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Direct Metal-free C-H Functionalization of Cyclic Ethers with Schiff Bases through an Azobisisobutyronitrile (AIBN) Initiated Radical Chain Process

Haipeng Zeng,[a] Dengfu Lu,*[a] and Yuefa Gong*[a]

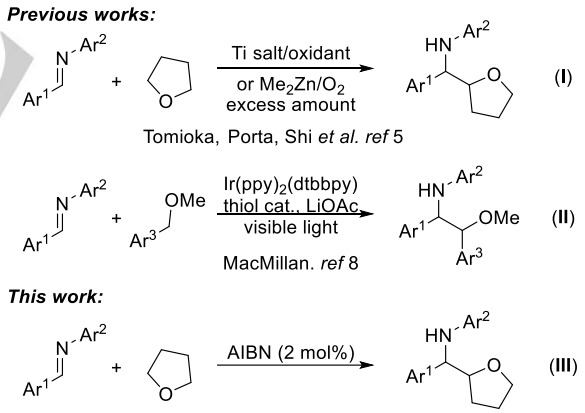
Dedication ((optional))

Abstract: Radical-initiated C-H bond functionalization of cyclic ethers with imines represents an efficient way to form C-C bonds as well as to construct 1,2-amino ethers. Despite the fact that it's a net redox-neutral process, most of previous examples require an excess amount of radical reagents or oxidants to continuously generate radical species. Herein we report an atom-economic radical addition reaction of cyclic ethers to imines without using any oxidant, metal salt, delicate catalyst or UV irradiation. In the presence of small amount of AIBN (2 mol%), tetrahydrofuran reacts smoothly with a variety of imines to affords 1,2-amino ethers in moderate to good yields. Preliminary mechanistic studies suggest that this transformation likely goes through a radical chain process and the hydrogen atom abstraction is the rate-determining step.

Introduction

The exploitation of small oxygen-containing molecules such as ethers is of great significance to synthetic chemistry because of their abundance and sustainability.[1] sp^3 C-H bonds in these structures are known to be stable in polar reactions so that ethers are widely used as solvents rather than carbon synthons. Nonetheless, the *α* C-H bonds are substantially weakened towards radical processes due to the stabilization effect of the oxygen atom,[2] rendering a feasibility of direct C-H functionalization through radical pathways. Based on this unique reactivity, we debuted our exploration on the activation of these materials, intending to develop some redox-neutral and atom-economic transformations, meanwhile minimize the production of hazardous wastes. As its derivatives are potentially useful in polymer science,[3] and their frequent occurrence in the frameworks of many important organic compounds,[4] tetrahydrofuran (THF) was chosen as the model for our initial study. Since imines are known to react with alkyl radicals,[5] we envisioned to establish a "green" method for the synthesis of valuable 1,2-amino ethers via the addition of cyclic etheric radicals to imines,[6] provided the radical species, once initiated, can be repeatedly regenerated throughout the reaction.

However, to the best of our knowledge, the vast majority of current examples of this reaction require a stoichiometric or even an excess amount of radical initiators. Tomioka[5a,5b] discovered that 3-12 equivalents of Me_2Zn could promote the addition reaction of THF to imines in the presence of constant air/oxygen flow. Methyl radical was proposed to implement the C-H abstraction in these reactions. In a later study, Lewiński et al. reported that under similar conditions, the actual initiator is more likely to be oxygen-centered radicals.[5j] Another frequently-used system described by Porta,[5d] Punta[5g] and Shi[5h] et al. comprises stoichiometric amounts of titanium salts, oxidants, and sometimes UV irradiation. Copper salts along with extra oxidants were also reported to do similar jobs.[7] All the above methods consume at least one equivalent of oxygen-centered radicals to generate the reactive species, making this reaction less practical and inefficient. Recently, MacMillan's group established a delicate $Ir(ppy)_2(dtbbpy)$/thiol co-catalyzed system for the addition of highly reactive benzyl ethers to Schiff bases, under the irradiation of visible light.[8] Therefore, an efficient and practical protocol for this transformation is highly desired.



Scheme 1. Comparison of previous works and our current work.

From our understanding, if the nitrogen radical that formed from the addition to imine could effectively abstract another hydrogen atom from THF to regenerate a 2-tetrahydrofuranyl radical, the reaction might be able to propagate in a chain manner. This would allow us to decrease the loading of radical reagent to a catalytic level. Herein, we disclose a simple, efficient and metal-free method for the addition of THF and its analogues to a series of Schiff Bases without using any oxidants or delicate catalyst.

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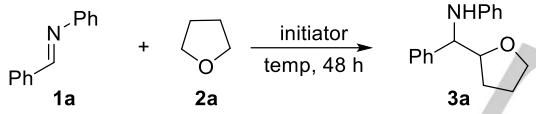
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Results and Discussion

We started our work from the reaction of tetrahydrofuran **2** with simple (*E*)-*N*,1-diphenylmethanimine **1a** to seek for an optimal initiating method. Since oxygen radicals are known for being able to abstract hydrogen atom form ethers, a few common oxygen-based radical initiators, such as benzoyl peroxide (BPO), di-*tert*-butyl peroxide (DTBP), or *tert*-butyl hydroperoxide (TBHP) were preferentially examined. The reaction was performed in THF at 100 °C in a sealed tube. Unexpectedly, in the presence of 10 mol% peroxides, the conversions of imine **1a** were almost negligible after being heated for 48 hours (Table 1, entries 1-3). An *N*-oxyl radical, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was also tested, but no desired product was detected (entry 4). To our delight, product **3a** was obtained in 63% yield when the same amount of azobisisobutyronitrile (AIBN) was employed (entry 5, *d.r.* = 1.2:1), indicating a carbon-centered radical could be an effective initiator and this reaction probably goes through a chain pathway as we proposed. The infertile outcome in the absence of radical source demonstrates that it's not a thermo-induced process (entry 6). Nevertheless, temperature does play a role. The reaction at 80 °C under otherwise the same condition resulted in a slightly lower yield (55%, entry 7), and only 28% product was isolated when the reaction was performed at 60 °C (entry 8). Additionally, we investigated the loadings of initiator for this reaction. Interestingly, increasing the amount of AIBN to 20 mol% led to a substantial yield drop (53%, entry 9), while lowering the loading of AIBN to 2 mol% improved the yield significantly (76%, entry 11). When we further decrease AIBN dosage to 1 mol%, the reaction became slower and the yield of **3a** slightly dropped to 66% within the same reaction time (entry 12).

