Coupling Reactions

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Mild Ullmann-Type Biaryl Ether Formation Reaction by Combination of *ortho*-Substituent and Ligand Effects**

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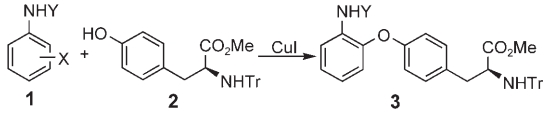
Many natural cyclopeptides bearing a biaryl ether bridge[1] possess remarkable physiological activities. These include antibiotics (vancomycin,[1,2] ristocetin,[3] and teicoplanin[1,4]), antitumor agents (K-13[5,6e] and bouvardin[6a–c]), neurotensin antagonist RP-66453,[7] and anti-HIV agents (e.g., chloropeptins[8]). For elaboration of these synthetically challenging molecules, several elegant methods that feature biaryl ether formation have been developed. Examples include oxidative phenolic coupling,[1c] *o*-nitro-[1b,2e,f,7] or metal-activated[1c,5a] nucleophilic aromatic substitution, modified Ullmann-type coupling reactions,[1,2a,6] and boronic acid based biaryl ether synthesis.[4,8–10] However, more practical and flexible protocols are still required to improve the synthetic approaches to these biologically important cyclopeptides.

The Ullmann-type coupling reaction of aryl halides and phenols is a reliable method for elaborating biaryl ethers.[10,11] Although this reaction has been employed for the assembly of certain cyclopeptides,[1c,6] the danger of racemization of the amino acid moieties under basic conditions and high reaction temperatures ($\approx 130\,^{\circ}C$) prevents its wide application in this area. In 1997, Nicolaou et al. found that a triazene unit *ortho* to the halogen atom facilitates coupling with phenol moieties so that the reaction proceeds at 80 °C.[2a] Successful application of the method to the total synthesis of vancomycin has been reported.[1a,2b–d] However, good conversion of the substrates requires at least five equivalents of $CuBr{\cdot}SMe_2$. Recently, we and other groups discovered that some special ligands could promote CuI-catalyzed C(aryl)–O bond formation.[10,11] Unfortunately, these new reaction conditions still fall short of that needed for cyclopeptide synthesis because the reaction temperatures are still too high. Recently, we found that the NHCOR groups in 2-haloacetanilides could greatly promote the Ullmann-type biaryl formation reaction, which in combination with the known ligand effect led to this reaction taking place at room temperature. Herein, we wish to disclose these results.

As indicated in Table 1, the reaction of 2-bromotrifluoroacetanilide (**1a**) with L-tyrosine derivative **2** using CuI/*N*,*N*-dimethylglycine in the presence of Cs_2CO_3 at room temperature is completed in 2 h and delivers the coupling product **3a** in 88% yield (entry 1). Low yields were observed with *N*-methyl-L-proline or L-proline as the ligands (entries 2 and 3), and no coupling occurred in the absence of a ligand (entry 4). Relative to aryl bromide **1a**, aryl iodide and chloride were poorer substrates (entries 5 and 6). In addition, a reactivity trend for the *N*-substituent ($Y = COCF_3 > COCH_3 > COPh \gg SO_2Me$) was noted (entries 1 and 7–9). Furthermore, little or no conversion was noticed in the case of 3-bromotrifluoroacetanilide or 4-bromotrifluoroacetanilide as the substrates (entries 10 and 11). These results clearly show the existence of an accelerating effect caused by an *ortho*-amide group and that its combination with ligand effects is essential for this reaction to take place at room temperature.

