



A fluoros ethylenediamine promoted direct C—H arylation of unactivated arenes with aryl halides



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ABSTRACT

A novel and recyclable fluoros ethylenediamine was prepared. Together with potassium *tert*-butoxide, the fluoros ethylenediamine showed a good activity in promoting the coupling of aryl halides with benzene derivatives without the aid of transition-metal catalysts. Furthermore, a chain homolytic aromatic substitution mechanism was proposed in this paper.

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1. Introduction

As is known to all, biaryl compounds are essential substructures in a variety of natural products, drugs (Scheme 1), and ligands for cross-coupling reactions [1,2]. Among various synthetic strategies, the recent emergence of transition metal catalyzed direct arylation of aromatic C—H bonds provides a valuable and efficient alternative to the conventional cross-coupling approach for the synthesis of biaryl compounds [3–7].

While mainstream developments are still focusing on transition metal catalyzed/mediated processes, radical chemistry offers a valuable alternative to transition metal based arylations. Years ago, there have been reports about syntheses of biaryl compounds by using homolytic aromatic substitution (HAS) mediated by $\text{Bu}_3\text{SnH}/2,2'$ -azobisisobutyronitrile (AIBN) or $(\text{Me}_3\text{Si})_3\text{SiH}$ [8–17]. Recently, an attractive alternative to the C—H arylation of arenes by using base-promoted HAS reactions appeared, and it avoids the use of tin, silicon reagents or any transition metals. These transition-metal-free reactions involving the direct C—H arylation of unactivated arenes through radical anion intermediates and utilizing organomolecules [14–23]. These reactions have opened the door to a new approach to HAS (Scheme 2) [24–37]. Very recently, our group became interested in single-electron transfer (SET) systems, also inspired by idea of fluoros ponytail tag, by trial

and error, we found a novel fluoros ethylenediamine could smoothly promote the direct C—H arylation of unactivated arenes with aryl halides through a chain HAS mechanism. To the best of our knowledge, there is no example using any effective fluoros source to promote the direct arylation of unactivated aromatic C—H bonds.

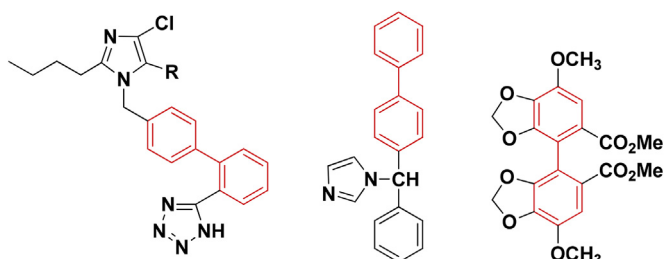
2. Results and discussion

Initially, we prepared a fluoros ethylenediamine (**L**) with perfluorohexyl iodide and ethylenediamine as initial components [38–40], the synthetic route showed in Scheme 3, this fluoros ethylenediamine has 3 CH_2 spacers which show some electron-donating character.

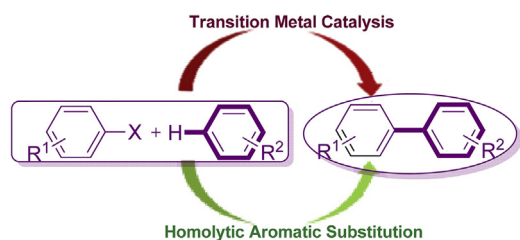
The coupling between 4-iodotoluene (**1a**) and unactivated benzene (**2a**) was selected as model reaction for our investigations (Table 1). Treatment of 4-iodotoluene (**1a**, 1 equiv.) with $\text{KO}^t\text{-Bu}$ (5 equiv.) and the fluoros ethylenediamine **L** (3 equiv.) in benzene (**2a**, 6 mL) at 120°C for 24 h gave 4-methylbiphenyl (**3a**) in an encouraging 72% yield (Table 1, entry 5) [41]. The use of reduced amounts of ligand **L** resulted in lower yields within the same reaction period (Table 1, entries 1 and 2), and we obtained similar results if the reaction was conducted at lower temperature (Table 1, entries 3 and 4). However, the ligand loading employed in the model reaction is higher than that in some previous reports, maybe the fluoros ponytail affects (e.g. solubility or structure). No coupling product was obtained in the reaction without adding any ligand or using any base (Table 1, entries 6 and 7). By using benzene

