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Ligand-free Cu-catalyzed O-arylation of aliphatic diols

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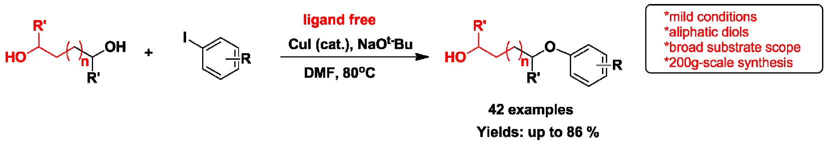
Abstract: Coupling reaction between aryl iodides and aliphatic diols was realized with a ligand-free copper catalyst under mild conditions. This method was successfully applied in the process of scale–up synthesis of medicinal candidate product EMB-3.



Introduction

Since Ma et al. reported the first effective ligand amino acid (**L1**, Figure 1) for copper catalysis in the synthesis of enantiopure *N*-aryl-α-amino acids from *R*-amino acids with aryl halides in 1998,[1,2] Brønsted base,[3,4] phenanthroline (**L2**, Fig. 1),[5] 1,2-diamino-cyclohexane (**L3**, Fig. 1)[6,7,8] and several other representative ligands (**L4–L7**, Fig. 1) were reported as effective ligands in the CuI-catalyzed aryl amination.[9] Based on these novel ligands, many chemoselective methods, such as C_{sp2}- or C_{sp3}-*N*-arylation[10], C_{sp2}-S-arylation[11] and C_{sp2}-O-arylation[12] have been studied. However, only a few reported copper catalyst systems could facilitate the coupling between aryl halides and aliphatic alcohols[13] because of the weak nucleophilic ability of aliphatic alcohols. For example, researchers, including Buchwald *et al.*, reported a highly efficient phenanthroline ligand (**L2**, R^1, R^2, R^3, R^4 = Me, Fig. 1) in the amination of aryl iodides under mild conditions.[14, 15, 16]

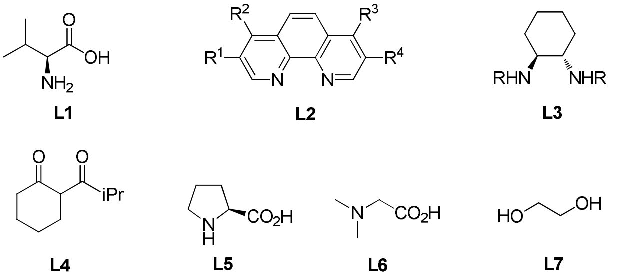
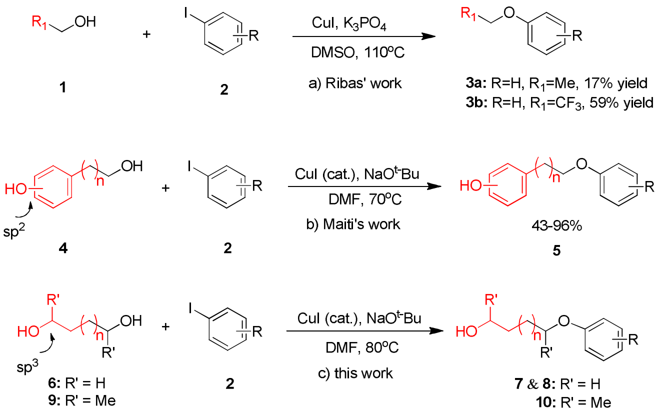


