Organic LETTERS

Letter

pubs.acs.org/OrgLett

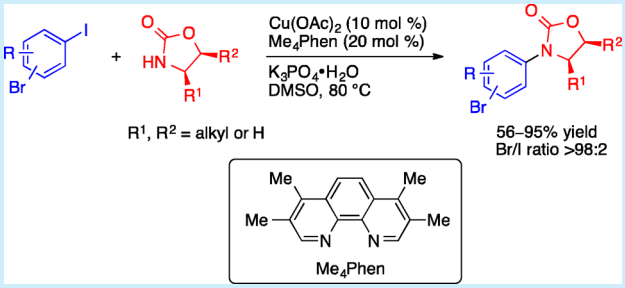
Chemoselective Copper-Catalyzed Ullmann-Type Coupling of Oxazolidinones with Bromoiodoarenes

Sean M. Kelly, Chong Han,* Laura Tung, and Francis Gosselin

Department of Small Molecule Process Chemistry, Genentech, Inc., South San Francisco, California 94080, United States

Supporting Information

ABSTRACT: We describe the highly selective copper-catalyzed Ullmann-type coupling of bromoiodoarenes with oxazolidinones. 3,4,7,8-Tetramethyl-1,10-phenanthroline (Me_4Phen) was identified as an optimal ligand promoting the desired C−N bond formation, while minimizing the competitive bromo−iodo exchange pathway that leads to formation of iodo-substituted and bis-coupled side products. The developed method is highly selective with a >98:2 ratio of the bromo- vs iodo-substituted compounds obtained in the isolated products.



N-Aryl oxazolidinones represent interesting structural motifs in the area of pharmaceutical research and development. Examples include marketed antibiotic linezolid[1] and tedizolid[2] (Figure 1)

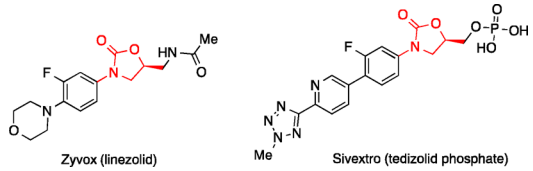


Figure 1. FDA approved oxazolidinone antibiotics.

that represent a novel class of antibiotics with a unique mechanism of action against multiple-drug resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE). In the course of a chemical development effort on an internal program in our laboratories, we became interested in developing a chemoselective Ullmann coupling of oxazolidinones with bromoiodoarenes to access a series of bromo *N*-aryloxazolidinones that can be further functionalized via a subsequent cross-coupling reaction.

Since the pioneering work from the Ma,[3] Buchwald,[4] and Taillefer[5] research groups on ligand-accelerated Cu-catalyzed Ullmann-type couplings,[6] there have been numerous literature reports on Cu-catalyzed C−N coupling of oxazolidinones using various types of ligands such as *N*,*N*′-dimethylethylenediamine (**L2**; see Table 1),[7a] *trans*-1,2-diaminocyclohexane (**L3**; see Table 1),[7b,c] and *N*,*N*-dimethylglycine (**L6**; see Table 1).[7d] Complementary approaches utilizing amino alcohol carbamates as oxazolidinone surrogates have also been described.[8] However, few studies have been reported on the selective monocoupling between oxazolidinones or surrogates and dihaloarenes such as bromoiodoarenes.[9] The challenges of developing such a selective cross-coupling reaction are not only differentiation between the reactivity of aryl iodides and bromides but also inhibition of the competitive aromatic Finkelstein pathway leading to the scrambling of aryl halides. The latter can be quite challenging under copper catalysis since the common diamine-type ligands (**L1**−**L3**; see Table 1) developed by Buchwald and co-workers for Ullmann-type couplings have been shown to promote the Cu-catalyzed aromatic Finkelstein reaction, converting aryl bromides to aryl iodides very effectively.[10]

We report herein our studies leading to a copper catalyst system composed of 1,10-phenanthroline ligands[11] that has been shown to strike the right balance between sustaining a reasonable reaction rate for the desired C−N bond formation and minimizing the undesired aromatic Finkelstein pathway leading to halogen scrambling.

