Site-Specific Functionalization of 1,3-Dioxolane with Imines: A Radical Chain Approach to Masked #-Amino Aldehydes

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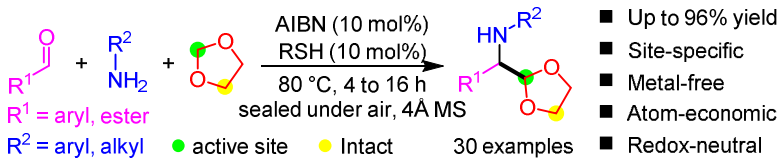
Supporting Information Placeholder

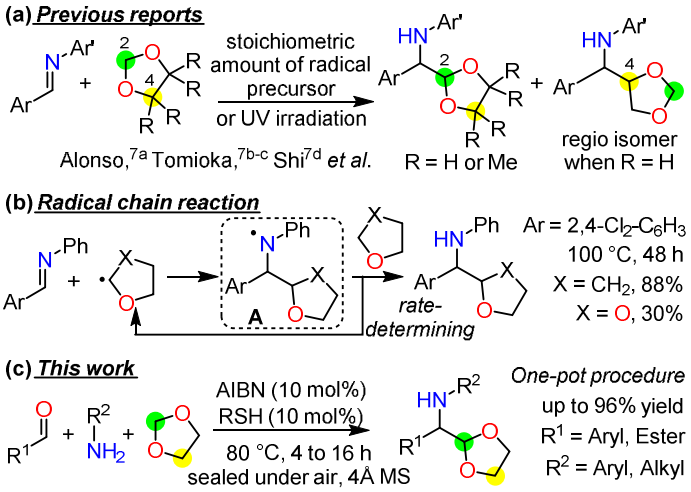


Abstract: A thiol promoted site-specific addition of 1,3-dioxolane to imines through radical chain process is described. This process represents a metal-free and redox-neutral way to convert inexpensive materials to a broad range of protected α-amino aldehydes in good to excellent yields using only catalytic amount of radical precursor. Control experiments revealed that both the thiol and a small amount of oxygen from air are indispensable to the success of this reaction.

Introduction

Converting abundant ethers and alcohols to valuable building blocks through direct sp^3 C–H functionalization is a challenging endeavor in synthetic chemistry.[1] Due to the α-effect of the adjacent oxygen atom, radical activation of the α-C–H bonds has emerged as a popular strategy,[2] for example, the flourishing oxidative coupling reactions.[1b,1d-g] Within these methods, the C–H bonds are prevailingly activated by strongly electron-deficient oxygen-centered radicals generated from stoichiometric amounts of oxidants such as peroxides[3] and persulfates.[4] Besides oxidative coupling processes, we noticed that numerous redox-neutral reactions, e.g., radical addition to multiple bonds, also require excess amount of radical precursors,[5] probably due to the irreversible generation of highly active radical species.

Scheme 1. Radical addition of 1,3-dioxolane to imines



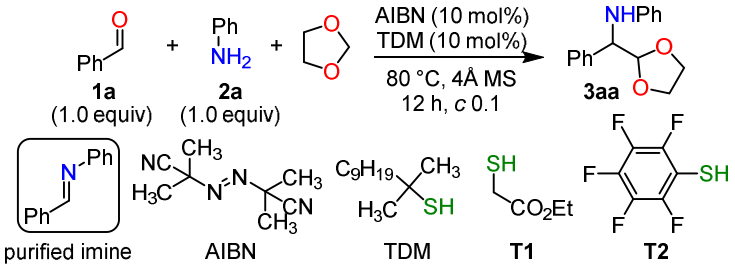
Our lab has recently developed an azobisisobutyronitrile (AIBN) initiated radical chain addition of cyclic ethers to imines, demonstrating that etheric radicals can be regenerated from the reaction intermediate.[6] This discovery led us to explore more general and synthetically useful redox-neutral radical functionalization methods. The functionalization of 1,3-dioxolane with imines[7] is of special interest since it represents a practical route to masked amino aldehydes, which are important building blocks in organic synthesis. However, the existing methods developed by Alonso[7a], Tomioka[7b-c], and Shi[7d] et al. require either stoichiometric amount of radical precursors or UV irradiation (Scheme 1, **a**). Meanwhile, due to the close dissociation energy of the C–H bonds,[8] the site-selectivity of 1,3-dioxolane remains a challenge with oxygen-centered radicals,[3a,3d,3f-g,4b,5a-b,5h] (usually from 1.5:1 to 6:1). A method that can regioselectively convert 1,3-dioxolane and imines to masked amino aldehydes without using a stoichiometric radical precursor is highly desirable.

Most recently, Doyle[8] reported a formylation of aryl chlorides which selectively activates the 2-C–H bond of 1,3-dioxolane with a chlorine radical. While in our radical chain reaction, an exclusive 2-C–H selectivity was also observed for 1,3-dioxolane, despite a low conversion.[6] Based on the mechanistic studies, it is assumed that this selectivity may stem from the inferior reactivity of a stabilized nitrogen radical intermediate **A** (Scheme 1, **b**). However, compared to tetrahydrofuran, the more complicated reactivity of 1,3-dioxolane could increase the rate of chain termination other than the effective propagation, thus the less reactive radical **A** may also be responsible for the poor chain efficiency. Therefore, we envisioned to introduce a suitable radical mediator to balance the reactivity and selectivity in the hydrogen atom transfer (HAT) step. Inspired by the pioneering works of Roberts[9] and Newcomb[10] et al., we proposed that thiols

could be potential candidates as they are reported to readily reduce nitrogen radicals and the resulting thiyl radical is capable of H-atom abstraction from specific C–H bonds.[11] Herein we report a thiol mediated radical chain addition of 1,3-dioxolane to different types of imines with exclusive site-selectivity. (Scheme 1, **c**)

Results and discussion

Table 1. Reaction condition optimization[a]



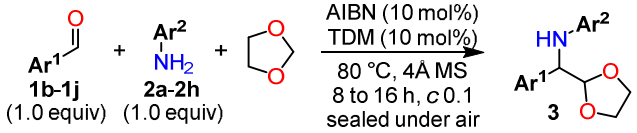
Entry	Variations from the standard conditions	Conv.[b]	Yield (**3aa**)
1	none	66%	62%
2	without AIBN	<5%	<5%[c]
3	20 mol% AIBN	34%	33%
4	without TDM	<5%	<5%[c]
5	20 mol% TDM.	60%	55%
6	**T1** instead of TDM	62%	52%
7	**T2** instead of TDM	10%	<5%[c]
8	without 4Å MS	36%	31%
9	purified imine	68%	63%
10[d]	reaction at 65 °C	52%	44%
11	under N_2 or Ar	<5%	<5%[c]
12	under O_2	20%	15%[c]

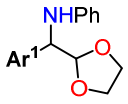
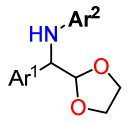
[a]Unless otherwise stated, the reactions were carried out under air in a 20 mL sealed tube with benzaldehyde (0.2 mmol), aniline (0.2 mmol) and 4Å molecular sieves (80 mg) in freshly distilled 1,3-dioxolane (2 mL) in the presence of AIBN (0.02 mmol) and TDM (0.02 mmol); [b]The conversion was determined with crude ^{1}H NMR by calculating the remaining aldehyde and imine; [c]Determined by ^{1}H NMR; [d]Reaction time: 24 h.