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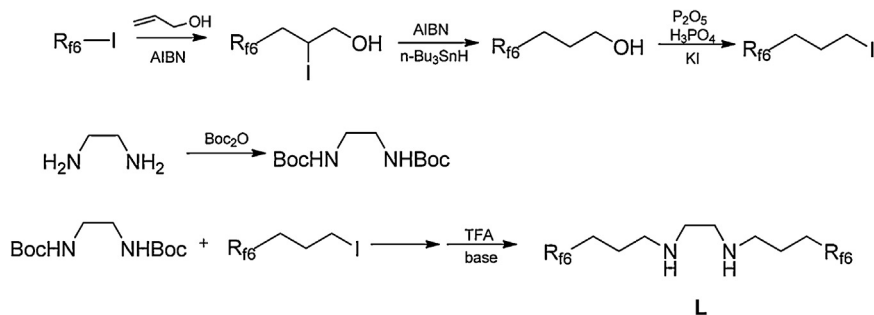
E-mail address: yiwei.zhu@ahpu.edu.cn (Y.-W. Zhu).



Scheme 1. Biaryl compounds with biological activity.

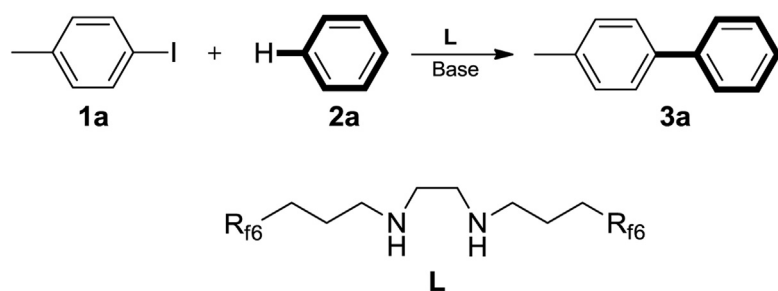


Scheme 2. Approaches for direct arylation reactions.



Scheme 3. Synthetic route of fluoruous ethylenediamine L.

Table 1
Optimization of arylation reaction conditions.^a



Entry	Base	Ligand (equiv.)	T (°C)	Yield (%) ^b
1	KOt-Bu	L (1)	80	15
2	KOt-Bu	L (2)	80	28
3	KOt-Bu	L (3)	80	47
4	KOt-Bu	L (3)	100	59
5	KOt-Bu	L (3) ^c	120	72 (63)
6	KOt-Bu	–	120	Trace
7	–	L (3)	120	Trace
8	K ₂ CO ₃	L (3)	120	Trace
9	NaOt-Bu	L (3)	120	Trace
10	LiOt-Bu	L (3)	120	Trace
11	KOH	L (3)	120	Trace

^a Reaction conditions: **1a** (0.5 mmol), base (5 equiv.), **2a** (6.0 mL), 24 h.

^b GC yield (internal standard method); value in parentheses indicates the yield of the isolated product.

^c The fluoruous ethylenediamine **L** could be easily recovered by phase separation using perfluorotoluene (C₇F₈) with excellent purity (99%) and good recover yield (91%).

as the solvent, **L** as ligand, reactions with the use of other bases, including K₂CO₃, NaOt-Bu, KOH, and LiOt-Bu, were explored. Bases weaker than KOt-Bu were found to be much less effective, and no coupling product was formed in these cases (Table 1, entries 8–11). Interestingly, GC–MS analysis of the crude reaction mixture (Table 1, entry 5) revealed the formation of biphenyl, but it was afforded in a very low yield.

The substrate scope of the reaction promoted by the KOt-Bu/fluorous ethylenediamine under the optimal conditions described above was explored next. Several electronically and structurally diverse aryl iodides were investigated. In general, aryl iodides of various electronic character reacted with benzene to give desired products in moderate to high yields (Table 2, entries 1, 4–14). Yields for the direct arylation of unactivated benzene with electron-rich aryl iodides containing methyl, methoxy, and phenyl groups (Table 2, entries 4–8) were moderate to good and higher than the yield obtained with an electron-deficient substrate such as 4-iodobenzonitrile (Table 2, entry 13). The couplings of iodobenzene, bromobenzene, and chlorobenzene with benzene were also studied (Table 2, entries 1–3), and it was found that iodobenzene delivered **3b** in good yield, bromobenzene afforded a low yield of the product, and chlorobenzene gave almost none of the desired

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