The coupling of 4-bromoiodobenzene (**1a**) and (*R*)-4-methyl oxazolidin-2-one (**2a**) was selected as a model reaction to examine the product distribution under standard literature conditions for Cu-catalyzed Ullmann-type couplings using $Cu(OAc)_2$ as the copper source, *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (**L1**; see Table 1) as the ligand, potassium phosphate monohydrate ($K_3PO_4{\cdot}H_2O$) as the base, and 1,4-dioxane as the solvent (Figure 2). The deliberate selection of $Cu(OAc)_2$ over the more common CuI for Ullmann-type couplings was to minimize bromo−iodo exchange by avoiding the introduction of additional iodide to the reaction system. Under these conditions at 80 °C, the desired product (**3a**) reached a maximum level after 2 h at approximately 61 area (A) % with 30 A % unreacted starting material (**1a**) still remaining based on HPLC analysis. Complete consumption of **1a** was observed after 4 h, resulting in a mixture of desired product (**3a**, 41 A %) and two other side products identified as halogen-exchanged iodo-substituted product (**3a**′, 34 A %) and bis-coupled product (**3a**″, 22 A %)[12] by HRMS analysis. If heating was continued for a total reaction time of 8 h,

Received: May 1, 2017

DOI: 10.1021/acs.orglett.7b01304
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Ligands and Solvents for the Cu-Catalyzed Coupling of 1a and 2a[a]

entry	ligand	time (h)	solvent	conv[b] (%)	3a/(3a′+3a″)[b]
1	**L1**	8	1,4-dioxane	100	3:97
2	**L2**	24	1,4-dioxane	85	38:62
3	**L3**	24	1,4-dioxane	100	35:65
4	**L4**	48	1,4-dioxane	97	75:25
5	**L5**	48	1,4-dioxane	55	60:40
6	**L6**	48	1,4-dioxane	71	41:59
7	**L7**	48	1,4-dioxane	62	92:8
8	**L8**	24	1,4-dioxane	80	85:15
9	**L7**	24	MeCN	92	89:11
10	**L7**	24	DMF	93	91:9
11	**L7**	24	DMSO	73	92:8
12	**L8**	24	MeCN	87	81:19
13	**L8**	24	DMF	99	72:28
14	**L8**	4	DMSO	97 (85[c])	94:6
15	**L8**	24	toluene	78	87:13
16	**L8**	24	MeTHF	83	85:15

[a]Reaction conditions: **1a** (1 mmol), **2a** (120 mol %), $Cu(OAc)_2$ (10 mol %), ligand (20 mol %), $K_3PO_4{\cdot}H_2O$ (200 mol %), solvent (1 mL), 80 °C. [b]Based on HPLC analysis. [c]Isolated yields after purification by flash column chromatography using 110 mol % of **2a**.

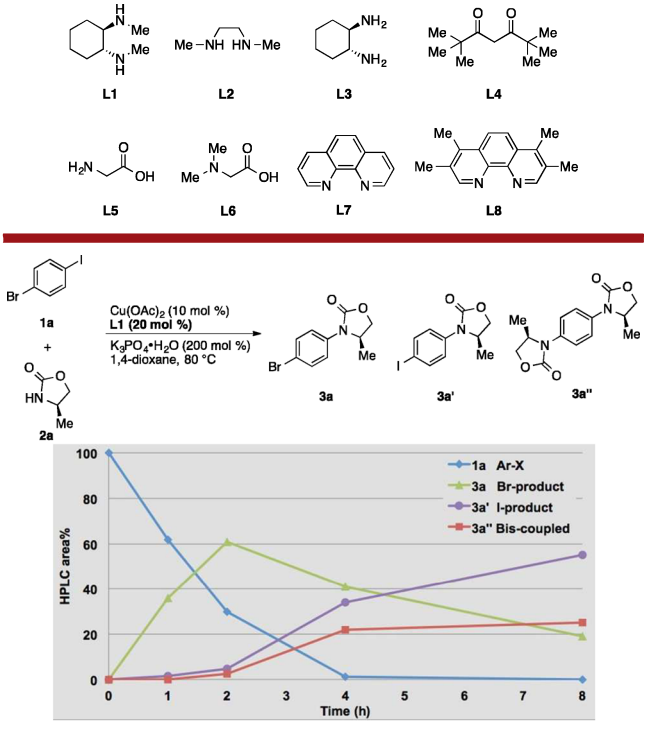


Figure 2. Time course of the Cu-catalyzed C−N coupling of **1a** and **2a** using **L1** as the ligand.

disappearance of **3a** was observed as **3a′** became the major product at 55 A %, driven by copper-catalyzed halogen exchange. Subsequent bis-coupled product (**3a″**) remained around 20% despite extended aging due to the complete consumption of the oxazolidinone **2a** (120 mol % relative to **1a**).