Starting with a relatively less reactive *N*,1-diphenylmethan-imine, after extensive screening of the conditions, the reaction of in-situ formed imine was able to achieve good conversion in the presence of 10 mol % of AIBN and *tert*-dodecyl mercaptan (TDM) at 80 °C with 4 Å molecular sieves, affording product **3aa** in 62% yield as the only regio-isomer (Table 1, entry 1). A few conditions that may be mechanistically important are described here. As previously observed, the

reaction doesn't occur in the absence of AIBN (entry 2). Interestingly, for this substrate, the reaction hardly proceeds without TDM, while more of it doesn't improve the yield either (entries 4-5). Aliphatic thiols are more effective than aromatic ones and the bulkiness of aliphatic thiols may also play a role, presumably because of their potential nucleophilic addition to imines (entries 6-7). Since the imine is formed in-situ, 4 Å molecular sieves are essential to remove the water, and the same yield was obtained with purified imine (entries 8-9). The reaction slows down at 65 °C and the yield was not improved after extended reaction time (entry 10). Surprisingly, product **3aa** was hardly observed when the reaction was strictly conducted under inert atmosphere (entry 11), implying the participation of O_2. However, O_2 atmosphere also caused an inefficient transformation (entry 12).

Table 2. Addition of 1,3-dioxolane to *N*,1-diarylmethan-imines[a]



Structure	Entry	Substituent	Product	Yield
	1	**Ar**^{1} = 4-CO_2Me-C_6H_4	**3ba**	86%[b]
	2	**Ar**^{1} = 4-Me-C_6H_4	**3ca**	67%[b]
	3	**Ar**^{1} = 4-MeO-C_6H_4	**3da**	72%[b]
	4	**Ar**^{1} = 4-F-C_6H_4	**3ea**	75%
	5	**Ar**^{1} = 4-Cl-C_6H_4	**3fa**	79%
	6	**Ar**^{1} = 3-Cl-C_6H_4	**3ga**	65%
	7	**Ar**^{1} = 2-Cl-C_6H_4	**3ha**	60%
	8	**Ar**^{1} = 2,4-Cl_2-C_6H_3	**3ia**	91%
	9	**Ar**^{1} = 2-pyridyl	**3ja**	84%
 Ar^1 = 2,4-Cl_2-C_6H_3	10	**Ar**^{2} = 4-Me-C_6H_4	**3ib**	95%[b]
	11	**Ar**^{2} = 4-MeO-C_6H_4	**3ic**	77%
	12	**Ar**^{2} = 4-Cl-C_6H_4	**3id**	95%[b]
	13	**Ar**^{2} = 3-Cl-C_6H_4	**3ie**	74%
	14	**Ar**^{2} = 4-Br-C_6H_4	**3if**	97%[b]
	15	**Ar**^{2} = 4-F-C_6H_4	**3ig**	73%
	16	**Ar**^{2} = 3,5-$(CF_3)_2$-C_6H_3	**3ih**	55%

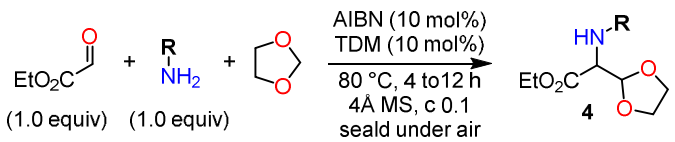
[a]Unless otherwise stated, the reaction was performed under air in a 20 mL sealed tube with a corresponding aldehyde (0.2 mmol), an amine (0.2 mmol) and 4Å molecular sieves (80 mg) in freshly distilled 1,3-dioxolane (2 mL) in the presence of AIBN (0.02 mmol) and TDM (0.02 mmol); [b]Reaction performed with purified imine.

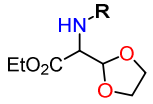
After establishing the optimized condition, we tested a combination of various aromatic aldehydes and aniline derivatives with 1,3-dioxolane. Both electron-rich and electron-deficient aldehydes including heterocycles are well tolerated in combination with aniline to afford the products **3ba-3ja** regioselectively in good to excellent yields (Table 2, entries 1-9). Different substituted anilines are also compatible with 2,4-dichlorobenzaldehyde (entries 10-16). In cases that imines are not formed in-situ with sufficient efficiency and purity, purified imines are employed to ensure reproducibility.

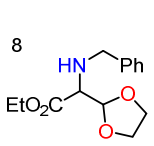
While most reports of radical additions to imine are limited to *N*,1-diaryl substrates, the functionality performance of this method encouraged us to explore more synthetically intriguing aldehydes and amines (Table 3). The three component reaction of ethyl glyoxylate, aniline and 1,3-dioxolane gives the α-amino ester **4a** as a single regio-isomer with excellent yield (entry 1). Several substituted anilines are also suitable for this "one-pot" procedure (60%-96% yields, entries 2-7). The α C–H bonds of amines are normally considered unstable towards radical species. Surprisingly, aliphatic amines bearing very labile C–H bonds, such as benzylamine and 1-phenylethylamine, are compatible with this process, leading to products **4h** and **4i** with removable *N*-protecting groups (entries 8-9). The reaction of cyclohexylamine and amantadine proceed smoothly to afford product **4j** and **4k** in moderate to good yields (entries 10-11). Gratifyingly, amines with multiple functional groups are also well applied, offering densely functionalized products **4l** and **4m** in practical yields (entries 12-13).