Fig 1. Representative ligands for the Ullmann reaction

Avoiding the use of different complex and expensive ligands, "ligand-free" copper catalyst systems have been reported recently in the O-arylation of aliphatic alcohols (17–59% yields, Scheme 1a).[17] However, the reaction substrate was very narrow and high temperatures were required. In addition, the yield of desired ethers was very low and was just determined exclusively using ^{1}H-NMR spectroscopy. Maiti reported an efficient ligand-free Cu-catalyzed O-arylation of aliphatic alcohols **4** and aryl iodide **2** to produce alkyl aryl ether **5** in the presence of 2.3 equivalents of NaO^{t}Bu (Scheme 1b).[18] Although this "ligand-free" methodology was further tested in the one-step synthesis of 2-(2-(4-fluorophenoxy)ethyl)-phenol (**CRE 10904**: 2-OH, n=1, R=4-F, Scheme 1b), it could not be transposed on industrial scale because of its relative low yield of 50%. Very recently, Chae reported a Cu-catalyzed O-arylation of aliphatic alcohols with aryl bromide as substrate and $CuCl_2$ as catalyst (83-99% yields). However, this protocol was effective for the aryl bromide and the required temperature (at 130°C) was high.[19] Therefore, ligand-free Cu-catalyzed O-arylation of aliphatic alcohols remains a challenge.



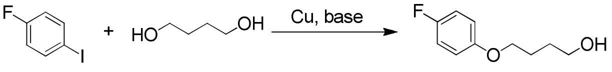
Scheme 1. Ligand-free Cu-catalyzed O-arylation of aliphatic alcohols

Our research group has engaged in metal-catalyzed coupling transformation including C–C coupling reactions[20] and C–S coupling reactions[21]. For the purpose of extending to C–O coupling reactions, the efficiency of ligand-free copper-catalyzed C_{sp3}-O-alkyl chain was investigated. Herein, we disclose a simple and practical ligand-free procedure for the copper-catalyzed arylation of different primary and secondary aliphatic diols (Scheme 1c).

Results and Discussion

4-Fluoro-iodobenzene **2a** and 1, 4-butanediol **6a** were selected as model substrates in the experiment under various conditions (Table 1). After **2a** was treated with **6a** (3.0 equiv.) in the presence of CuI (5 mol%) and NaO^{t}Bu (3.0 equiv.) in *N*, *N*-dimethylformamide at 70 °C for 18 h, product **7a** was isolated with a yield of 76% (Table 1, entry 1). Upon using CuBr as the catalyst, product **7a** was obtained in lower yield (Table 1, entry 2). As shown in Table 1 (Entries 1, 3–5), the amount of CuI had limited influence on the yield. Entries 6–9 in Table 1 show that NaO^{t}Bu was essential for the coupling reaction because **7a** was not obtained with K_2CO_3, K_3PO_4, Cs_2CO_3 or Et_3N. Entries 10–14 in Table 1 also show that solvent effects were significant and product **7a** could not be produced in THF, DMSO, 1, 4-dioxane, MeCN or toluene instead of DMF. When reaction temperature was increased to 80 °C from 70 °C, the yield of **7a** was unchanged, but a further increase over 80 °C evidently decreased the yields (Table 1, entries 15–18). When the dosage of diol was increased to 5.0 equiv. or decreased to 1.5 equiv., **7a** was isolated in a yield of 78% and 55%, respectively (Table 1, entries 19 and 20). As shown in Table 1, **7a** wasn't obtained when CuI wasn't used (Entry 22) or when a small amount of water was added (Entry 23) or when 1, 4-butanediol was replaced by 1-butanol (Table 1, Entry 21), suggesting that 1, 4-butanediol was the starting material and also the ligand. Therefore, reaction conditions were determined to include CuI (10 mol%) as the catalyst and NaO^{t}Bu (3.0 equiv.) as the base in DMF at 80 °C with a **2a/6a** molar ratio of 1:3 for 18 h (Table 1, entry 15).

Table 1. Optimization of Reaction Conditions[a]