We next focused our efforts on identifying conditions capable of selective arylation of substituted oxazolidinones by bromoiodoarenes while minimizing the rate of competitive halogen exchange. A preliminary screening identified $K_3PO_4{\cdot}H_2O$ as an optimal base compared to Cs_2CO_3 or K_2CO_3. A set of eight ligands was then evaluated for the coupling of **1a** and **2a** using $K_3PO_4{\cdot}H_2O$ in 1,4-dioxane (Table 1). Conversion was observed by HPLC analysis based on disappearance of **1a**, while monitoring the appearance of product **3a**, along with formation of side products **3a′** and **3a′′** via halogen-exchange pathways. Diamine ligands **L1**−**L3**[4] (Table 1, entries 1−3) showed excellent arylation reactivity, but expectedly suffered from high levels of aromatic halogen exchange,[10] resulting in poor selectivities and low product yields. Literature precedents suggest the utility of 1,3-dione (**L4**)[9d] or glycine (**L5**)[9c] as ligands for the selective *N*-arylation of sterically accessible amides. Unfortunately, these ligands resulted in only modest improvement in selectivity for the coupling of 4-methyl-oxazolidinone (**2a**) (Table 1, entries 4−6), while significantly decreasing the rate of desired C−N coupling compared to **L1**. 1,10-Phenanthroline-type ligands (**L7** and **L8**) (Table 1, entries 7−8) were shown to reduce the rate of aromatic halogen exchange dramatically, at the expense of a more minor reduction in cross-coupling rate.

The impact of ligands on the rate of bromo−iodo exchange was separately evaluated by the deliberate conversion of **3a** to **3a′** under standard reaction conditions at 80 °C in 1,4-dioxane with 200 mol % of NaI added (Figure 3). Ligands **L1**−**L3** were shown

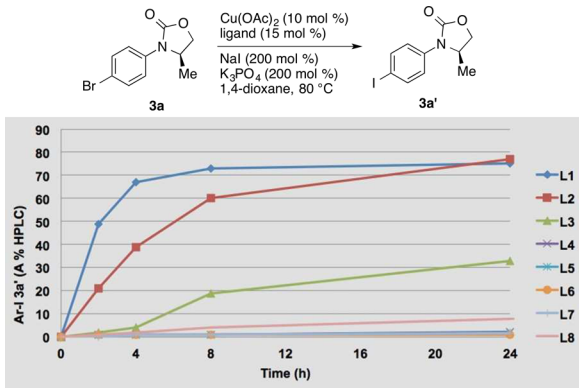


Figure 3. Evaluation of ligand effect on halogen−exchange reaction rate for conversion of **3a** to **3a′**.

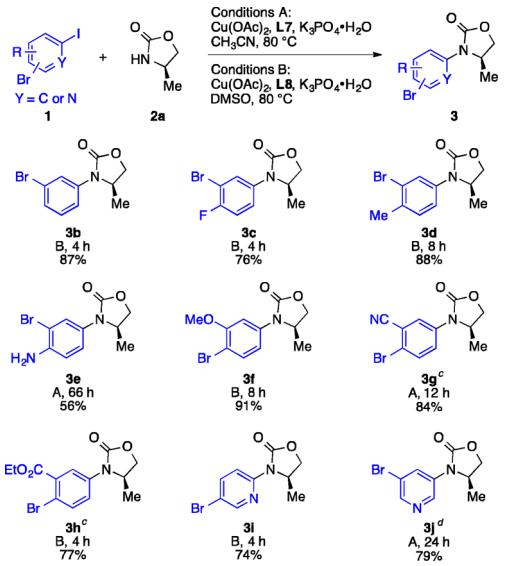
to promote the highest level of bromo−iodo exchange, matching the significant halogen scrambling observed in the cross-coupling reaction, while <10% of halogen exchange was observed for all other ligands even after 24 h, including phenanthroline-type ligands **L7** and **L8**.

Replacing 1,4-dioxane with polar aprotic solvents such as acetonitrile or DMF enabled the Cu-catalyzed C−N coupling to reach >90% conversion in 24 h using **L7**, while maintaining exceptionally low levels of undesired halogen exchange (Table 1, entries 9−10). Increased cross-coupling rates were achieved using a more electron-rich ligand 3,4,7,8-tetramethyl-1,10-phenanthroline (**L8**)[11f] in DMSO reaching 97% conversion in 4 h (Table 1, entry 14). The reaction rates using nonpolar solvents were found to be slower (Table 1, entries 15−16). After examining the reaction parameters including ligands, bases, and solvents, we selected two optimal conditions to evaluate the substrate scope further: condition A using **L7** as the ligand in acetonitrile proceeded at a comparatively slower rate, but was found to be more compatible with sensitive substrates and allow easier isolation amenable to larger scale runs; condition B using **L8** in DMSO approached the fastest rate as in the initial system using **L1** in 1,4-dioxane, while still minimizing the undesired halogen−exchange pathways.