To demonstrate the synthetic utility of this method, we tested two representative substrates on gram-scale and obtained comparative yields (Table 3, entries 4 and 8). As shown in Scheme 2, product **4h**, for example, can be readily converted to key intermediate **5** that serves as a versatile precursor to various unnatural amino acid derivatives. Products **6** and **7** are also typical substrates for asymmetric hydrogenation to produce chiral amino acids.[13]

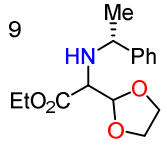
Table 3. Addition of 1,3-dioxolane to ethyl glyoxylate imines[a]



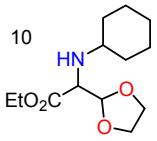
	Entry	Substituent	Product	Yield
	1	**R** = Ph[b]	**4a**	96%
	2	**R** = 4-CO_2Me-C_6H_4	**4b**	60%
	3	**R** = 4-Me-C_6H_4	**4c**	91%
	4	**R** = 4-OMe-C_6H_4	**4d**	96% (90%)[d]
	5	**R** = 4-F-C_6H_4	**4e**	60%
	6	**R** = 4-Cl-C_6H_4	**4f**	85%
	7	**R** = 3-Cl-C_6H_4	**4g**	61%



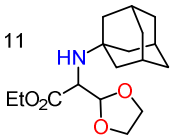
4h, 62%[c] (55%)[d]



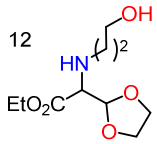
4i, 65%[c] *dr* 1.2:1



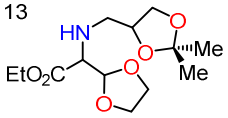
4j, 62%[c]



4k, 75%



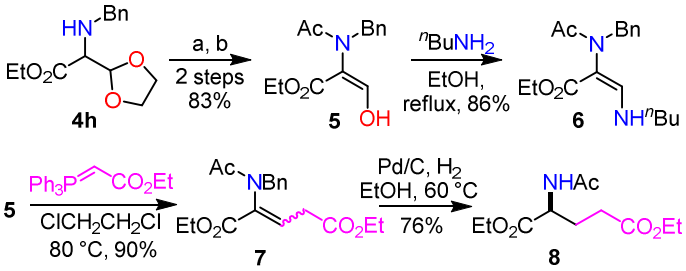
4l, 45%



4m, 66%, *dr* 1.5:1

[a]Unless otherwise stated, the reaction was performed under air in a 20 mL sealed tube with ethyl glyoxylate (0.2 mmol), a corresponding amine (0.2 mmol) and 4Å molecular sieves (80 mg) in freshly distilled 1,3-dioxolane (2 mL) in the presence of AIBN (0.02 mmol) and TDM (0.02 mmol); [b]Aniline: 2 equiv; [c]Reaction performed at 65 °C without thiol; [d]Reaction on 10 mmol scale.

Scheme 2. Product derivatizations

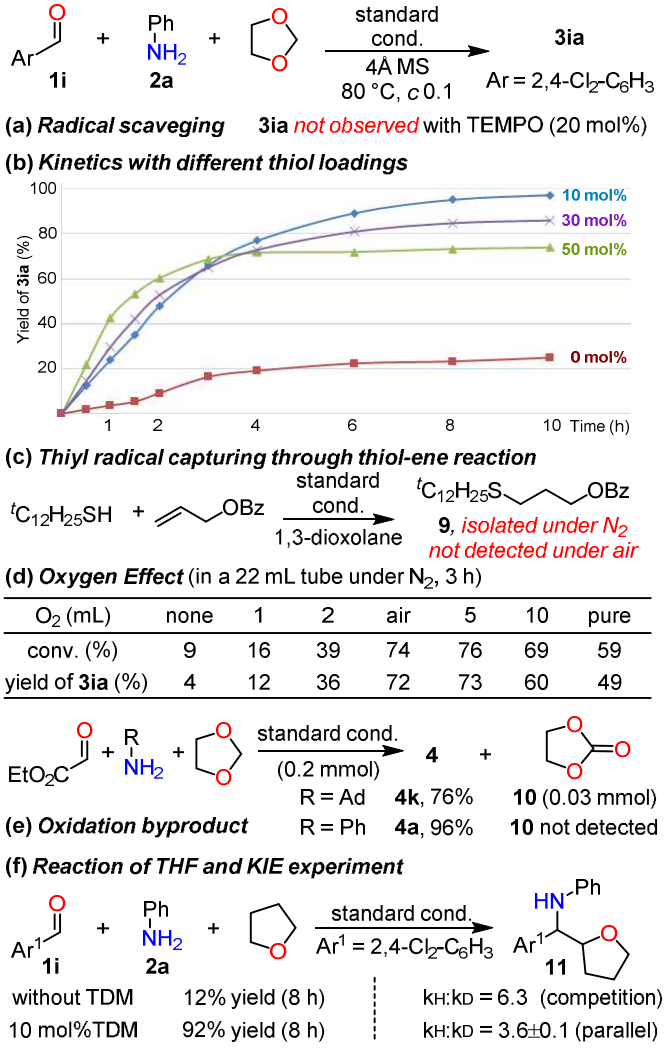


[a]Condition: AcCl (1.5 equiv.), NEt_3 (1.5 equiv.), $ClCH_2CH_2Cl$, room temperature, 4 h; [b]Condition: AcOH/HI, 65 °C, 2 h.

To gather evidences for mechanistic insights of this transformation, a series of control experiments were carried out.[13] Firstly, the reaction of **1i** and **2a** in 1,3-dioxolane was inhibited by 20 mol% of the radical scavenger TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl, Scheme 3, **a**). Secondly, the kinetic studies showed the reaction was significantly accelerated by thiol and, unexpectly, a lower loading of thiol led to a more durable process (**b**). Thirdly, when a non-activated alkene was mixed with TDM under the reaction conditions to capture the thiyl radical

through the thiol-ene process,[14] the click product **9** was isolated under inert atmosphere, but not detected in the presence of air (**c**). Then, in a 20 mL sealed tube (22-24 mL gas space), 5 mL of O_2 in otherwise N_2 promoted the reaction most efficiently, which is consistent with its good performance under air (**d**). Next, carbonate **10** was identified as a side product in aliphatic amines participated reactions (about 15% yield based on imine), which possibly comes from the O_2 entrapment of a 1,3-dioxolane radical. Interestingly, **10** was not observed in the reaction of aromatic amines (**e**). In addition, the reaction of tetrahydrofuran revealed a similar thiol-accelerating trend, which indicates this is not an individual effect for 1,3-dioxolane (**f**). Furthermore, primary kinetic isotope effect was observed for THF under these conditions in both intermolecular competition ($k_H/k_D = 6.3$) and parallel ($k_H/k_D = 3.6\pm0.1$) experiments.