2a **6a** **7a**

Entry	copper	base	solvent	Temp.(^{o}C)	Yields (%)[b]
1	CuI (5 mol%)	NaO^{t}Bu	DMF	70	76
2	CuBr (5 mol%)	NaO^{t}Bu	DMF	70	58
3	CuI (10 mol%)	NaO^{t}Bu	DMF	70	77
4	CuI (15 mol%)	NaO^{t}Bu	DMF	70	65
5	CuI (20 mol%)	NaO^{t}Bu	DMF	70	76
6	CuI (10 mol%)	K_2CO_3	DMF	70	0
7	CuI (10 mol%)	K_3PO_4	DMF	70	0
8	CuI (10 mol%)	Cs_2CO_3	DMF	70	0
9	CuI (10 mol%)	Et_3N	DMF	70	0
10	CuI (10 mol%)	NaO^{t}Bu	THF	70	0
11	CuI (10 mol%)	NaO^{t}Bu	DMSO	70	0[f]
12	CuI (10 mol%)	NaO^{t}Bu	1, 4-dioxane	70	0
13	CuI (10 mol%)	NaO^{t}Bu	MeCN	70	0
14	CuI (10 mol%)	NaO^{t}Bu	toluene	70	0
15	**CuI (10 mol%)**	**NaO^{t}Bu**	**DMF**	**80**	**78**
16	CuI (10 mol%)	NaO^{t}Bu	DMF	90	69
17	CuI (10 mol%)	NaO^{t}Bu	DMF	100	58
18	CuI (10 mol%)	NaO^{t}Bu	DMF	110	67
19	CuI (10 mol%)	NaO^{t}Bu	DMF	80	78[c]
20	CuI (10 mol%)	NaO^{t}Bu	DMF	80	55[d]
21	CuI (10 mol%)	NaO^{t}Bu	DMF	80	0[e]
22	CuI (0 mol%)	NaO^{t}Bu	DMF	80	0[f]
23	CuI (10 mol%)	NaO^{t}Bu	DMF	80	0[g]

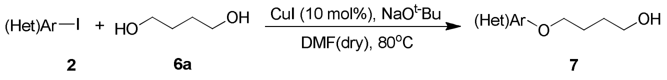
[a] Reaction conditions: **2a** (0.5 mmol), **6a** (1.5 mmol, 3.0 equiv.), copper catalyst (0.05–0.2 mmol), base (1.5 mmol, 3.0 equiv.), solvent (2 mL), 18h. [b] Isolated yields calculated based on **2a**. [c] 5.0 equiv. 1, 4-butanediol was used. [d] 1.5 equiv. butanediol was used. [e] 1, 4-butanediol was replaced by 1-butanol. [f] 4-(4-iodophenoxy)butan-1-ol **7t** instead of **7a** was obtained and the structure was confirmed by ^{19}F-NMR, ^{1}H-NMR and ^{13}C-NMR. [g] 0.5 mL H_2O was added to the reaction system.

To further test this reaction, **6a** was reacted with various aryl iodides under the optimized reaction conditions. As shown in Table 2, with some electron-withdrawing groups, such as Cl, Br and phenyl, the desired products were obtained in relatively moderate yields (Table 2, entries 4, 5 and 9). However, with other electron-withdrawing groups, such as cyano, trifluoromethyl and benzoyl, the corresponding products were obtained only in very low yield probably due to their strong electron–withdrawing effects (Table 2, entries 6-8). Iodobenzenes bearing one or two electron-donating groups on the phenyl ring, such as **2j**, **2k**, **2l**, **2m**, **2n**, **2r** and **2s** reacted with **6a** to form the coupled products in low to moderate yields (Table 2, entries 10–14, 18 and 19). In addition to *para*-substituted iodobenzene **2a** and **2l**, *meta*–substituted substrate **2b**, *ortho*–substituted substrate **2c** and **2m** were also successfully applied to this transformation with relatively low yield (Table 2, entries 2 and 3). Furthermore, iodides with phenyl ring, pyridine ring or thiophene ring gave the desired coupled products (**7o**: 77%, **7p**: 74% and **7q**: 53%) without much yield loss (Table 2, entries 15–17). When reaction temperature was decreased to 70°C from 80°C, product **7l** and **7o** were obtained in slightly lower yield (73 and 74% respectively), proving 80°C was more efficient than 70°C (Table 2, entries 12 and 15).