DOI: 10.1021/acs.orglett.7b01304
Org. Lett. XXXX, XXX, XXX−XXX

Following identification of this optimized catalytic system, we first examined the reaction scope by coupling **2a** with a host of substituted bromoiodoarenes (**1**) (Scheme 1). In general, both

Scheme 1. Scope of Bromoiodoarenes in Cu-Catalyzed Selective Couplings with Oxazolidinone 2a[a,b]

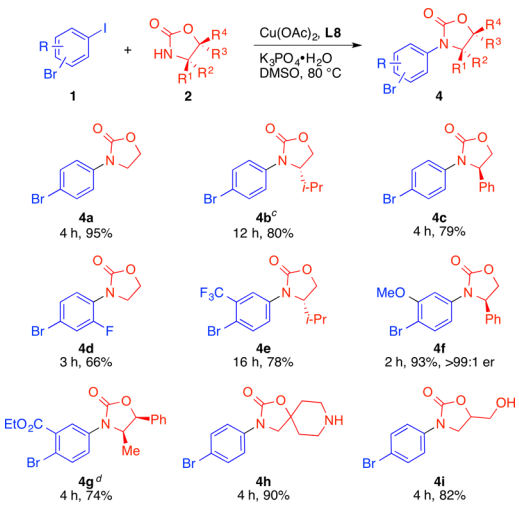


[a]Conditions A: **1** (1 mmol), **2a** (110 mol %), $Cu(OAc)_2$ (10 mol %), **L7** (20 mol %), $K_3PO_4{\cdot}H_2O$ (200 mol %), CH_3CN (1 mL); conditions B: **1** (1 mmol), **2a** (110 mol %), $Cu(OAc)_2$ (10 mol %), **L8** (20 mol %), $K_3PO_4{\cdot}H_2O$ (200 mol %), DMSO (1 mL). [b]Isolated yields after flash column chromatography with >98:2 ratio of bromo-substituted product **3** vs iodo-substituted product. [c]Anhydrous K_3PO_4 was used. [d]A 96:4 ratio of bromo vs iodo product was observed.

para- and meta-substitutions on **1** were well tolerated; however, the additional steric hindrance created by ortho-substituents resulted in increased reaction duration and high levels of competitive halogen exchange, leading to nonproductive reactions (cf. **4d** in Scheme 2). In general, the halogen−exchange pathway was effectively inhibited with a >98:2 ratio of bromo- vs iodo-substituted compound in every isolated product shown in Scheme 1 except for **3j**. Isolated yields ranging from 56% to 91% were obtained for a wide variety of arenes with electron-deficient substrates such as **3c** showing faster reaction rates compared to electron-rich substrates such as **3d**. A series of functional groups including fluoro (**3c**), amino (**3e**), methoxy (**3f**), nitrile (**3g**), and ester (**3h**) were found to be well tolerated under the optimized reaction conditions, although the milder reaction condition A using **L7** as the ligand in acetonitrile was preferred for substrates containing relatively more sensitive functional groups such as amino (**3e**) and nitrile (**3g**), necessitating longer reaction times but still resulting in 56% and 84% yields, respectively. It is also worth noting that the use of anhydrous K_3PO_4 in place of the more easily handled monohydrate $K_3PO_4{\cdot}H_2O$ as base minimized hydrolysis and allowed the isolation of product **3h** or aforementioned **3g** bearing a sensitive ester or nitrile moiety in 77% and 84% yields, respectively. C−N couplings of heteroaryl substrates such as bromoiodopyridines were also found to be successful, providing the desired products **3i** and **3j** in 74% and 79% yields, respectively.

We next examined the scope of oxazolidinones for the selective C−N coupling (Scheme 2). Using the optimized reaction conditions, a series of 4-substituted oxazolidinones were coupled

Scheme 2. Scope of Oxazolidinones in Cu-Catalyzed Selective Couplings with Bromoiodoarenes[a,b]



[a]Reaction conditions: **1** (1 mmol), **2** (110 mol %), $Cu(OAc)_2$ (10 mol %), **L8** (20 mol %), $K_3PO_4{\cdot}H_2O$ (200 mol %), DMSO (1 mL). [b]Isolated yields after flash column chromatography with >98:2 ratio of bromo-substituted product **4** vs iodo-substituted product. [c]85% conversion was obtained based on HPLC analysis of the reaction mixture. [d]Anhydrous K_3PO_4 was used.