Table 1: CuI-catalyzed reaction of aryl halides **1** with phenol **2**.[a]



a: Y = $COCF_3$, b: Y = $COCH_3$, c: Y = COPh, d: Y = SO_2Me

Entry	Y	X	Ligand[b]	*t* [h]	Yield [%][c]
1	$COCF_3$	2-Br	A	2	88
2	$COCF_3$	2-Br	B	4	49[d]
3	$COCF_3$	2-Br	C	2	26[d]
4	$COCF_3$	2-Br	–	5	0[d]
5	$COCF_3$	2-I	A	5	43[d]
6	$COCF_3$	2-Cl	A	24	7[d]
7	$COCH_3$	2-Br	A	15	53[d]
8	COPh	2-Br	A	24	14[d]
9	SO_2Me	2-Br	A	24	0[d]
10	$COCF_3$	3-Br	A	2	–[e]
11	$COCF_3$	4-Br	A	2	–[f]

[a] Reaction conditions: CuI (0.15 mmol), ligand (0.5 mmol), **1** (0.5 mmol), **2** (0.75 mmol), Cs_2CO_3 (1.5 mmol), 1,4-dioxane (2 mL), RT. [b] A: *N*,*N*-dimethylglycine, B: *N*-methyl-L-proline, C: L-proline. [c] Yield of the isolated products. [d] Aryl halide was recovered in 40–90% yield. [e] Corresponding cross-coupling product was isolated in less than 3% yield. [f] No conversion was observed. Tr = triphenylmethyl.

With the optimized reaction conditions in hand, we studied the process with a few other aryl bromides and phenols (Table 2). Both *N*-Cbz- and *N*-Boc-L-tyrosine methyl esters were suitable for this reaction and gave **6a** and **6b** in good yields without any racemization, as determined by chiral-column HPLC analysis. Some loss of optical purity was observed when *N*-Boc-(*R*)-4-hydroxyphenylglycine methyl ester was used (see **6c**). Fortunately, this problem could be obviated by changing the *N*-protecting group from Boc to Tr

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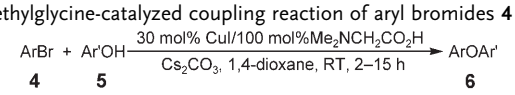
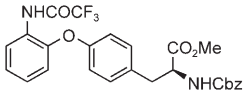
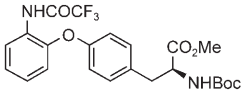
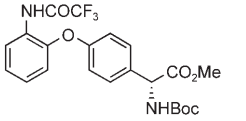
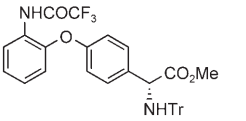
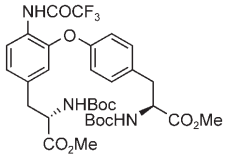
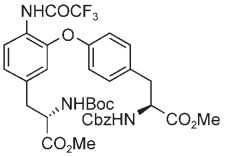
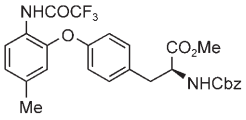
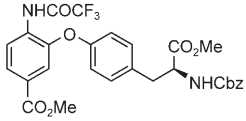
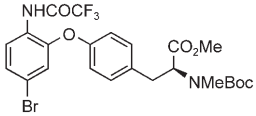
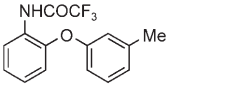
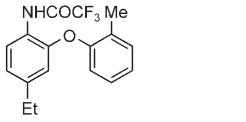
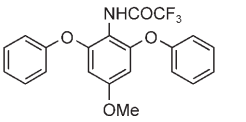
Table 2: CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction of aryl bromides **4** with phenols **5**.[a]



4 **5** **6**

Product		*t* [h]	Yield [%]	Product		*t* [h]	Yield [%]
	**6a**[b]	5	82		**6b**[b]	5 h	90
	**6c**[c]	8	88		**6d**[b]	8	82
	**6e**	14	85		**6f**	14	80
	**6g**	3	88		**6h**[d]	10	51
	**6i**	4	81		**6j**	4	82
	**6k**	4	76		**6m**[e]	4	70