With the optimized reaction condition in hand, we next explored the compatibility of other imines that possess different functional groups. As shown in Table 2, the substituents on the aldehyde part apparently have an influence on the reactivity of imines (Table 2, entries 1-8). Compared to the model substrate **1a**, imine **1b** with an electron-deficient *para*-ester group is more reactive and offers a slightly better yield (entries 1-2), while a weakly electron-donating methyl group causes an opposite effect. A strongly electron-donating *para*-methoxyl renders a dramatic drop of the yield of **3d** (entry 4). Halogen substituents

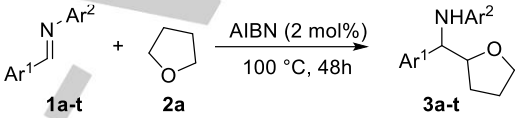
Table 1. Initiator evaluation and condition optimization.[a]

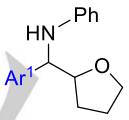
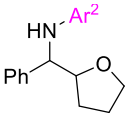
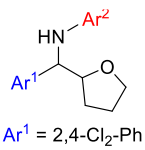


Entry	Initiator	Loading	Temp[c]	Yield of **3a**[c,d]
1	BPO	10 mol%	100 ˚C	<5%[e]
2	DTBP	10 mol%	100 ˚C	<5%[e]
3	TBHP	10 mol%	100 ˚C	<5%[e]
4	TEMPO	10 mol%	100 ˚C	n.d.[e,f]
5	AIBN	10 mol%	100 ˚C	63%
6	None	--	100 ˚C	n.d.[e,f]
7	AIBN	10 mol%	80 ˚C	55%
8	AIBN	10 mol%	60 ˚C	28%
9	AIBN	20 mol%	100 ˚C	53%
10	AIBN	5 mol%	100 ˚C	68%
11	AIBN	2 mol%	100 ˚C	76%
12	AIBN	1 mol%	100 ˚C	66%

[a] Reactions conditions: 0.5 mmol of **1**, initiator, 4.0 mL of THF, 48h. [b] The reaction was conducted in a sealed tube when the temperature was above 60 °C. [c] Isolated yield. [d] *d.r.* were mostly within 1:1 to 1.3:1, which were determined by ^{1}H NMR. [e] Determined by ^{1}H NMR of the crude sample. [f] Not detected. BPO = benzoyl peroxide; DTBP = di-*tert*-butyl peroxide; TBHP = *tert*-butyl hydro peroxide; TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl; AIBN = azobisisobutyronitrile.

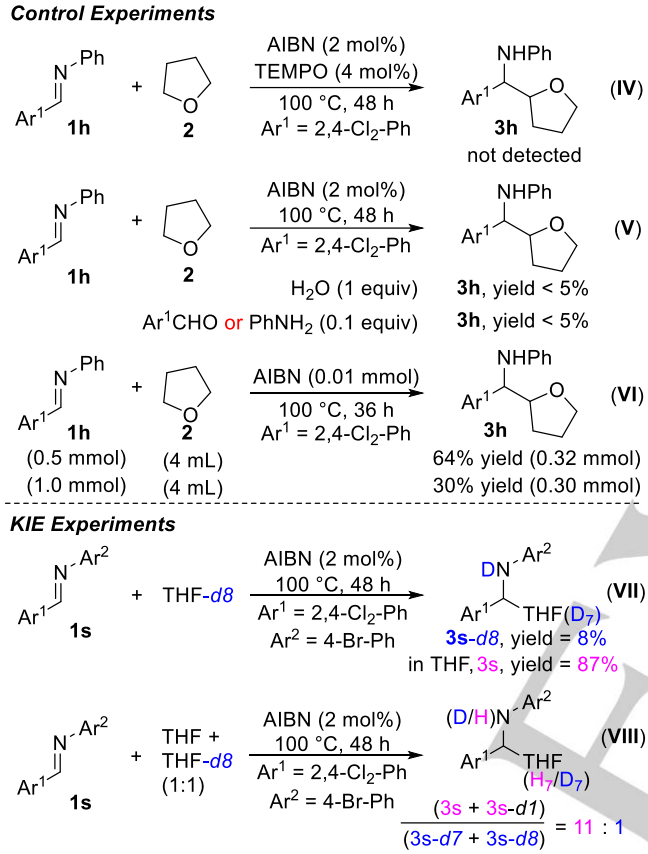
Table 2. Substrate scope of the reaction between tetrahydrofuran and imines.[a]



structure	entry	substitution	product	Yield[b,c]
	1	**Ar¹** = Ph	**3a**	76%
	2	**Ar¹** = 4-CO_2MePh	**3b**	82%
	3	**Ar¹** = 4-Me-Ph	**3c**	65%
	4	**Ar¹** = 4-OMe-Ph	**3d**	40%
	5	**Ar¹** = 4-F-Ph	**3e**	75%
	6	**Ar¹** = 4-Cl-Ph	**3f**	78%
	7	**Ar¹** = 3-Cl-Ph	**3g**	72%
	8	**Ar¹** = 2,4-Cl_2Ph	**3h**	88%
	9	**Ar²** = 4-Me-Ph	**3i**	62%
	10	**Ar²** = 4-OMe-Ph	**3j**	47%
	11	**Ar²** = 4-Cl-Ph	**3k**	55%
	12	**Ar²** = 3-Cl-Ph	**3l**	68%
	13	**Ar²** = 4-Br-Ph	**3m**	57%
	14	**Ar²** = 4-Me-Ph	**3n**	83%
	15	**Ar²** = 2-Me-Ph	**3o**	30%
	16	**Ar²** = 4-OMe-Ph	**3p**	68%
	17	**Ar²** = 4-Cl-Ph	**3q**	73%
	18	**Ar²** = 3-Cl-Ph	**3r**	78%
	19	**Ar²** = 4-Br-Ph	**3s**	87%

[a] Reactions were carried out using 0.5 mmol of **1**, 2 mol% AIBN, in 4.0 mL of THF at 100 °C in a sealed tube for 48h. [b] Isolated yield. [c] *d.r.* were mostly within 1:1 to 1.3:1, which were determined by ^{1}H NMR, for details, see SI. AIBN = azobisisobutyronitrile