When various diols, including aliphatic diols **6b–e** and methyl or benzyl substituted diethanol amine **6f–g**, were used, the desired products were obtained in 45-86% yields (Table 3, entries 1–9). Compared with **6a**, aliphatic diols **6b–e** gave the corresponding products **8a–d** in lower yields (Table 3, entries 1–4), which indicated that the chain length of aliphatic diols might affect the reaction efficiency. Comparing between *N*-methyl diethanol amine **6f** and *N*-benzyl diethanol amine **6g,** which had comparable reactivities as **6a**, **6g** exhibited higher reactivity with better yields (Table 3, entries, 5–

6). Aryl iodides **2a**, **2o** and **2r** reacted with **6f** or **6g** to afford the desired products in 52–77% yields (Table 3, entries 7–9).

Table 2. Synthesis of alkyl aryl ethers **7** from aryl iodides **2** and 1, 4-butane -diol **6a**[a].

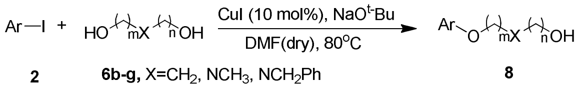


Entry	Ar (Het)	7	Yields (%)[b]
1	**2a** 4-F-C_6H_4	**7a**	78
2	**2b** 3-F-C_6H_4	**7b**	68
3	**2c** 2-F-C_6H_4	**7c**	58
4	**2d** 4-Br-C_6H_4	**7d**	82
5	**2e** 4-Cl-C_6H_4	**7e**	80
6	**2f** 4-CN-C_6H_4	**7f**	30
7	**2g** 4- CF_3-C_6H_4	**7g**	44
8	**2h** 4- Bz-C_6H_4	**7h**	38
9	**2i** 4- Ph-C_6H_4	**7i**	64
10	**2j** 4-NHAc-C_6H_4	**7j**	35
11	**2k** 4-OMe-C_6H_4	**7k**	63
12	**2l** 4-Me-C_6H_4	**7l**	78 (73[c])
13	**2m** 2-Me-C_6H_4	**7m**	58
14	**2n** 4-OCF_3-C_6H_4	**7n**	70
15	**2o** C_6H_5	**7o**	77 (74[c])
16	**2p** 2-pyridinyl	**7p**	74 (Trace[d])
17	**2q** 3-thiophenyl	**7q**	53
18	**2r** 3,5-dimethyl-C_6H_3	**7r**	72
19	**2s** 2,4-dimethoxyl-C_6H_3	**7s**	49

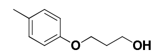
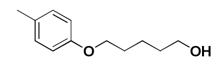
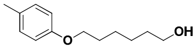
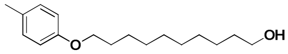
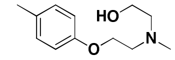
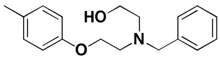
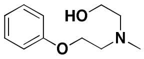
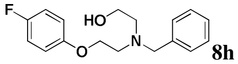
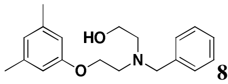
[a] Reaction conditions: **2** (0.5 mmol), **6a** (1.5 mmol, 3.0 equiv.), CuI (0.05 mmol, 10 mol%), NaO^{t}Bu (1.5 mmol, 3.0 equiv.), DMF (2 mL), 80°C, 18h. [b] Isolated yields calculated based on **2**. [c] At 70°C. [d] CuI was not added.

To further examine the scope of diols, 2, 5-hexanediol **9** was tested under the optimized conditions. As shown in Table 4, iodobenzene derivatives containing electron-donating or electron-withdrawing groups on the aryl moiety reacted with 2, 5-hexanediol to produce the corresponding products in 36–78% yields, which indicated that the steric hindrance on diols had limited impact on the reaction.