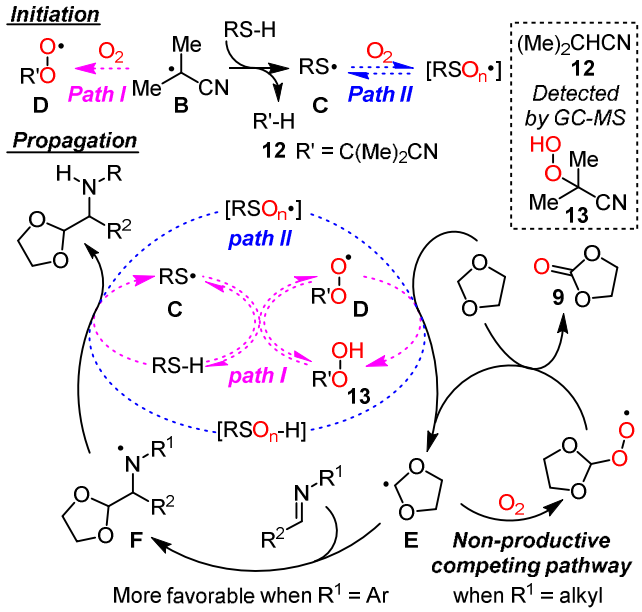
Scheme 3. Mechanistic related control experiments



O_2 (mL)	none	1	2	air	5	10	pure
conv. (%)	9	16	39	74	76	69	59
yield of **3ia** (%)	4	12	36	72	73	60	49

The above observations together with the results in **table 1** reveal mechanistic information. First, radical species are involved in this reaction, and AIBN, thiol and O_2 are all essential to the reaction. Then, according to the thiol-ene reaction, thiol and AIBN should be able to generate thiyl radical under inert atmosphere. So, the necessity of O_2 suggests that the thiol-thiyl radical pair alone could not promote the chain reaction efficiently as we proposed in the introduction. An O_2-related species is highly likely involved in the radical chain propagation cycle. Additionally, the generation of carbonate **10** reveals O_2 could also act as a competing electrophile when imine is not reactive enough. Furthermore, no matter which radical is the real abstracting species, it has excellent regioselectivity, and the HAT process from the substrate is probably rate-determining.

Scheme 4. Plausible reaction mechanism



Based on these results, we proposed a plausible reaction mechanism as illustrated in Scheme 4. *In the initiation stage*, AIBN firstly decomposes under heating condition to generate isobutyl nitrile radical **B**, which is known[15] to react with a thiol to yield a thiyl radical **C** and isobutyl nitrile **12** (detected by GC-MS). Then, O_2 could participate in two different ways: either combines with radical **B** to form a peroxyl radical **D** (path I), or reacts with thiyl radical **C** to furnish a thiylperoxyl radical RSOO·,[16] which could be further converted to a series of derivatives according to previous studies (path II), such as sulfonyl radical [RS(O)O·], sulfonyl peroxyl radical [RS(OO·)O_2] and sulfinyl [RSO·] radical. These species are presented as one general formula [RSO_n·] in Scheme 4.

In the case of path I, the peroxyl radical **D** may abstract an H-atom from 1,3-dioxolane to generate **13** (detected by GC-MS) and radical **E**, which would quickly add to an imine to furnish a nitrogen-centered radical **F**. This nitrogen radical would be readily reduced by one molecule of thiol to afford the product and a thiyl radical **C**.[10,17] Since RS–H and R'OO–H have very similar bond dissociation energy (both around 87–88 kcal/mol),[11,18] radical **C** may abstract an H-atom from peroxide **13** to regenerate the peroxyl radical **D**. *On the other hind*, thiyl peroxyl radical and its derivatives [$RSO_n\cdot$] normally have mild reactivity and form weak O–H bonds. Therefore, they may also be able to abstract a hydrogen atom from 1,3-dioxolane and then reduce the nitrogen radical G. However, in this scenario, there might multiple species (n = 1, 2 or 4) involved and we currently cannot identify the real effective one (*path II*). Based on the evidence we have, neither *path I* nor *II* could be ruled out, and maybe both of them contribute to the reaction. In addition, although O_2 is essential to the desired radical chain propagation, it also acts as a competing electrophile toward radical **E** to cause a non-productive oxidation cycle to yield carbonate **10**, especially in the reactions of *N*-aliphatic imines.

Conclusion

In summary, we have developed an AIBN/thiol promoted site-specific and redox-neutral functionalization procedure of 1,3-dioxolane with imines to synthesize masked amino aldehydes, avoiding the use of stoichiometric amount of radical precursors. This method is scalable and tolerates a range of functional groups, including those were normally incompatible with imine radical additions. Mechanistic studies demonstrate this transformation proceeds through a thiol and O_2 promoted radical chain pathway with the initiation of AIBN. Further synthetic applications and mechanistic studies of this reaction are ongoing in our laboratory.

Experimental Section

i. General procedures. All reactions were performed in oven-dried round-bottom flasks and tubes. Solvents were dried and freshly distilled before use. 4 Å molecular sieves were freshly activated before use. Aldehydes and amines are purified either by distillation or recrystallization before use. Reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F-254 plates. TLC plates were normally visualized under UV irradiation (254 nm or 365 nm), stained with basic $KMnO_4$ or phosphomolybdic acid. Flash column chromatography was performed using silica gel 60 (200−300 mesh).

ii. Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker Ascend 400 MHZ or 600 MHZ. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$: δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ 77.0). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants in Hertz (Hz), and integration. HRMS was measured on a Bruker SolariX 7.0 T spectrometer equipped with an ESI or APCI source.

iii. Abbreviations used: TLC–thin layer chromatography; AIBN–azobisisobutyronitrile; TDM–*tert*-dodecyl mercaptan; PE–Petroleum Ethers; TEMPO–2,2,6,6-tetramethylpiperidine-*N*-oxyl; NOE–Nuclear Overhauser Effect.

iv. General procedures for Initiator evaluation and condition optimization (Table 1)

To an oven-dried 20 mL sealable tube charged with a stir bar were added benzaldehyde (21.2 mg, 0.2 mmol), aniline (18.6 mg, 0.2 mmol), AIBN (0.02 or 0.04 mmol) and freshly activated 4 Å molecular sieves (80 mg, if any). Freshly distilled 1,3-dioxolane (2 mL) was added through a syringe followed by the addition of a corresponding thiol (0.02 or 0.04 mmol). The reaction tube was then sealed with a septum under air, heated up to the indicated temperature and stirred for 12 hours. The reaction was then cooled down, filtered through a Celite® pad, washed with ether, and the filtrate was concentrated *in vacuo*. The residue was submitted for ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. For reactions with decent conversions, yield of **3aa** was obtained after purification through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1).