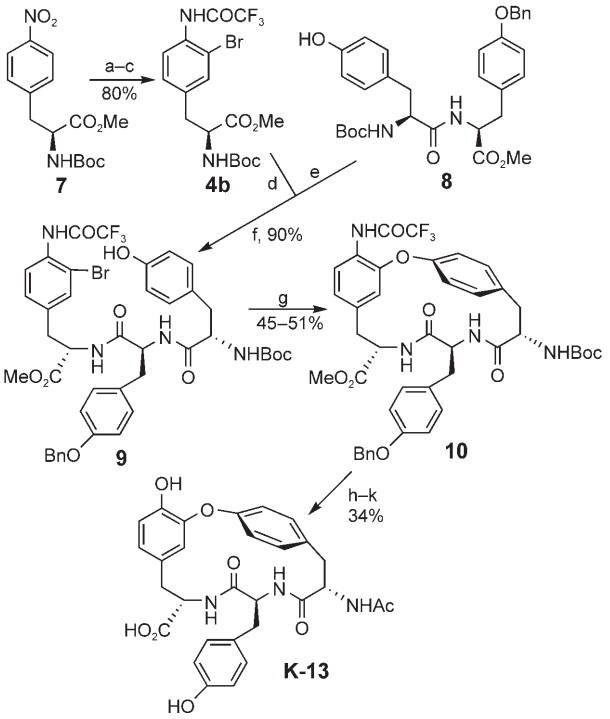
[a] Reaction conditions: CuI (0.15 mmol), *N*,*N*-dimethylglycine (0.5 mmol), **4** (0.5 mmol), **5** (0.75 mmol), Cs_2CO_3 (1.5 mmol), 1,4-dioxane (2 mL), RT. [b] 99% *ee*, as determined by HPLC. [c] 91% *ee*, as determined by HPLC. [d] 40% aryl bromide was recovered. [e] Phenol (1.5 mmol) was added. Cbz = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl.

(see **6d**). From a L-phenylalanine-derived bromide **4b** (see Scheme 1 for the preparation), two isodityrosine analogues **6e** and **6f** were produced in good yields. These compounds are promising synthetic intermediates for isodityrosine,[9] K-13,[5] and related natural products. We found that electron-deficient aryl bromides are less reactive (see **6h**). The exclusive formation of **6i** from a coupling of 2,4-dibromotrifluoroacetanilide provided further support of an *ortho*-substituent effect by an NHCOR group. An amino acid residue in the phenol component is not necessary for the reaction, as demonstrated by examples **6j**–**6m**. The formation of **6k** and **6m** also indicated that steric factors might not be critical and a twofold *ortho*-substitution is possible, for example, with 2,6-dibromotrifluoroacetanilides.

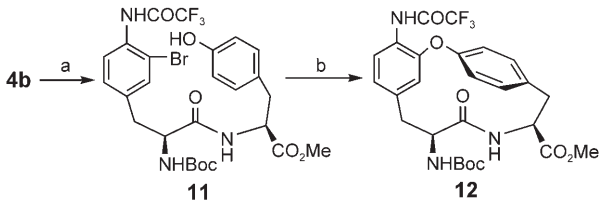
Encouraged by the above success, we extended our work to intramolecular macrocyclization, with the total syntheses of antitumor agent K-13 and a cycloisodityrosine derivative. As shown in Scheme 1, **7** was reduced by hydrogenation, brominated with NBS, and treated with $(CF_3CO)_2O$ to afford aryl bromide **4b**. Hydrolysis of **8** with LiOH was followed by coupling with a liberated amine from **4b**. Tripeptide **9**, thus obtained, was subjected to macrocyclization in the presence of CuI (3 equiv) *N*,*N*-dimethylglycine (3 equiv), and Cs_2CO_3 (3 equiv) in dilute dioxane (0.01M), and the desired cyclization product **10** was isolated in 45–51% yields. Next, the macrolactam **10** was converted into K-13 in 34% overall yield through five routine transformations, which included proper changes of the protecting groups, hydrolysis of the ester and trifluoroacetanilide groups, and diazotization of the aniline unit to a phenol moiety.