Table 3. Synthesis of alkyl aryl ethers **8** from aryl iodides **2** and diols **6**[a]



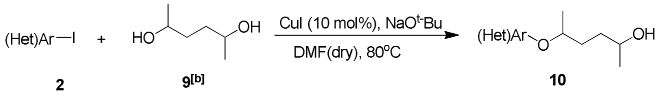
6b, m=1, n=1, X=CH_2; **6c**, m=2, n=2, X=CH_2; **6d**, m=2, n=3, X=CH_2; **6e**, m=4, n=5, X=CH_2; **6f**, m=2, n=2, X=NCH_3; **6g**, m=2, n=2, X=NCH_2Ph

Entry	2	6	8	Yield [%][b]
1	**2l**	**6b**	 **8a**	59
2	**2l**	**6c**	 **8b**	60
3	**2l**	**6d**	 **8c**	61
4	**2l**	**6e**	 **8d**	45
5	**2l**	**6f**	 **8e**	76
6	**2l**	**6g**	 **8f**	86
7	**2o**	**6f**	 **8g**	52
8	**2a**	**6g**	 **8h**	77
9	**2r**	**6g**	 **8i**	65

[a] Reaction conditions: **2** (0.5 mmol), **6** (1.5 mmol, 3.0 equiv.), CuI (0.05 mmol, 10 mol%), NaO^{t}Bu (1.5 mmol, 3.0 equiv.), DMF (2 mL), 80°C, 18h. [b] Isolated yields calculated based on **2**.

According to Maiti's excellent work, the ligand-free Cu-catalyzed chemoselective mono-arylation of aliphatic alcohols could be applied to modify Ullmann coupling reaction between diols **6** and aryl iodides **11** from commercial available 4-chloro-6-iodo-quinazoline and different anilines, thus to provide [4-phenylamino-6-quinazolinyl]-oxyl-propanol **12,** a key intermediate of anticancer drug candidate EMB–3.[22, 23] Under the optimized conditions, **11a–c** reacted with aliphatic diols **6a–c** to form the corresponding compounds successfully in 60–82% yields (Table 5, entries 1–7). And this intermediate **12** could shorten the synthesis steps of EMB–3 from **6** to **3.** Furthermore, under these optimized reaction conditions, 200g–scale synthesis (yield: 82%) of **12a**, which was a key intermediate of anti-tumor compound EMB–3, was realized.

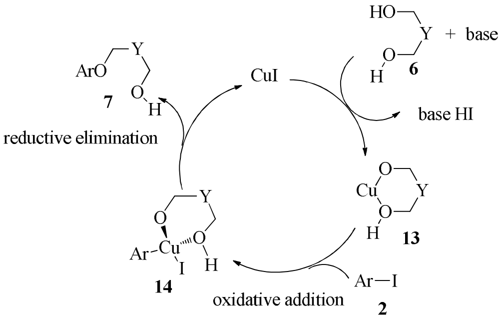
Table 4. Synthesis of alkyl aryl ethers **10** from aryl iodides **2** and 2, 5-hexanediol **9**[a]



Entry	Ar (Het)	10	Yield [%][c]
1	**2a** 4-F-C_6H_4	**10a**	47
2	**2k** 4-OMe-C_6H_4	**10b**	56
3	**2l** 4-Me-C_6H_4	**10c**	64
4	**2o** C_6H_5	**10d**	51
5	**2p** 2-pyridinyl	**10e**	54
6	**2r** 3,5-dimethyl-C_6H_3	**10f**	78
7	**2m** 2-Me-C_6H_4	**10g**	36

[a] Reaction conditions: **2** (0.5 mmol), **9** (1.5 mmol, 3.0 equiv.), CuI (0.05 mmol, 10 mol%), NaO^{t}Bu (1.5 mmol, 3.0 equiv.), DMF (2 mL), 80°C, 18h. [b] Mixture of isomers. [c] Isolated yields calculated based on **2**.

On the basis of the above results and literature reports,[24] we formulated a possible mechanism for the copper-catalyzed tandem cyclization in scheme 2. In the presence of a base, the chelation of CuI with diols **6** forms a reactive species **13**. In this process of forming intermediate **13**, diols **6** act as reactant and ligand. The ring strain of intermeditae **13** is not supposed to be too strong. Herein, glycol could not react with CuI to form the transition state. Subsequent oxidative addition of intermediate **13** with aryl iodides **2** leads to the intermediate **14**. Then CuI is regenerated by a putative reductive elimination, giving the desired products **7** simultaneously.