N-((1,3-Dioxolan-2-yl)(phenyl)methyl)aniline (**3aa**): compound **3aa** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as a yellow solid (32 mg, 62% yield, m.p. 76–78 °C), which is a known compound[7d] and the characterization data are in accordance with the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 6.9 Hz, 2H), 7.24 (t, J = 7.4 Hz, 2H), 7.20 – 7.15 (m, 1H), 7.00 (t, J = 7.8 Hz, 2H), 6.57 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 7.9 Hz, 2H), 5.10 (d, J = 2.8 Hz, 1H), 4.49 (d, J = 2.8 Hz, 2H), 3.77 (m, 4H); ^{13}C{^{1}H}NMR (100 MHz,

$CDCl_3$) δ 147.0, 138.7, 129.1, 128.4, 127.7, 127.6, 117.7, 113.8, 105.5, 65.5, 65.3, 60.2; IR ν_{max} (neat)/cm^{-1}: 3361, 3027, 2876, 1603, 1505, 1294, 1123, 1031, 749, 700.

v. Addition of 1,3-dioxolane to *N*,1-diarylmethanimines (Table 2)

Procedure A: To an oven-dried 20 mL sealable tube charged with a stir bar were added an aldehyde (0.2 mmol), an amine (0.2 mmol), AIBN (3.3 mg, 0.02 mmol) and freshly activated 4 Å molecular sieves (80 mg). The tube was sealed with a septum and 1,3-dioxolane (2 mL, freshly distilled) was added through a syringe, followed by the addition of TDM (5 μL, 0.02 mmol). The reaction mixture was stirred at 80 °C for indicated time and then cooled down, filtered through a Celite® pad and washed with ether. After the filtrate was concentrated *in vacuo*, the resulting residue was purified through a silica gel column chromatography to afford the corresponding product **3**.

Procedure B: To an oven-dried 20 mL sealable tube charged with a stir bar were added a corresponding purified imine (0.2 mmol), AIBN (3.3 mg, 0.02 mmol) and freshly activated 4 Å molecular sieves (40 mg). The tube was sealed with a septum and 1,3-dioxolane (2 mL, freshly distilled) was added through a syringe, followed by the addition of TDM (5 μL, 0.02 mmol). The reaction mixture was stirred at 80 °C for indicated time and then cooled down, filtered through a Celite® pad and washed with ether. After concentrated *in vacuo*, the resulting residue was purified through a silica gel column chromatography to afford the corresponding product **3**.

Methyl 4-((1,3-dioxolan-2-yl)(phenylamino)methyl)benzoate (**3ba**) was prepared according to procedure B through the reaction of methyl (*E*)-4-((phenylimino)methyl)benzoate in 1,3-dioxolane for 12 hours. Compound **3ba** was isolated through a silica gel column chromatography (PE: EtOAc from 20:1 to 10:1) as a yellow solid (54 mg, 86% yield, m.p. 79–81 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 2H), 5.20 (d, *J* = 2.8 Hz, 1H), 4.64 (d, *J* = 2.8 Hz, 2H), 3.90 (s, 3H), 3.91 – 3.80 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 167.0, 146.6, 144.1, 129.7, 129.6, 129.2, 127.9, 118.0, 113.8, 105.0, 65.5, 65.4, 60.2, 52.1; IR ν_{max} (neat)/cm^{-1}: 3376, 3027, 2878, 1722, 1605, 1510, 1315, 1125, 1033, 747, 695; HRMS (ESI/FT-ICR, m/z): calcd for $C_{18}H_{19}NNaO_4$ $[M + Na]^+$ 336.1206, found 336.1212

N-((1,3-Dioxolan-2-yl)(p-tolyl)methyl)aniline (**3ca**) was prepared according to procedure B through the reaction of (*E*)-*N*-phenyl-1-(p-tolyl)methanimine in 1,3-dioxolane for 12 hours.

Compound **3ca** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as a yellow solid (36 mg, 67% yield, m.p. 58–60 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.8 Hz, 2H), 6.66 (t, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 7.4 Hz, 2H), 5.16 (d, *J* = 3.2 Hz, 1H), 4.55 (d, *J* = 3.2 Hz, 1H), 3.96 – 3.73 (m, 4H), 2.33 (s, 3H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 147.1, 137.2, 135.6, 129.2, 129.1, 127.5, 117.7, 113.8, 105.6, 65.4, 65.3, 60.0, 21.2; IR ν_{max} (neat)/cm^{-1}: 3376, 3027, 2876, 1606, 1510, 1317, 1125, 1033, 746, 696; HRMS (ESI/FT-ICR, m/z): calcd for $C_{17}H_{19}NNaO_2$ $[M + Na]^+$ 292.1308, found 292,1315.

N-((1,3-Dioxolan-2-yl)(4-methoxyphenyl)methyl)aniline (**3da**) was prepared according to procedure B through the reaction of (*E*)-1-(4-methoxyphenyl)-*N*-phenylmethanimine in 1,3-dioxolane for 12 hours. Compound **3da** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as a yellow solid (41 mg, 72% yield, m.p. 81–83 °C). **3da** is a known compound[7d] and the characterization data are in accordance with the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.7 Hz, 2H), 7.14 – 7.05 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 2H), 5.15 (d, *J* = 3.1 Hz, 1H), 4.56 (s, 1H), 4.52 (d, *J* = 3.1 Hz, 1H), 3.87 (m, 4H), 3.78 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 159.1, 147.1, 130.6, 129.1, 128.7, 117.6, 113.9, 113.8, 105.5, 65.4, 65.3, 59.7, 55.2; IR ν_{max} (neat)/cm^{-1}: 3372, 3023, 2881, 1606, 1512, 1306, 1251, 1178, 1125, 1035, 746, 693.

N-((1,3-Dioxolan-2-yl)(4-fluorophenyl)methyl)aniline (**3ea**) was prepared according to procedure A through the reaction of 4-fluoro-benzaldehyde and aniline in 1,3-dioxolane for 12 hours. Compound **3ea** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as a yellow solid (41 mg, 75% yield, m.p. 44–47 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (td, *J* = 5.6, 2.3 Hz, 2H), 7.11 (t, *J* = 8.0 Hz, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 2H), 5.17 (d, *J* = 3.1 Hz, 1H), 4.56 (d, *J* = 3.1 Hz, 1H), 3.93 – 3.82 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 162.3 (d, *J* = 245.5 Hz), 146.8, 134.2 (d, *J* = 3.1 Hz), 129.3 (d, *J* = 8.1 Hz), 129.1, 117.9, 115.3 (d, *J* = 21.4 Hz), 113.8, 113.8, 105.2, 65.5, 65.4, 59.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.16 (tt, *J* = 8.8, 5.3 Hz); IR ν_{max} (neat)/cm^{-1}: 3374, 3062, 2877, 1605, 1509, 1394, 1297, 1230, 1122, 1028, 748, 698; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{16}FNNaO_2$ $[M + Na]^+$ 296.1057, found 296,1068.

