TsOH and TfOH allowed for substantial increase of substrate scope and improvement of C–H amination yields compared to the previously published method.[14] The new conditions are suitable for *para*-selective C-H amination of a wide range of relatively electron-rich arenes. The high *para*-regioselectivity of the C–H amination is controlled at the stage of the formation of the unsymmetrical diaryl-λ^3-iodane intermediates. Although the regioselectivity is a result of the combined directing effects of arene substituents, in general it is consistent with that of electrophilic aromatic substitution (S_EAr) reactions. Thus, the C–H amination takes place at the *para*-position to the strongest electron-releasing substituent. Hammett substituent σ-constants can be used to predict the regioselectivity of the C–H amination in carbocyclic arenes possessing multiple substituents. The developed method provides a complementary regioselectivity to the well-developed *ortho*-C-H amination approach and it may be especially useful for late-stage *para*-regioselective C–H amination of pharmaceutically relevant carbocyclic arenes.

Associated Content

Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/csXXXXXXX.

Experimental details, characterization data, and NMR spectra (PDF)

X-ray crystallographic data for λ^3-iodane **3d** (CIF)

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Notes

The authors declare no competing financial interest.

Acknowledgements

This work was supported by Latvian Science Council Grant No. 274/2012. I.S. thanks the European Social Fund for a scholarship within the project "Support for Doctoral Studies at University of Latvia". We thank Dr. S. Belyakov for X-ray crystallographic analysis and Dr. I. Nakurte (Universty of Latvia) for HRMS analyses.

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(21) Equimolar amount of water was formed in the reaction of TIPP–I(OH)OTf with arene.

(22) Addition of TfOH to electron-rich arenes resulted in exotherm and formation of more side-products.

(23) Trifluoromethoxy benzene and bromobenzene do not react with ArI(OH)OTs in the presence of TfOH.

(24) The formation of regioisomeric *ortho*-C–H amination side-product **4n'** was observed only for 3-(trifluoromethoxy)anisole **4n** (50:14 *para*:*ortho*).

(25) Major side-product was the corresponding 3,4-dihydroisoquinoline, which presumably was formed by acidic hydrolysis of **1q** followed by oxidation of the intermediate 1,2,3,4-tetrahydroisoquinoline by I(III) species. *N*-Acetyl tetrahydroisoquinoline (related to **1q**) was less stable toward the acidic hydrolysis.

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(28) At room temperature the intermediate diaryliodonium triflate **3u** appeared to be unstable. Among major decomposition products there was O-Tf analog of **4u**, which apparently was formed by C–O bond forming reductive elimination from **3u**. For thermally unstable intermediate iodanes the use of low temperatures is recommended.

(29) Mallesham, B.; Rajesh, B. M.; Rajamohan Reddy, P.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**,*5*, 963-965.

(30) The reaction of the intermediate **31** with morpholine in the presence of catalytic Cu(I) amounts (10 mol%) stalled after 4 days at 27% conversion suggesting inhibition of Cu(I) catalyst with substrate. Consequently, the use of stoichiometric amounts of $Cu(MeCN)_4BF_4$ is recommended for substrates possessing functional groups capable of chelating Cu(I) species.

(31) Copper(I) iodide in stoichiometric amounts is incompatible with the C–H amination conditions because it acts as a source of iodide and affords C–H iodination product instead of the desired Linezolid **32**. However, CuI can be employed in catalytic amounts (10 mol%; see entry 9, Table 1).

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(33) The Cu^{I}/Cu^{III} catalytic cycle in reactions involving diaryliodonium salts has been recently proposed based on *ab-initio* DFT calculations: see Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Organometallics* **2014**, *33*, 5525–5534.

(34) For C−N bond-forming reductive elimination from well-defined Cu(III)−aryl species, see: (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196-9197. (b) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, *1*, 326-330. (c) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068-12073. (d) Huffman, L. M.; Stahl, S. S. *Dalton Trans.* **2011**, *40*, 8959-8963.

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