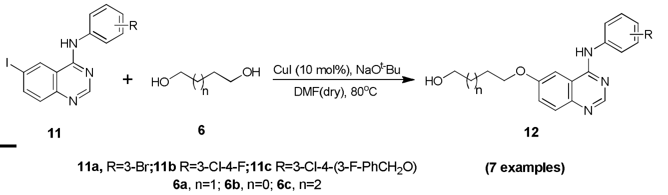


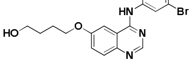
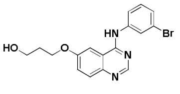
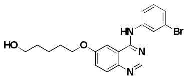
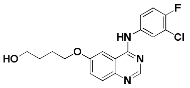
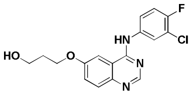
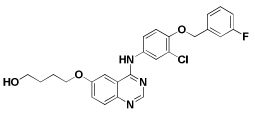
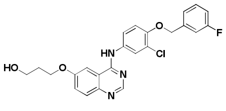
Scheme 2. Possible mechanism of copper-catalyzed O-arylation of aliphatic alcohols

Conclusions

In summary, we have successfully developed a ligand-free Cu-catalyzed protocol to synthesize alkyl aryl ethers from multi-substituted aryl iodides and aliphatic diols under mild conditions with moderate to good yields. Furthermore, with this method, under the optimized reaction conditions, 200g–scale synthesis (yield: 82%) of a key intermediate of medicine EMB–3 was realized.

Table 5. Applied synthesis of **12** from *N*-phenyl-6-iodo-4-quinazolinamine **11** and aliphatic diols **6**[a]



Entry	11	6	12	Yield [%][b]
1	**11a**	**6a**	 **12a**	82
2	**11a**	**6b**	 **12b**	73
3	**11a**	**6c**	 **12c**	76
4	**11b**	**6a**	 **12d**	65
5	**11b**	**6b**	 **12e**	60
6	**11c**	**6a**	 **12f**	72
7	**11c**	**6b**	 **12g**	77

[a] Reaction conditions: **11** (0.5 mmol), **6** (1.5 mmol, 3.0 equiv.), CuI (0.05 mmol, 10 mol%), NaO^{t}Bu (1.5 mmol, 3.0 equiv.), DMF (2 mL), 80°C, 18h. [b] Isolated yields calculated based on **11**.

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Notes and references

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(1) D. Ma, Y. Zhang, J. Yao, S. Wu, F. Tao, *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467.

(2) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, 41, 1450–1460.

(3) a) F. Ullmann, J. Bielecki, *Ber. Dtsch. Chem. Ges.***1901**, *34*, 2174–2185; b) F. Ullmann, *Ber. Dtsch. Chem. Ges.***1903**, *36*, 2382–2384.

(4) I. Goldberg, *Ber. Dtsch. Chem. Ges.***1906**, *39*, 1691–1692.

(5) H. B. Goodbrand, N.-X. Hu, *J. Org. Chem.* **1999**, *64*, 670–674.

(6) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.

(7) D. S. Surry, S. L. Buchwald, *Chem. Sci*. **2010**, 1, 13–31.

(8) F. Monnier, M. Taillefer, *Angew. Chem., Int. Ed.* **2008**, *47*, 3096–3099.

(9) K. Okano, H. Tokuyama, T. Fukuyama, *Chem. Commun.* **2014**, *50*, 13650–13663.

(10) a) W. Yang, Y. Long, S. Zhang, Y. Zeng, C. Qian, *Org. Lett.* **2013**, *15*, 3598–3601; b) K. Kunz, U. Scholz, D. Ganzer, *Synlett.* **2003**, 2428–2439; c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev*. **2004**, *248*, 2337–2364; d) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793–796; e) D. W. Ma, Q. Cai, H. Zhang, *Org. Lett.* **2003**, *5*, 2453–2455; f) Z. K. Lu, R. J. Twieg, S. P. D. Huang, *Tetrahedron Lett.* **2003**, *44*, 6289–6292.