N-((4-Chlorophenyl)(1,3-dioxolan-2-yl)methyl)aniline (**3fa**) was prepared according to procedure A through the reaction of 4-chloro-benzaldehyde and aniline in 1,3-dioxolane for 12 hours. Compound **3fa** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as a yellow solid (46 mg, 79% yield, m.p. 58–60 °C). ^{1}H NMR (600 MHz, $CDCl_3$) 7.38 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.11 (t, *J* = 7.7 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 7.9 Hz, 2H), 5.16 (d, *J* = 3.2 Hz, 1H), 4.55 (d, *J* = 3.2 Hz, 1H), 3.92 – 3.79 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 146.7, 137.2, 133.4, 129.2, 129.2, 128.6, 118.0, 113.8, 105.1, 65.5, 65.4, 59.8; IR ν_{max} (neat)/cm^{-1}: 3391, 3053, 2883, 1604, 1513, 1317, 1125, 1031, 749, 694 cm^{-1}; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{16}ClNNaO_2$ $[M + Na]^+$ 312.0762, found 312.0781.

N-((3-Chlorophenyl)(1,3-dioxolan-2-yl)methyl)aniline (**3ga**) was prepared according to procedure A through the reaction of 3-chloro-benzaldehyde and aniline in 1,3-dioxolane for 12 hours. Compound **3ga** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as a yellow solid (37 mg, 65% yield, m.p. 56–58 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.38 – 7.33 (m, 1H), 7.32 – 7.26 (m, 2H), 7.14 (t, *J* = 7.9 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 7.9 Hz, 2H), 5.19 (d, *J* = 3.2 Hz, 1H), 4.57 (d, *J* = 3.2 Hz, 1H), 3.95 – 3.85 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 146.7, 141.0, 134.4, 129.6, 129.2, 127.9, 127.9, 126.0, 118.0, 113.7, 105.1, 65.5, 65.4, 60.0; IR ν_{max} (neat)/cm^{-1}: 3367, 3056, 2873, 1603, 1510, 1315, 1130, 1035, 749, 693; HRMS ESI/FT-ICR, m/z): calcd for $C_{16}H_{16}ClNNaO_2$ $[M + Na]^+$ 312.0762, found 312.0774.

N-((2-Chlorophenyl)(1,3-dioxolan-2-yl)methyl)aniline (**3ha**) was prepared according to procedure A through the reaction of 2-chloro-benzaldehyde and aniline in 1,3-dioxolane for 12 hours. Compound **3ha** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as a yellow solid (34 mg, 60% yield, m.p. 57–59 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 1H), 7.44 – 7.38 (m, 1H), 7.25 – 7.18 (m, 2H), 7.11 (t, *J* = 7.9 Hz, 2H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 2H), 5.22 (s, 2H), 4.04 – 3.86 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 146.5, 136.2, 133.8, 129.5, 129.2, 128.9, 128.8, 127.1, 117.9, 113.5, 104.1, 65.6, 65.3, 55.8; IR ν_{max} (neat)/cm^{-1}: 3358, 3020, 2900, 1602, 1523, 1498, 1318, 1112, 1028, 746, 693; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{16}ClNNaO_2$ $[M + Na]^+$ 312.0762, found 312.0766.

N-((2,4-Dichlorophenyl)(1,3-dioxolan-2-yl)methyl)aniline (**3ia**) was prepared according to procedure A through the reaction of 2,4-dichloro benzaldehyde and aniline in 1,3-dioxolane for 8 hours. Compound **3ia** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as colorless oil (59 mg, 91% yield), which we have reported[6] in a previous publication. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 2H), 6.69 (t, *J* = 7.4 Hz, 1H), 6.51 (m, 2H), 5.19 (d, *J* = 2.5 Hz, 1H), 5.16 (d, *J* = 2.5 Hz, 1H), 4.51 (s, 1H), 4.06 – 3.76 (m, 4H); ^{13}C{^{1}H}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; IR ν_{max} (neat)/cm^{-1}: 3402, 3027, 2873, 1602, 1514, 1317, 1125, 1033, 746, 696.

N-((1,3-dioxolan-2-yl)(pyridin-2-yl)methyl)aniline (**3ja**) was prepared according to procedure A through the reaction of 2-pyridinecarboxaldehyde and aniline in 1,3-dioxolane for 12 hours. Compound **3ja** was isolated through a silica gel column chromatography (PE:EtOAc from 10:1 to 5:1 as a yellow solid (48 mg, 84% yield, m.p. 106–108 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 6.1 Hz, 1H), 7.63 (td, *J* = 7.7, 1.9 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.19 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 2H), 6.72 – 6.60 (m, 3H), 5.33 (d, *J* = 2.9 Hz, 1H), 4.96 (d, *J* = 6.7 Hz, 1H), 4.78 (dd, *J* = 6.7, 2.9 Hz, 1H), 4.01 – 3.83 (m, 4H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 158.3, 149.3, 147.2, 136.5, 129.2, 122.5, 122.5, 117.8, 113.7, 105.1, 65.5, 65.4, 61.2; IR ν_{max} (neat)/cm^{-1}: 3312, 3055, 2875, 1603, 1515, 1311, 1119, 1035, 748, 690; HRMS (ESI/FT-ICR, m/z): calcd for $C_{15}H_{16}N_2NaO_2$ $[M + Na]^+$ 279.1104, found 279.1108.

N-((2,4-Dichlorophenyl)(1,3-dioxolan-2-yl)methyl)-4-methylaniline (**3ib**) was prepared according to procedure B through the reaction of (*E*)-1-(2,4-dichlorophenyl)-*N*-(p-tolyl)methanimine in 1,3-dioxolane for 10 hours. Compound **3ib** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as colorless oil (64 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 5.18 (d, *J* = 2.8 Hz, 1H), 5.12 (d, *J* = 2.8 Hz, 1H), 4.49 (s, 1H), 4.04 – 3.79 (m, 4H), 2.19 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 143.9, 135.1, 134.5, 133.8, 130.0, 129.7, 129.2, 127.5, 127.3, 113.6, 103.9, 65.6, 65.4, 55.8, 20.4; IR ν_{max} (neat)/cm^{-1}: 3407, 3022, 2889, 1617, 1520, 1313, 1110, 1028, 811, 733; HRMS (ESI/FT-ICR, m/z): calcd for $C_{17}H_{17}Cl_2NNaO_2$ $[M + Na]^+$ 360.0529, found 360.0538.