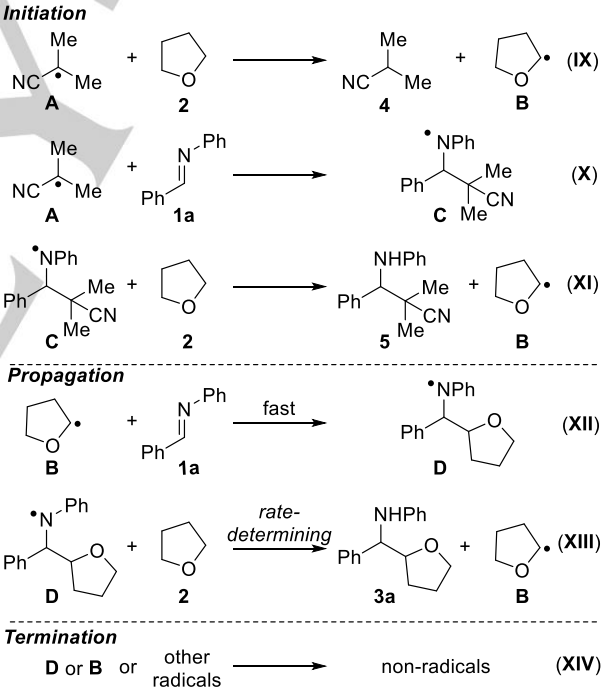
are perfectly tolerated that the yields of addition products **3e**-**3h** remain the same level (entries 5-8). Among them, the imine **1h** derived from 2,4-dichlorobenzaldehyde was converted to **3h** with the best yield (88%, entry 8). Next, we surveyed a couple of imines prepared from benzaldehyde with different anilines, like 4-methyl, 4-methoxyl and 4-chloro. There is no obvious trend observed between these imines and different substituents, most of the reactions afford the desired product **3i**-**3m** in moderate yields (47% to 68%, entries 9-13).



Scheme 2. A few control experiments and Kinetic Isotope Effect Study.

Considering good results were achieved when the aldehyde part is electron-deficient, a few substrates synthesized from 2,4-dichlorobenzaldehyde with various anilines were thereby inspected. To our delight, both electron-rich and electron-deficient substrates (Ar^2) participate the reaction smoothly and furnish corresponding 1,2-amino ethers **3n**, **3p**-**3s** in satisfactory yield (68%-87%, entries 14-19). A lower conversion and yield were observed in the case of the substrate made by 2-methyl aniline, which could probably be attributed to the steric hindrance (**3o**).

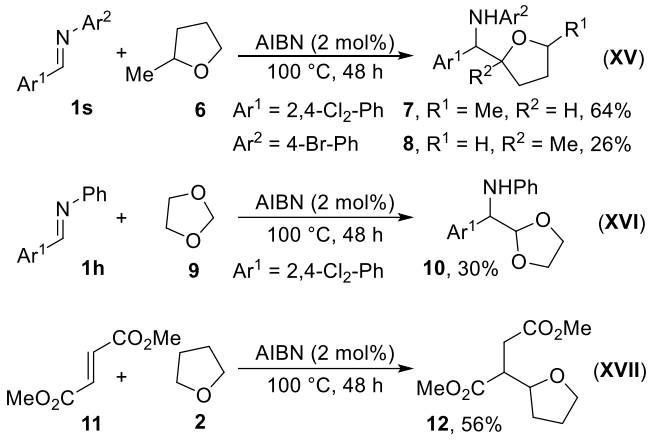
In order to gather evidences for a mechanistic working hypothesis of this efficient transformation, we designed and carried out several sets of control experiments. Firstly, a small amount of persistent radical, TEMPO, was found to inhibit the reaction of imine **1h** (eq. **IV**). Although no specific trapped product was identified, this result strongly suggests the involvement of radical intermediates. Secondly, one equivalent of water suppresses the reaction, and the conversion was also very low when "one-pot" procedure was applied with *in-situ* formed imines.[9] As H_2O has strong O-H bonds and is less likely to interact directly with radicals, these phenomena might be caused by a small amount of free aldehyde or aniline hydrolyzed from imine, which are not stable to radicals and could, therefore, increase the chance of termination pathways. This assumption was verified by control reactions with additional aldehyde or aniline (eq. **V**). Additionally, kinetic isotope experiments were performed in both parallel and competing fashions. The reaction in THF-*d8* only afford 8% of **3s**-*d8* under the same condition after the same time (eq. **VII** versus entry 19 in table 2). When the reaction was conducted in 1:1 mixture of THF/THF-*d8*, the results are in good agreement (kH/kD = 11:1, eq. **VIII**). These results demonstrate that the hydrogen atom transfer (HAT) from THF may be the rate-determining step, which is different with the previous case induced by oxygen radicals.[5h] Probably because this HAT event is involved twice to afford the final product, the KIE observed in this reaction is more significantly than a typical one. "Tunneling effect"[10] could also be an explanation since a small hydrogen atom is involved. Furthermore, we discovered that the reaction rate does not depend on the concentrations of imines, (eq. **VI**) corroborating that the addition of THF-2-yl radical **B** to imine is a faster step.



Scheme 3. Proposed chain reaction mechanism.

Based on the obtaining results, a plausible radical chain mechanism was proposed as depicted in scheme 3. First, the homolysis of AIBN generates isobutyronitrile radical **A**, which may then initiate the reaction in two different ways: i) H atom was directly abstracted from THF by isobutyronitrile radical **A**, resulting a THF-2-yl radical **B**; (eq. **IX**) or ii) isobutyronitrile radicals **A** adds to imine **1a** to generate an amine radical **C**, which then abstract a H from THF to yield the same species **B**. (eq. **X**-**XI**) Because neither isobutyl nitrile **4**, nor adduct **5** were isolated, we currently cannot rule out any of these possibilities.

After the generation of THF-2-yl radical **B**, the rapid nucleophilic addition to **1** furnishes the amine radical **D** as the major radical species in this reaction, managing to abstract a hydrogen from THF to propagate the chain. (eq. **XII**-**XIII**) The termination process may happen between two radical species. When the overall concentration of radicals is high, the chance of termination increases, which may explain the lower yield with high AIBN loading. As shown in equation **XIV**, the termination phase may associate with radical **D**, radical **B**, trace amount of oxygen or any other radicals.



Scheme 4. Reactions of other cyclic ethers and electrophiles.