We also carried out a synthesis of **12** (see Scheme 2) from dipeptide **11**, which was obtained by coupling a liberated acid from **4b** with L-tyrosine methyl ester. Although an initial attempt to effect its macrocyclization under our standard conditions failed, when the solvent was changed to MeCN/pyridine (4:1), and the reaction temperature was raised to 45°C, we were pleased to notice that the desired cyclic product **12**, which might serve as an intermediate for synthesizing RP 66453, was isolated in 42% yield.[7] This cyclization is comparable with those reported by two groups who used *o*-nitro-activated nucleophilic aromatic substitution,[7] but in our case two amino acid units could be readily obtained from L-phenylalanine and L-tyrosine. This advantage would allow large-scale preparation.

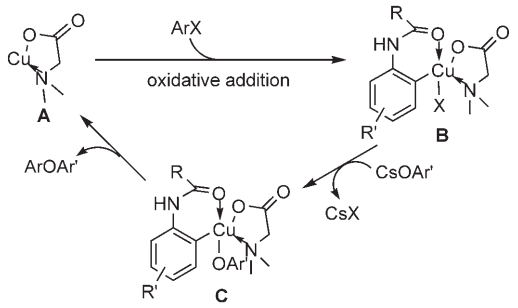
Since the Hurtley reaction was disclosed in 1929, considerable efforts have been devoted to identifying suitable *ortho*-substituents that can promote Ullmann-type couplings.[2a,12] However, only carboxylate and triazene units have been found to have the desired accelerating effect prior to our present work. Two mesomerism models have been proposed for interpreting the early results,[2a,12c] but a similar model is not suitable for rationalizing the present *ortho*-substituent effect. Consequently, we propose a plausible mechanism as follows (Scheme 3): Oxidative addition of the chelated Cu^I center **A** to ArX produces complex **B**, in which the oxygen of the NHCOR group may coordinate with the Cu center to provide additional stabilization. It is noteworthy that similar Pd^{II} complexes have been determined by Tremont and Rahman in their palladium acetate catalyzed *ortho*-alkylation of acetanilides.[13a] After reaction of **B** with cesium phenoxides to give **C**, reductive elimination occurs to afford the biaryl ethers and regenerate the catalytic species. This model was supported by the difference in reactivity between the trifluoroacetanilides and acetanilides discussed above. The higher reactivity of the aryl bromides might be explained by



Scheme 1. Synthesis of K-13. Reagents and conditions: a) $Pd/C/H_2$, MeOH, RT; b) NBS, DMF, RT; c) $(CF_3CO)_2O$, CH_2Cl_2; d) TFA, CH_2Cl_2; e) aq. LiOH, THF, MeOH; f) HATU/DIPEA, DMF; g) Cs_2CO_3, CuI, *N*,*N*-dimethylglycine, 1,4-dioxane, RT; h) TFA then Ac_2O/TEA; i) aq. NaOH, MeOH; j) *t*BuONO/HBF_4, MeCN; k) $Cu(NO_3)_2/Cu_2O$. NBS = *N*-bromosuccinimide, DMF = dimethylformamide, TFA = trifluoroacetic acid, HATU = 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, DIPEA = diisopropylethylamine, TEA = triethylamine.



Scheme 2. Synthesis of a cycloisodityrosine derivative. Reagents and conditions: a) 1. aq. LiOH, MeOH, THF; 2. L-tyrosine methyl ester, EDCI, HOBt, DIPEA, CH_2Cl_2, 90% for two steps; b) CuI (3 equiv), $Me_2NCH_2CO_2H$ (4 equiv), Cs_2CO_3 (4 equiv), MeCN/Py (4:1), 0.01 M, 45 °C, 42%. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.



Scheme 3. Plausible mechanism for mild biaryl formation.

the different contributions of the bromide and iodide anions to the stabilization of **B**. Besides this speculation, more work should be performed to prove this mechanism further or other possible mechanisms should be put forward.

In summary, we have found that the NHCOR group has a strong *ortho*-substituent effect on an Ullmann-type biaryl ether formation reaction. This *ortho*-substituent effect is the third type discovered to date, which should facilitate the development of more mild Ullmann-type coupling reactions.[10] In addition, although the substrates tested so far are limited, our new reaction is rather mild and fast relative to the previous Cu^I-catalyzed coupling reactions of aryl halides with phenols,[11] and therefore should find further applications in organic synthesis.

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