N-((2,4-Dichlorophenyl)(1,3-dioxolan-2-yl)methyl)-4-methoxyaniline (**3ic**) was prepared according to procedure A through the reaction of 2,4-dichlorobenzaldehyde and 4-anisidine in 1,3-dioxolane for 10 hours. Compound **3ic** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as colorless oil (54 mg, 77% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.20 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.71 (d, *J* = 9.0 Hz, 2H), 6.47 (d, *J* = 9.0 Hz, 2H), 5.18 (d, *J* = 2.9 Hz, 1H), 5.09 (d, *J* = 2.9 Hz, 1H), 4.36 (s, 1H), 4.01 – 3.86 (m, 4H), 3.69 (s, 3H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 152.5, 140.3, 135.1, 134.6, 133.9, 130.0, 129.3, 127.5, 114.8, 114.7, 104.0, 65.6, 65.4, 56.3, 55.7; IR ν_{max} (neat)/cm^{-1}: 3389, 3064, 2892, 1618, 1514, 1384, 1240, 1037, 820, 733; HRMS (ESI/FT-ICR, m/z): calcd for $C_{17}H_{17}Cl_2NNaO_3$ $[M + Na]^+$ 376.0478, found 376.0490.

4-Chloro-N-((2,4-dichlorophenyl)(1,3-dioxolan-2-yl)methyl)aniline (**3id**) was prepared according to procedure B through the reaction of (*E*)-*N*-(4-chlorophenyl)-1-(2,4-dichlorophenyl) methanimine in 1,3-dioxolane for 10 hours. Compound **3ia** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as colorless oil (67 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 7.19 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 8.8 Hz, 2H), 5.16 (d, *J* = 2.7 Hz, 1H), 5.13 – 5.08 (m, 1H), 4.63 (d, *J* = 5.4 Hz, 1H), 4.02 – 3.82 (m, 4H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 144.8, 134.5, 134.4, 134.1, 129.8, 129.4, 129.1, 127.6, 122.8, 114.6, 103.6, 65.6, 65.4, 55.6; IR ν_{max} (neat)/cm^{-1}: 3421, 3068, 2890, 1599, 1500, 1315, 1121, 1027, 816, 734 cm^{-1}; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{14}Cl_3NNaO_2$ $[M + Na]^+$ 379.9982, found 379.9993.

3-Chloro-N-((2,4-dichlorophenyl)(1,3-dioxolan-2-yl)methyl)aniline (**3ie**) was prepared according to procedure A through the reaction of 2,4-dichlorobenzaldehyde and 3-chloro aniline in 1,3-dioxolane for 10 hours. Compound **3ie** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as colorless oil (53 mg, 74% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.21 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.68 – 6.63 (m, 1H), 6.53 (t, *J* = 2.2 Hz, 1H), 6.37 – 6.32 (m, 1H), 5.16 (d, *J* = 2.6 Hz, 1H), 5.12 (d, *J* = 2.6 Hz, 1H), 4.69 (s, 1H), 4.01 – 3.86 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 147.4, 134.9, 134.4, 134.3, 134.2, 130.3, 129.8, 129.4, 127.6, 118.1, 113.5, 111.4, 103.6, 65.6, 65.4, 55.4; IR ν_{max} (neat)/cm^{-1}: 3421, 3068, 2890, 1598, 1500, 1324, 1120, 1028, 842, 766; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{14}Cl_3NNaO_2$ $[M + Na]^+$ 379.9982, found 379.9985.

4-Bromo-N-((2,4-dichlorophenyl)(1,3-dioxolan-2-yl)methyl)aniline (**3if**) was prepared according to procedure **B** through the reaction of (*E*)-*N*-(4-bromophenyl)-1-(2,4-dichlorophenyl) methanimine in 1,3-dioxolane for 10 hours. Compound **3if** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as colorless oil (77 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.34 (m, 2H), 7.23 – 7.14 (m, 3H), 6.37 (d, *J* = 8.7 Hz, 2H), 5.15 (d, *J* = 2.6 Hz, 1H), 5.09 (s, 1H), 4.63 (s, 1H), 4.04 – 3.83 (m, 4H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 145.2, 134.5, 134.3, 134.2, 132.0, 129.8, 129.4, 127.6, 115.1, 109.9, 103.6, 65.6, 65.3, 55.5; IR ν_{max} (neat)/cm^{-1}: 3417, 3067, 2889, 1594, 1498, 1315, 1120, 1028, 815, 735; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{14}BrCl_2NNaO_2$ $[M + Na]^+$ 423.9477, found 423.9483.

N-((2,4-Dichlorophenyl)(1,3-dioxolan-2-yl)methyl)-4-fluoroaniline (**3ig**) was prepared according to procedure A through the reaction of 2,4-dichlorobenzaldehyde and 4-fluoroaniline in 1,3-dioxolane for 12 hours. Compound **3ig** was isolated through a silica gel column chromatography (PE: EtOAc from 20:1 to 10:1) as colorless oil (50 mg, 73% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.20 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.81 (t, *J* = 8.7 Hz, 2H), 6.47 – 6.42 (m, 2H), 5.16 (d, *J* = 2.5 Hz, 1H), 5.08 (d, *J* = 2.5 Hz, 1H), 4.51 (s, 1H), 4.03 – 3.86 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 156.1 (d, *J* = 235.7 Hz), 142.5, 134.6 (d, *J* = 18.1 Hz), 134.1, 129.9, 129.3, 127.5, 115.7 (d, *J* = 22.5 Hz), 114.34 (d, *J* = 7.5 Hz), 103.8, 65.6, 65.4, 56.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -127.2 (tt, *J* = 8.6, 4.3 Hz); IR ν_{max} (neat)/cm^{-1}: 3421, 3063, 2891, 1612, 1513, 1312, 1220, 1120, 1028, 820, 733; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{14}Cl_2FNNaO_2$ $[M + Na]^+$ 364.0278, found 364.0286.