At last, we put some preliminary efforts to examine the compatibility of other cyclic ethers and electrophiles with this method. The results are as described in Scheme 4. 2-Methyl THF **6** shows excellent reactivity, affording a mixture of two regio-isomers **7** and **8** with a moderate ratio. (eq. **XV**) The reaction of 1,3-dioxolane **9** suffers a low conversion and provide the product **10** in only 30% yield. (eq. **XVI**) On the other hand, beside imines, dimethyl fumarate **11** can also serve as the electrophile, the desired product **12** was obtained in a decent yield, (eq. **XVII**) corroborating that an electron-deficient carboradical is also capable of H atom abstraction from THF, similar to what we have mentioned in the mechanistic part. (eq. **IX**)

Conclusions

In summary, we have developed an efficient and practical method for the direct functionalization of THF and other cyclic ethers with various imines by using only 2 mol% of AIBN as the initiator. Considering the solvent could be easily recycled by distillation, nothing much is wasted in this reaction and no oxidants, metal salt, delicate catalyst or any irradiation was required. Different imines could be well tolerated, transformed into the corresponding addition products in moderate to good yields. According to the experimental results, the reaction is proposed to undergo a radical chain pathway and the efficiency of this chain is critical to the reaction outcomes. Further studies on the synthetic applications of this method are currently ongoing in our laboratory.

Experimental Section

General procedures for Initiator evaluation and condition optimization: Imine **1a** (90.5 mg, 0.5 mmol) and a corresponding initiator (0.005 - 0.1 mmol) were added in an oven-dried sealable tube charged with a stir bar. The tube was filled with freshly distilled tetrahydrofuran (4 mL) and sealed with a Teflon cap. The reaction was then heated-up to the indicated temperature and kept stirring for 48 hours. After completion of the reaction, the solvent was evaporated *in vacuo*, and then the residue was submitted for ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. For those reactions with a reasonable yield, isolated yield was obtained after purifying product **3a** through a silica gel flash column.

***N*-(Phenyl(tetrahydrofuran-2-yl)methyl)aniline** (**3a**): compound **3a** was isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Colorless oil (Table 1, entry 11, 96 mg, 76% yield, *d.r.* = 1.2:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.40 – 7.33 (m, 2H), 7.30 – 7.23 (m, 2H), 7.22 – 7.15 (m, 1H), 7.02 (t, *J* = 7.9 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 2H), 4.66 (s, 1H), 4.40 (d, *J* = 4.2 Hz, 0.45H), 4.24 – 4.15 (m, 1H), 4.03 – 3.96 (m, 0.55H), 3.92 – 3.82 (m, 0.55H), 3.78 – 3.66 (m, 1.45H), 1.91 – 1.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 147.6, 141.9, 140.2, 129.1, 128.7, 128.4, 127.9, 127.5, 127.4, 117.6, 117.6, 114.0, 114.0, 83.1, 82.2, 68.9, 68.7, 62.3, 60.9, 29.0, 27.4, 25.9, 25.7; HRMS (ESI, m/z): calcd for $C_{17}H_{19}NONa$ $[M + Na]^+$ 276.1359, found 276.1375.

General procedure for synthesis of compound 3b-3s: an imine (**1b**-**1s**) (0.5 mmol) and AIBN (1.6 mg, 0.01 mmol) were added in an oven-dried sealable tube charged with a stir bar. The tube was filled with freshly distilled tetrahydrofuran (4 mL) and sealed with a Teflon cap. The sealed tube was then heated-up to 100 °C and kept stirring for 48 hours. After completion of the reaction, the solvent was evaporated *in vacuo,* and the residue was then purified through a silica gel flash column to give the corresponding addition product **3b**-**3s.**

Methyl 4-((phenylamino)(tetrahydrofuran-2-yl)methyl)benzoate (**3b**): Compound **3b** was prepared form **1b** according to the general procedure, and isolated through a flash column (PE: EtOAc from 15:1 to 10:1); Colorless oil (127 mg, 82% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 8.03 – 7.92 (m, 2H), 7.54 – 7.43 (m, 2H), 7.10 – 6.98 (m, 2H), 6.69 – 6.58 (m, 1H), 6.49 (d, *J* = 8.2 Hz, 2H), 4.63 (s, 1H), 4.45 (d, *J* = 4.4 Hz, 0.5H), 4.29 (d, *J* = 5.9 Hz, 0.5H), 4.27 – 4.18 (m, 0.5H), 4.06 – 3.97 (m, 0.5H), 3.94 – 3.84 (m, 3.5H), 3.83 – 3.70 (m, 1.5H), 1.98 – 1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 167.0, 147.4, 147.3, 147.0, 145.8, 130.0, 129.6, 129.4, 129.3, 129.1, 129.1, 128.0, 127.3, 117.8, 113.9, 113.9, 82.6, 81.7, 68.8, 68.7, 61.9, 60.8, 52.1, 28.8, 27.5, 25.8, 25.5; HRMS (ESI, m/z): calcd for $C_{19}H_{21}NO_3Na$ $[M + Na]^+$ 334.1414, found 334.1426.

***N*-((Tetrahydrofuran-2-yl)(p-tolyl)methyl)aniline (3c)**: Compound **3c** was prepared form **1c** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Pale yellow oil (86 mg, 65% yield, *d.r.* = 1.2:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.28 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.13 – 7.06 (m, 2H), 7.03 (t, *J* = 7.8 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 2H), 4.58 (s, 1H), 4.37 (d, *J* = 4.3 Hz, 0.55H), 4.23 – 4.13 (m, 1H), 4.02 – 3.96 (m,0.55H), 3.92 – 3.85 (m, 0.55H), 3.80 – 3.69 (m, 1.45H), 2.28 (s, 1.65H), 2.28 (s, 1.35H), 1.93 – 1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 147.6, 138.7, 137.1, 137.0, 136.8, 129.4, 129.1, 129.1, 127.7, 127.2, 117.5, 114.0, 83.2, 82.2, 68.8, 68.6, 62.0, 60.7, 28.9, 27.4, 25.8, 25.7, 21.2; HRMS (ESI, m/z): calcd for $C_{18}H_{21}NONa$ $[M + Na]^+$ 290.1515, found 290.1533.