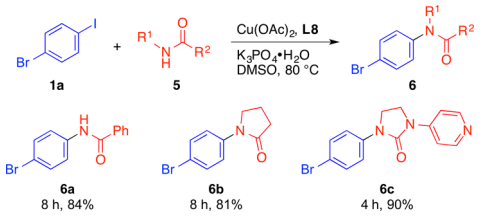
with **1a** to understand the impact of steric bulk at C-4 on the reaction rate. Products **4a** and **3a** (see Table 1), derived from parent and 4-methyl substituted oxazolidinones respectively, could be obtained in high yields within 4 h. A prolonged reaction time (12 h) was needed for coupling sterically hindered 4-isopropyloxazolidinone and afforded an 80% isolated yield of product **4b**. Even under these conditions, halogen exchange derived impurities were controlled at <5 A % HPLC in the crude reaction mixture. Interestingly, coupling of even more sterically hindered 4-phenyloxazolidinone[13] was found to be a facile reaction with complete conversion and an 82% isolated yield of product **4c** after 4 h. Arylation of the parent oxazolidinone by a 2-fluoro-4-bromoiodobenzene proceeded with a modest 66% yield (**4d**), but larger ortho substituents than the fluoro group on the arenes were not well tolerated even with the more accommodating catalytic system. The C−N bond formation was found to be chemoselective for the oxazolidinone over other potential coupling partners such as an unprotected cyclic secondary amine (**4h**, 90%) or a primary alcohol (**4i**, 82%).[14] It is noteworthy that stereochemical integrity at C-4 remained intact under the standard reaction conditions, exemplified by >99:1% er for product **4f** bearing the most acidic proton at C-4 among other 4-substituted oxazolidinones evaluated. Overall, a variety of novel *N*-aryl oxazolidinones were isolated in a >98:2 ratio of bromo- versus iodo-substituted product utilizing a series of 4- and/or 5-substituted oxazolidinones, greatly expanding the available design space for SAR studies in the discovery chemistry domain.

Without further optimization, the developed catalytic system was also applied to coupling of other nucleophile classes such as a primary or secondary amide and a urea producing the corresponding desired products (Scheme 3, **6a**−**6c**) in 81−90% yield and >95:5 Br/I ratio upon isolation.

Finally, the utility of the featured sequential functionalization via a chemoselective coupling was demonstrated by performing the formal synthesis of the marketed antibiotic linezolid (Scheme 4). Arylation of the oxazolidinone **2b** with 3-fluoro-4-

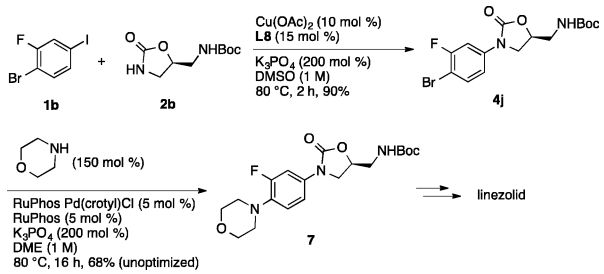
DOI: 10.1021/acs.orglett.7b01304
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Coupling with Other Nitrogen Nucleophiles[a,b]



[a]Reaction conditions: **1** (1 mmol), **5** (110 mol %), $Cu(OAc)_2$ (10 mol %), **L8** (20 mol %), $K_3PO_4{\cdot}H_2O$ (200 mol %), DMSO (1 mL). [b]Isolated yields after flash column chromatography with >95:5 ratio of bromo-substituted product **6** vs iodo-substituted product.

Scheme 4. Formal Synthesis of Linezolid via Sequential C−N Couplings



bromoiodobenzene (**1b**) proceeded in 2 h with hydrolytic opening of the oxazolidinone ring limited to <3% by the use of anhydrous K_3PO_4. The desired product **4j** was obtained in 90% isolated yield and with a >98:2 Br/I ratio, which was subjected to elaboration via a Pd-catalyzed amination with morpholine[15] to provide compound **7** that would afford linezolid following a deprotection and an acylation step.[16]

In summary, we have developed a chemoselective, Cu-catalyzed, Ullmann-type coupling of bromoiodoarenes with oxazolidinones to prepare a series of structurally diverse bromo *N*-aryloxazolidinones in 56−95% yields and >98:2 Br/I ratios. The key to the success of the developed method is identification of 1,10-phenanthroline-type ligands that minimize the competitive bromo−iodo exchange pathways while promoting the desired C−N coupling. The application through sequential functionalization of the aryl iodide and the aryl bromide has been demonstrated in the formal synthesis of antibiotic linezolid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01304.