(11) a) C.-F. Lee, Y.-C. Liu, S. S. Badsara, *Chem. Asian J.* **2014**, *9*, 706–722; b) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3517–3520; c) M. S. Kabir, M. Lorenz, M. L. Van Linn, O. A. Namjoshi, S. Ara, J. M. Cook, *J. Org. Chem.* **2010**, *75*, 3626–3643; d) Y.-J. Chen, H.-H. Chen, *Org. Lett.* **2006**, *8*, 5609–5612; e) N. R. Jogdand, B. B. Shingate, M. S. Shingare, *Tetrahedron Lett.* **2009**, *50*, 6092–6094; f) S. Murru, H. Ghosh, S. K. Sahoo, B. K. Patel, *Org. Lett.* **2009**, *11*, 4254–4257; g) Y. Feng, X. Zhao, J. Wang, F. Zheng, H. Xu, *Chin. J. Chem.* **2009**, *27*, 2423–2425; h) R. Xu, J.-P. Wan, H. Mao, Y. Pan, *J. Am. Chem. Soc.* **2010**, *132*, 15531–15533; i) R.-S. Xu, L. Yue, Y.-J. Pan, *Tetrahedron.* **2012**, *68*, 5046–5052; j) X. Lv, W. Bao, *J. Org. Chem.* **2007**, *72*, 3863–3867.

(12) a) A. Tlili, F. Monnier, M. Taillefer, *Chem. Eur. J.* **2010**, *16*, 12299–12302; b) M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 973–976; c) Also see: G. Nordmann, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 4978–4979.

(13) a) Zhang, H.; Ma, D.; Cao, W. *Synlett.* **2007**, *2*, 243–246; b) Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. *Synlett.* **2005**, *7*, 1101–1104.

(14) a) A. Shafir, P. A. Lichtor, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491; b) R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, S. L. Buchwald, *J. Org. Chem*. **2008**, *73*, 284–286; c) G. O. Jones, P. Liu, K. N. Houk, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 6205–6213.

(15) Y.-J. Jian, Y. Wu, *Tetrahedron*. **2010**, *66*, 637–640.

(16) F. Monnier, M. Taillefer, *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971.

(17) a) I. Gueell, X. Ribas, *Eur. J. Org. Chem.* **2014**, *15*, 3188–3195; b) J. W. W. Chang, S. Chee, S. Mak, P. Buranaprasertsuk, W. Chavasiri, P. W. H. Chan, *Tetrahedron Lett.* **2008**, *49*, 2018–2022.

(18) D. Maiti, *Chem. Commun*. **2011**, *47*, 8340–8342.

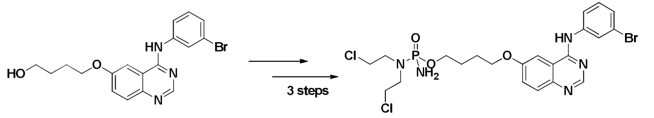
(19) Y. Liu, S. K. Park, Y. Xiao, J. Chae, *Org. Biomol. Chem*. **2014**, *12*, 4747–4753.

(20) a) Q. Sun, F. Suzenet, G. Guillaumet, *Tetrahedron Lett.* **2012**, *53*, 2694–2698; b) Q. Sun, F. Suzenet, G. Guillaumet, *J. Org. Chem.* **2010**, *75*, 3473–3476; c) Y. Wu, Y. Xing, J. Wang, Q. Sun, W. Kong, F. Suzenet, *RSC Adv.* **2015**, *5*, 48558–48562.

(21) D. Xiao, L. Han, Q. Sun, Q. Chen, N. Gong, Y. Lv, F. Suzenet, G. Guillaumet, T. Cheng, R. Li, *RSC Adv*. **2012**, *2*, 5054–5057.

(22) R. Li, Z. Ge, S. Lin, R. Li, Q. Sun, X. Wang, T. Cheng, Preparation method and application of antitumor compounds with multiple target points. *Faming Zhuanli Shenqing* (**2013**), CN 102850397 A 20130102.

(23) Unpublished results.



12a EMB-3

(24) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev*. **2014**, 43, 3525–3550.