***N*-((4-Methoxyphenyl)(tetrahydrofuran-2-yl)methyl)aniline** (**3d**): Compound **3d** was prepared form **1d** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1);

Yellow oil (56 mg, 40% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.30 (dd, *J* = 14.0, 8.3 Hz, 2H), 7.05 (dd, *J* = 8.3, 7.3 Hz, 2H), 6.83 (t, *J* = 8.1 Hz, 2H), 6.62 (td, *J* = 7.3, 3.3 Hz, 1H), 6.52 (dd, *J* = 8.1, 1.6 Hz, 2H), 4.67 (s, 1H), 4.36 (d, *J* = 4.2 Hz, 0.5H), 4.21 (dd, *J* = 11.0, 6.7 Hz, 0.5H), 4.16 (d, *J* = 6.7 Hz, 0.5H), 4.00 (q, *J* = 6.7 Hz, 0.5H), 3.90 (dd, *J* = 14.7, 7.0 Hz, 0.5H), 3.82 – 3.69 (m, 4.5H), 1.96 – 1.48 (m, 4H); ^{13}C NMR (100MHz, $CDCl_3$) δ 158.9, 158.8, 147.8, 147.4, 133.5, 132.0, 129.0, 128.8, 128.3, 117.5, 117.5, 114.1, 114.0, 113.7, 83.1, 82.2, 68.8, 68.6, 61.7, 60.3, 55.2, 55.2, 28.8, 27.4, 25.8, 25.6; HRMS (ESI, m/z): calcd for $C_{18}H_{21}NO_2Na$ $[M + Na]^+$ 306.1465, found 306.1483.

***N*-((4-Fluorophenyl)(tetrahydrofuran-2-yl)methyl)aniline** (**3e**): Compound **3e** was prepared form **1e** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Pale yellow oil (101 mg, 75% yield, *d.r.* = 1.2:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.37 – 7.30 (m, 2H), 7.07 – 7.03 (m, 2H), 7.0 – 6.94 (m, 2H), 6.65 – 6.61(m, 1H), 6.55 – 6.45 (m, 2H), 4.60 (s, 1H), 4.37 (d, *J* = 4.2 Hz, 0.45H), 4.19 (m, 1H), 3.98 (q, *J* = 6.6 Hz, 0.55H), 3.89 (dt, *J* = 13.7, 6.6 Hz, 0.55H), 3.81 – 3.70 (m, 1.45H), 1.91 – 1.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 160.9, 147.6, 147.2, 136.63 (d, *J* = 162.1 Hz), 136.60 (d, *J* = 162.1 Hz), 129.39 (d, J = 8.0 Hz),129.1, 129.1, 128.79 (d, J = 8.0 Hz), 117.7, 117.7, 115.53 (d, *J* = 21.3 Hz), 115.23 (d, *J* = 21.3 Hz), 114.0, 114.0, 83.0, 82.0, 68.8, 68.7, 61.5, 60.3, 28.8, 27.5, 25.8, 25.6; HRMS (ESI, m/z): calcd for $C_{17}H_{18}FNONa$ $[M + Na]^+$ 294.1265, found 294.1273.

***N*-((4-Chlorophenyl)(tetrahydrofuran-2-yl)methyl)aniline** (**3f**): Compound **3f** was prepared form **1f** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Colorless oil (112 mg, 78% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.36 – 7.21 (m, 4H), 7.05 (t, *J* = 7.4 Hz, 2H), 6.63 (td, *J* = 7.3, 2.7 Hz, 1H), 6.48 (dd, *J* = 8.4, 1.9 Hz, 2H), 4.60 (s, 1H), 4.36 (d, *J* = 4.3 Hz, 1H), 4.23 – 4.13 (m, 0.5H), 3.97 (q, *J* = 6.6 Hz, 1H), 3.88 (dt, *J* = 13.6, 6.6 Hz, 0.5H), 3.80 – 3.67 (m, 1.5H), 1.94 – 1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 147.1, 140.4, 138.8, 133.1, 133.0, 129.3, 129.2, 129.1, 128.9, 128.7, 128.6, 117.8, 114.0, 82.8, 81.8, 68.9, 68.7, 61.5, 60.4, 28.8, 27.5, 25.8, 25.6; HRMS (ESI, m/z): calcd for $C_{17}H_{18}ClNONa$ $[M + Na]^+$ 310.0969, found 310.0984.

***N*-((3-Chlorophenyl)(tetrahydrofuran-2-yl)methyl)aniline** (**3g**): Compound **3g** was prepared form **1g** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Pale yellow oil (103 mg, 72% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.41 (s, 0.5H), 7.38 (s, 0.5H), 7.32 – 7.25 (m, 1H), 7.25 – 7.19 (m, 2H), 7.08 (dd, *J* = 8.4, 7.5 Hz, 2H), 6.72 – 6.60 (m, 1H), 6.55 – 6.47 (m, 2H), 4.72 (s, 1H), 4.37 (d, *J* = 4.3 Hz, 0.5H), 4.21 (m, 1H), 4.01 (q, *J* = 6.6 Hz, 0.5H), 3.91 (dd, *J* = 14.5, 7.0 Hz, 0.5H), 3.85 – 3.71 (m, 1.5H), 1.99 – 1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 146.9, 144.0, 142.5, 134.6, 134.3, 129.9, 129.6, 129.1, 129.1, 127.9, 127.7, 127.6, 127.4, 126.1, 125.5, 117.9, 113.9, 82.7, 81.8, 68.9, 68.7, 61.7, 60.6, 28.8, 27.5, 25.8, 25.6; HRMS (ESI, m/z): calcd for $C_{17}H_{18}ClNONa$ $[M + Na]^+$ 310.0969, found 310.0986.

***N*-((2,4-Dichlorophenyl)(tetrahydrofuran-2-yl)methyl)aniline (3h)**: Compound **3h** was prepared form **1h** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Colorless oil (141 mg, 88% yield, *d.r.* = 1.4:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.47 – 7.34 (m, 2H), 7.15 – 7.11 (m, 1H), 7.10 – 7.04 (m, 2H), 6.66 – 6.62 (m, 1H), 6.47 (d, *J* = 7.8 Hz, 2H), 4.96 (d, *J* = 4.1 Hz, 0.6H), 4.82 (d, *J* = 4.3 Hz, 0.42H), 4.64 (s, 1H), 4.32 – 4.28 (m, 0.6H), 4.08 – 4.04(m, 0.42H), 4.00 – 3.94 (m, 0.42H), 3.80 – 3.69 (m, 1.6H), 2.02 – 1.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 146.5, 137.9, 136.2, 134.7, 133.7, 133.5, 133.5, 130.5, 129.5, 129.3, 129.3, 129.2, 129.0, 127.7, 127.5, 118.0, 117.9, 113.6, 113.5, 81.7, 80.6, 69.0, 68.7, 56.0, 28.5, 27.5, 25.9, 25.8; HRMS (ESI, m/z): calcd for $C_{17}H_{17}Cl_2NONa$ $[M + Na]^+$ 344.0579, found 344.0582.