Experimental procedures and detailed characterization data; copies of ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: han.chong@gene.com.

ORCID

Chong Han: 0000-0002-2863-3921

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Haiming Zhang for proofreading the manuscript, Dr. Mohammad Al-Sayah and Ms. Meenakshi Goel for analytical support, and Dr. Sarah Robinson for collecting HRMS data (Genentech, Inc.).

■ REFERENCES

(1) (a) Park, C.-H.; Brittelli, D. R.; Wang, C. L.-J.; Marsh, F. D.; Gregory, W. A.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1992**, *35*, 1156 and references therein. (b) Clemett, D.; Markham, A. *Drugs* **2000**, *59*, 815.

(2) Kanafani, Z. A.; Corey, G. R. *Expert Opin. Invest. Drugs* **2012**, *21*, 515.

(3) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(4) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(5) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F. Fr 2833947-WO 0353225 (Pr. Nb. Fr 2001 16547), 2001.

(6) For recent reviews, see: (a) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (c) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (d) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13.

(7) (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (b) Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963. (c) Ghosh, A.; Sieser, J. E.; Caron, S.; Couturier, M.; Dupont-Gaudet, K.; Girardin, M. *J. Org. Chem.* **2006**, *71*, 1258. (d) Li, J.; Zhang, Y.; Jiang, Y.; Ma, D. *Tetrahedron Lett.* **2012**, *53*, 3981.

(8) Mahy, W.; Plucinski, P. K.; Frost, C. G. *Org. Lett.* **2014**, *16*, 5020.

(9) For Cu-catalyzed coupling of *N*-arylation of parent 2-oxazolidinone, see: (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Heterocycles* **2003**, *61*, 505. For Cu-catalyzed coupling of oxazolidinones with 1,4-diiodobenzene, see: (b) Nandakumar, M. V. *Adv. Synth. Catal.* **2004**, *346*, 954. For selective Cu-catalyzed *N*-arylation of amides with bromoiodoarenes, see: (c) Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2004**, *45*, 2311. (d) Racine, E.; Monnier, F.; Vors, J.-P.; Taillefer, M. *Org. Lett.* **2011**, *13*, 2818. (e) Kundu, D.; Bhadra, S.; Mukherjee, N.; Sreedhar, B.; Ranu, B. C. *Chem. - Eur. J.* **2013**, *19*, 15759.

(10) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.

(11) For representative examples of use of 1,10-phenanthroline-type ligands in Cu-catalyzed Ullmann-type couplings, see: (a) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670. (b) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657. (c) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (d) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (e) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490. (f) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284.

(12) A control experiment showed <1% conversion to bis-coupled side product **3a″** in the reaction of aryl bromide **3a** with oxazolidinone **2a** under conditions shown in Figure 2 indicating bromo−iodo exchange to a more reactive aryl iodide **3a′** was accountable for the formation of **3a″**.

(13) (a) A-values of substituents: Me, 1.70; *i*-Pr, 2.15; Ph, 3.0. See: Hirsch, J. A. *Topics in Stereochemistry*, 1st ed.; John Wiley & Sons, Inc.: New York, 1967; pp 199−222. (b) Similar rate differences between 4-*i*-Pr and 4-Ph substituted oxazolidinones were observed by Ma and co-workers; see ref 7d.

(14) The observed chemoselectivity for the oxazolidinone over a primary alcohol was found to be interesting given **L8** was reported to be an optimal ligand for Cu-catalyzed *O*-arylation of alcohols; see ref 11f and references therein.

(15) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. *J. Org. Chem.* **2015**, *80*, 6794.

(16) Greco, A.; De Marco, R. D.; Tani, S.; Giacomini, D.; Galletti, P.; Tolomelli, A.; Juaristi, E.; Gentilucci, L. *Eur. J. Org. Chem.* **2014**, *2014*, 7614.

DOI: 10.1021/acs.orglett.7b01304
Org. Lett. XXXX, XXX, XXX−XXX