4-Methyl-*N*-(phenyl(tetrahydrofuran-2-yl)methyl)aniline (3i): Compound **3i** was prepared form **1i** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Pale yellow oil (82 mg, 62% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.38(m, 2H), 7.37 – 7.31 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.60 (m, 2H), 4.54 (d, *J* = 4.3 Hz, 0.5H), 4.47 (s, 1H), 4.41 – 4.34 (m, 0.5H), 4.33 (d, *J* = 6.5 Hz, 0.5H), 4.17 (q, *J* = 6.5 Hz, 0.5H), 4.07 – 4.00 (m, 0.5H), 3.95 – 3.83 (m, 1.5H), 2.30 (s, 3H), 2.08 – 1.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 145.2, 141.8, 140.3, 129.6, 128.7, 128.4, 127.9, 127.4, 127.4, 127.3, 126.8, 114.3, 114.3, 83.1, 82.2, 68.9, 68.7, 62.7, 61.3, 28.9, 27.4, 25.8, 25.7, 20.5; HRMS (ESI, m/z): calcd for $C_{18}H_{21}NONa$ $[M + Na]^+$ 290.1515, found 290.1529.

4-Methoxy-*N*-(phenyl(tetrahydrofuran-2-yl)methyl)aniline (3j): Compound **3j** was prepared form **1j** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Yellow oil (66 mg, 47% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.44 – 7.18 (m, 5H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 4.47 (s, 1H), 4.38 (d, *J* = 4.2 Hz, 0.5H), 4.26 – 4.19 (m, 0.5H), 4.12 (d, *J* = 6.8 Hz, 0.5H), 4.06 – 3.98 (m, 0.5H), 3.95 – 3.86 (m, 1H), 3.86 – 3.71 (m, 1.5H), 3.66 (s, 3H),1.98 – 1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 152.1, 142.0, 141.8, 141.6, 140.3, 128.6, 128.3, 127.7, 127.4, 127.2, 115.3, 115.2, 114.7, 114.6, 83.0, 82.2, 68.8, 68.5, 63.3, 61.6, 55.7, 55.7, 28.8, 27.1, 25.7, 25.6; HRMS (ESI, m/z): calcd for $C_{18}H_{21}NO_2Na$ $[M + Na]^+$ 306.1465, found 306.1473.

4-Chloro-*N*-(phenyl(tetrahydrofuran-2-yl)methyl)aniline (3k): Compound **3k** was prepared form **1k** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Pale yellow oil (79 mg, 55% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.42 – 7.19 (m, 5H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 8.7 Hz, 2H), 4.73 (s, 1H), 4.38 (d, *J* = 4.0 Hz, 0.5H), 4.27 – 4.21 (m, 0.5H), 4.15 (d, *J* = 6.5 Hz, 0.5H), 4.04 – 3.97 (m, 0.5H), 3.95 – 3.88 (m, 0.5H), 3.83 – 3.70 (m, 1.5H), 1.96 – 1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 146.0, 141.1, 139.5, 128.8, 128.7, 128.4, 127.8, 127.6, 127.4, 127.2, 122.1, 115.1, 115.0, 82.9, 81.9, 76.8, 68.8, 68.6, 62.4, 60.9, 28.9, 27.2, 25.7, 25.5; HRMS (ESI, m/z): calcd for $C_{17}H_{18}ClNONa$ $[M + Na]^+$ 310.0969, found 310.0987.

3-Chloro-*N*-(phenyl(tetrahydrofuran-2-yl)methyl)aniline (3l): Compound **3l** was prepared form **1l** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Colorless oil (97 mg, 68% yield, *d.r.* = 1.1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.41 – 7.20 (m, 5H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 6.52 – 6.49 (m, 1H), 6.40 – 6.35 (m, 1H), 4.79 (s, 1H), 4.38 (d, *J* = 4.1 Hz, 0.47H), 4.27 – 4.20 (m, 0.47H), 4.18 (d, *J* = 6.3 Hz, 0.53H), 4.04 – 3.97 (m, 0.53H), 3.95 – 3.88 (m, 0.53H), 3.83 – 3.67 (m, 1.47H), 1.99 – 1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.6, 141.1, 139.4, 134.7, 130.0, 128.8, 128.4, 127.8, 127.6, 127.5, 127.1, 117.4, 113.7, 112.0, 82.9, 81.8, 68.8, 68.7, 62.0, 60.7, 28.9, 27.3, 25.7, 25.5; HRMS (ESI, m/z): calcd for $C_{17}H_{18}ClNONa$ $[M + Na]^+$ 310.0969, found 310.0983.

4-Bromo-*N*-(phenyl(tetrahydrofuran-2-yl)methyl)aniline (3m): Compound **3m** was prepared form **1m** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Yellow oil (94 mg, 57% yield, *d.r.* = 1.2:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.40 – 7.19 (m, 5H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.39 (d, *J* = 8.7 Hz, 2H), 4.74 (s, 1H), 4.37 (d, *J* = 4.0 Hz, 0.45H), 4.26 – 4.20 (m, 0.45H), 4.15 (d, *J* = 6.5 Hz, 0.55H), 4.03-3.97 (m, 0.55H), 3.94 – 3.88 (m, 0.55H), 3.83 – 3.70 (m, 1.45H), 1.99 – 1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 146.4, 141.0, 139.4, 131.7, 128.7, 128.4, 127.8, 127.6, 127.2, 115.6, 109.2, 82.9, 81.8, 68.8, 68.6, 62.3, 60.8, 28.9, 27.2, 25.7, 25.5; HRMS (ESI, m/z): calcd for $C_{17}H_{18}BrNONa$ $[M + Na]^+$ 354.0464, found 354.0479.

***N*-((2,4-Dichlorophenyl)(tetrahydrofuran-2-yl)methyl)-4-methylaniline (3n)**: Compound **3n** was prepared form **1n** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Pale yellow oil (139 mg, 83% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.59 – 7.43 (m, 2H), 7.28 – 7.22 m, 1H), 7.03 – 6.98 (m, 1H), 6.53 (d, *J* = 7.8 Hz, 2H), 5.07 (d, *J* = 3.5 Hz, 0.5H), 4.93 (d, *J* = 3.8 Hz, 0.5H), 4.52 (s, 1H), 4.45 – 4.36 (m, 0.5H), 4.20 – 4.15(m, 0.5H), 4.10 – 4.06 (m, 0.5H), 3.88 – 3.84 (m, 1.5H), 2.29 (s, 1.5H), 2.28 (s, 1.5H), 2.13 –1.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 144.3, 138.1, 136.4, 134.7, 133.8, 133.5, 133.4, 130.5, 129.8, 129.8, 129.6, 129.3, 129.0, 127.7, 127.6, 127.1, 127.0, 113.8, 113.7, 81.8, 80.7, 68.9, 68.8, 56.3, 28.5, 27.5, 25.9, 25.9, 20.5; HRMS (ESI, m/z): calcd for $C_{18}H_{19}Cl_2NONa$ $[M + Na]^+$ 358.0736, found 358.0754.

***N*-((2,4-Dichlorophenyl)(tetrahydrofuran-2-yl)methyl)-2-methylaniline (3o)**: Compound **3o** was prepared form **1o** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Pale yellow oil (50 mg, 30% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.35 – 7.24 (m ,2H), 7.09 – 7.02 (m, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.86 (t, *J* = 7.7 Hz, 1H), 6.57 – 6.48 (m, 1H), 6.18 – 6.08 (m, 1H), 4.92 (d, *J* = 4.0 Hz, 0.5H), 4.54 (s, 1H), 4.77 (d, *J* = 4.0 Hz, 0.5H), 4.34 – 4.23 (m, 0.5H), 4.08 – 4.01 (m, 0.5H), 3.95 – 3.87 (m, 0.5H), 3.78 – 3.62 (m, 1.5H), 2.17 (s, 1.5H), 2.16 (s, 1.5H), 1.97 – 1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 143.4, 136.8, 135.1, 133.5, 132.6, 132.4, 132.3, 129.2, 129.0, 129.0, 128.2, 127.9, 126.6, 126.4, 126.1, 126.0, 121.3, 121.3, 116.5, 116.4, 109.9, 109.7, 80.7, 79.6, 68.0, 67.7, 54.9, 54.9, 27.6, 26.3, 25.0, 24.8, 16.5; HRMS (ESI, m/z): calcd for $C_{18}H_{19}Cl_2NONa$ $[M + Na]^+$ 358.0736, found 358.0752.

***N*-((2,4-Dichlorophenyl)(tetrahydrofuran-2-yl)methyl)-4-methoxyaniline (3p)** : Compound **3p** was prepared form **1p** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Yellow oil (119 mg, 68% yield, *d.r.* = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.45 – 7.35 (m, 2H), 7.23 – 7.10 (m, 1H), 6.70 – 6.64 (m, 2H), 6.42 (d, *J* = 8.9 Hz, 2H), 4.91 (d, *J* = 4.1 Hz, 0.5H), 4.75 (d, *J* = 4.8 Hz, 0.5H), 4.32 – 4.22 (m, 0.5H), 4.07 – 3.93 (m, 0.5H), 3.99 – 3.92 (m, 0.5H), 3.80 – 3.70 (m, 1.5H), 3.66 (s, 1.5H), 3.65 (s, 1.5H), 2.04 – 1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 152.3, 141.0, 140.7, 138.1, 136.4, 134.7, 133.8, 133.4, 133.4, 130.4, 129.6, 129.3, 129.0, 127.7, 127.5, 114.9, 114.8, 114.6, 81.9, 80.6, 68.9, 68.7, 56.8, 56.7, 55.7, 55.7, 28.4, 27.3, 25.9, 25.8; HRMS (ESI, m/z): calcd for $C_{18}H_{19}Cl_2NONa$ $[M + Na]^+$ 374.0685, found 374.0697.

4-Chloro-*N*-((2,4-dichlorophenyl)(tetrahydrofuran-2-yl)methyl)aniline (3q) : Compound **3q** was prepared form **1q** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Colorless oil (129 mg, 73% yield, *d.r.* = 1.2:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.36 – 7.26 (m, 2H), 7.12 – 7.05 (m, 1H), 6.97 – 6.91(m, 2H), 6.33 (d, *J* = 8.5 Hz, 2H), 4.85 (d, *J* = 3.8 Hz, 0.55H), 4.70 (d, *J* = 4.3 Hz, 0.45H), 4.28 – 4.21 (m, 0.55H), 4.03 – 3.95 (m, 0.45H), 3.94 – 3.87 (m, 0.45H), 3.76 – 3.61 (m, 1.55H), 1.98 – 1.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 144.9, 137.2, 135.5, 134.7, 133.7, 133.7, 130.3, 129.4, 129.3, 129.1, 129.0, 127.7, 127.6, 122.7, 114.8, 114.7, 81.6, 80.4, 68.9, 68.7, 56.3, 56.1, 28.4, 27.3, 25.8, 25.7; HRMS (ESI, m/z): calcd for $C_{17}H_{16}Cl_3NONa$ $[M + Na]^+$ 378.0190, found 378.0202.

3-Chloro-*N*-((2,4-dichlorophenyl)(tetrahydrofuran-2-yl)methyl)aniline (3r) : Compound **3r** was prepared form **1r** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Pale yellow oil (138 mg, 78% yield, *d.r.* = 1.2:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.35 – 7.24 (m, 2H), 7.11 – 7.05 (m, 1H), 6.93 – 6.84 (m, 1H), 6.56 – 6.48 (m, 1H), 6.42 – 6.38 (m, 1H), 6.23 (d, *J* = 8.2 Hz, 1H), 4.85 (d, *J* = 3.9 Hz, 0.55H), 4.71 (d, *J* = 4.2 Hz, 0.45H), 4.22 (m, 0.55H), 4.00 – 3.93 (m, 0.45H), 3.93 – 3.86 (m, 0.45H), 3.72 – 3.59 (m, 1.55H), 1.95 – 1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 147.7, 137.3, 135.5, 134.9, 134.9, 134.7, 133.8, 133.7, 133.6, 130.3, 130.3, 130.2, 129.4, 129.3, 129.0, 127.7, 127.6, 117.8, 117.7, 113.5, 113.4, 111.4, 81.5, 80.4, 68.9, 68.7, 55.8, 55.7, 28.5, 27.4, 25.8; HRMS (ESI, m/z):calcd for $C_{17}H_{16}Cl_3NONa$ $[M + Na]^+$ 378.0190, found 378.0206.

4-Bromo-*N*-((2,4-dichlorophenyl)(tetrahydrofuran-2-yl)methyl)aniline (3s) : Compound **3s** was prepared form **1s** according to the general procedure, and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Yellow oil (173 mg, 87% yield, *d.r.* = 1.3:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 7.40 – 7.31 (m, 2H), 7.17 – 7.10 (m, 3H), 6.37 – 6.30 (m, 2H), 4.91 (d, *J* = 3.9 Hz, 0.57H), 4.77 (d, *J* = 4.4 Hz, 0.43H), 4.35 – 4.25 (m, 0.57H), 4.07 – 4.00(m, 0.43H), 3.99 – 3.90(m, 0.43H), 3.79 – 3.65 (m, 1.57H), 2.01 – 1.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 145.6, 137.3, 135.6, 134.7, 133.7, 133.6, 132.0, 131.9, 130.3, 129.4, 129.4, 129.0, 127.8, 127.6, 115.1, 115.1, 109.6, 109.5, 81.6, 80.4, 68.9, 68.7, 56.1, 55.9, 28.5, 27.4, 25.8, 25.8; HRMS (ESI, m/z): calcd for $C_{17}H_{16}BrCl_2NONa$ $[M + Na]^+$ 421.9685, found 421.9692.

Reaction of 2-methyl-tetrahydrofuran with imine: Imine **1s** (0.5 mmol) and AIBN (1.6 mg, 0.01 mmol) were added in an oven-dried sealable tube charged with a stir bar. The tube was then filled with freshly distilled 2-methyl tetrahydrofuran (4 mL) and sealed with a Teflon cap. The reaction was then heated-up to 100 °C and kept stirring for 48 hours. After completion of the reaction, the solvent was evaporated *in vacuo* to afford the crude products. Compounds **7** and **8** were isolated through a silica gel flash column (PE: EtOAc from 20:1 to 10:1) as a mixture of regio-isomers and diastereomers. Colorless oil (187 mg, 90% overall yield) and the ratio was assigned by ^{1}H NMR analysis. As region-isomers **7** and **8** (each as a pair of diastereomers) are inseparable on column, so the characterization data are reported in a mixture form. HRMS (ESI, m/z): calcd for $C_{18}H_{19}BrCl_2NO_5Na$ $[M + H]^+$ 414.0022, found 414.0020. For details of NMR data and analysis, see supporting information.

Reaction of 1,3-Dioxolane with Imine: Imine **1h** (0.5 mmol) and AIBN (1.6 mg, 0.01 mmol) were added in an oven-dried sealable tube charged with a stir bar. The tube was then filled with freshly distilled 1,3-dioxolane (4 mL) and sealed with a Teflon cap. The reaction was then heated-up to 100 °C and kept stirring. After even 48 hours, **1h** was not consumed, the reaction was stopped and the solvent was evaporated *in vacuo* to afford the crude product **10** as a single regio-isomer.

***N*-((2,4-Dichlorophenyl)(1,3-dioxolan-2-yl)methyl)aniline (10)**: Compound **10** was isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Colorless oil (48 mg, 30% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 7.21 – 7.05 (m, 2H), 6.67 (t, *J* = 7.4 Hz, 1H), 6.49 (d, J = 7.8 Hz, 2H), 5.16 (m, 2H), 4.49 (s, 1H), 4.04 – 3.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 134.9, 134.5, 133.9, 130.0, 129.3, 129.3, 127.5, 118.2, 113.5, 103.8, 65.6, 65.4, 55.6; HRMS (ESI, m/z): calcd for $C_{16}H_{15}Cl_2NO_2Na$ $[M + Na]^+$ 346.0372, found 346.0387.

Reaction of tetrahydrofuran to dimethyl fumarate: Dimethyl fumarate **11** (0.5 mmol) and AIBN (1.6 mg, 0.01 mmol) were added in an oven-dried sealable tube charged with a stir bar. The tube was then filled with freshly distilled tetrahydrofuran (4 mL) and sealed with a Teflon cap. The reaction was then heated-up to 100 °C and kept stirring for 48 hours. After completion of the reaction, the solvent was evaporated *in vacuo* to afford the crude product **12** as a pair of diastereomers.

Dimethyl 2-(tetrahydrofuran-2-yl)succinate (12): Compound **12** was prepared with the standard procedure and isolated through a flash column (PE: EtOAc from 20:1 to 10:1); Colorless oil (48 mg, 56% yield, *d.r.* = 1.5:1); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 4.06 – 3.85 (m, 1H), 3.86 – 3.55 (m, 8H), 3.01 (m, 0.4H), 2.84 (m, 0.6H), 2.78 – 2.58 (m, 0.6H), 2.41 (dd, *J* = 16.6, 4.3 Hz, 0.4H), 2.01 – 1.48 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.3, 172.6, 172.2, 78.8, 78.7, 68.4, 68.1, 52.0, 51.8, 51.8, 46.6, 46.0, 33.2, 32.5, 29.6, 28.6, 25.6, 25.6; HRMS (ESI, m/z): calcd for $C_{10}H_{16}O_5Na$ $[M + Na]^+$ 239.0890, found 239.0801.

For more detailed information about mechanistic control experiments, kinetic isotope effect study and NMR spectra, see supporting information.

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Keywords: Radical reaction • Metal-free• Radical chain• Schiff bases • Oxygen heterocycles

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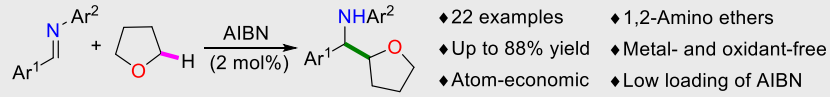
Layout 2:

FULL PAPER



Here we present an efficient and practical method to functionalize cyclic ethers with imines for the synthesis of 1,2-amino ethers. Different with previous works, this reaction goes through a radical chain process thus no stoichiometric amount of radical reagent or oxidant was required.

Radical Addition*

Haipeng Zeng, Dengfu Lu, and Yuefa Gong**

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Direct Metal-free C-H Functionalization of Cyclic Ethers with Schiff Bases through an Azobisisobutyronitrile (AIBN) Initiated Radical Chain Process