N-((2,4-Dichlorophenyl)(1,3-dioxolan-2-yl)methyl)-3,5-bis(trifluorome-thyl)aniline (**3ih**) was prepared according to procedure A through the reaction of 2,4-dichlorobenzaldehyde and 3,5-bis(trifluoromethyl)aniline in 1,3-dioxolane for 16 hours. Compound **3ih** was isolated through a silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) as a yellow solid (50 mg, 55% yield, m.p. 93–95 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.1 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.14 (s, 1H), 6.88 (s, 2H), 5.20 (d, *J* = 2.4 Hz, 1H), 5.16 (d, *J* = 2.4 Hz, 1H), 5.07 (s, 1H), 4.04 – 3.85 (m, 4H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 147.0, 134.7, 134.5, 133.3, 132.5 (q, *J* = 32.8 Hz), 129.7, 129.5, 127.7, 123.4 (q, *J* = 272.7 Hz), 112.6 (m), 111.1(m), 103.3, 65.7, 65.4, 55.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 (s); IR ν_{max} (neat)/cm^{-1}: 3440, 3085, 2902, 1626, 1520, 1388, 1280, 1174, 1122, 1028, 852, 681; HRMS (ESI/FT-ICR, m/z): calcd for $C_{18}H_{13}Cl_2F_6NNaO_2$ $[M + Na]^+$ 482.0120, found 482.0131.

vi. Addition of 1,3-dioxolane to ethyl glyoxylate imines (Table 3)

Procedure C: To an oven-dried 20 mL sealable tube charged with a stir bar were added ethyl glyoxylate (40 μL, 0.2 mmol, ~50% in toluene), a corresponding amine (0.2 mmol) and freshly activated 4 Å molecular sieves (80 mg). The tube was sealed with a septum and freshly distilled 1,3-dioxolane (1.5 mL) was added through a syringe. The mixture was stirred for 1 hour at room temperature before the addition of AIBN (3.3 mg, 0.02 mmol, dissolved in 0.5 mL 1,3-dioxolane) and TDM (5 μL, 0.02 mmol) through syringes. The reaction mixture was then heated up to 80 °C and monitored by TLC. Upon completion, the solvent was removed *in vacuo*, and the resulting residue was purified through a silica gel column chromatography to afford a corresponding product **4**.

Procedure D: To an oven-dried 20 mL sealable tube charged with a stir bar were added ethyl glyoxylate (40 μL, 0.2 mmol, ~50% in toluene), a corresponding amine (0.2 mmol) and freshly activated 4 Å molecular sieves (80 mg). The tube was sealed with a septum and freshly distilled 1,3-dioxolane (1.5 mL) was added through a syringe. The mixture was stirred for 1 hour at room temperature before the addition of AIBN (3.3 mg, 0.02 mmol, dissolved in 0.5 mL 1,3-dioxolane) through a syringe. The reaction mixture was then heated up to 65 °C and monitored by TLC. Upon completion, the solvent was removed *in vacuo*, and the resulting residue was purified through a silica gel column chromatography to afford a corresponding product **4**.

Ethyl 2-(1,3-dioxolan-2-yl)-2-(phenylamino)acetate (**4a**): was prepared according to procedure C through the reaction of ethyl glyoxylate and aniline in 1,3-dioxolane for 12 hours. Compound **4a** was isolated through a silica gel column chromatography (PE: EtOAc from 10:1 to 5:1) as a yellowish solid (48 mg, 96% yield, m.p. 70–72 °C), which is a known compound[3h] and the characterization data are in accordance with the literature. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (t, J = 7.9 Hz, 2H), 6.76 (t, J = 7.3 Hz, 1H), 6.71 (d, J = 7.8 Hz, 2H), 5.37 (d, J = 2.2 Hz, 1H), 4.31 (d, J = 2.2 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.12 – 4.06 (m, 1H), 4.03 – 3.97 (m, 1H), 3.95 – 3.89 (m, 2H), 3.28 (s, 1H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR NMR (151 MHz, $CDCl_3$) δ 170.4, 146.9, 129.4, 129.2, 118.7, 114.0, 103.4, 66.0, 65.6, 61.7, 60.3, 14.2; IR ν_{max} (neat)/cm^{-1}: 3385, 3054, 2895, 1739, 1604, 1510, 1308, 1160, 1026, 755, 694.

Ethyl 4-((1-(1,3-dioxolan-2-yl)-2-ethoxy-2-oxoethyl)amino)benzoate (**4b**): was prepared according to procedure C through the reaction of ethyl glyoxylate and ethyl 4-aminobenzoate in

1,3-dioxolane for 12 hours. Compound **4b** was isolated through a silica gel column chromatography (PE: EtOAc from 10:1 to 5:1) as colorless oil (39 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 5.38 (d, *J* = 2.2 Hz, 1H), 4.85 (d, *J* = 8.4 Hz, 1H), 4.40 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.36 – 4.20 (m, 4H), 4.12 – 3.99 (m, 1H), 3.97 – 3.86 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 169.6, 166.7, 150.7, 131.4, 120.1, 112.5, 103.2, 66.0, 65.6, 62.0, 60.3, 59.1, 14.4, 14.2; IR ν_{max} (neat)/cm^{-1}: 3374, 3052, 2899, 1740, 1703, 1607, 1530, 1278, 1175, 1106, 1022, 772; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{21}NNaO_6$ $[M + Na]^+$ 346.1261, found 346.1267.

Ethyl 2-(1,3-dioxolan-2-yl)-2-(p-tolylamino)acetate (**4c**): was prepared according to general C through the reaction of ethyl glyoxylate and 4-toluidine in 1,3-dioxolane for 12 hours. Compound **4c** was isolated through a silica gel column chromatography (PE: EtOAc from 10:1 to 5:1) as colorless oil (48 mg, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.1 Hz, 2H), 6.63 (d, *J* = 8.1 Hz, 2H), 5.36 (d, *J* = 2.3 Hz, 1H), 4.34 (d, *J* = 7.6 Hz, 1H), 4.31 – 4.18 (m, 3H), 4.13 – 4.05 (m, 1H), 4.05 – 3.97 (m, 1H), 3.97 – 3.88 (m, 2H), 2.23 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 170.5, 144.6, 129.7, 127.9, 114.1, 103.5, 66.0, 65.6, 61.6, 60.7, 20.4, 14.2; IR ν_{max} (neat)/cm^{-1}: 3388, 3033, 2887, 1735, 1616, 1522, 1302, 1167, 1030, 989, 808; HRMS (ESI/FT-ICR, m/z): calcd for $C_{14}H_{19}NNaO_4$ $[M + Na]^+$ 288.1206, found 288.1211.

Ethyl 2-(1,3-dioxolan-2-yl)-2-((4-methoxyphenyl)amino)acetate (**4d**): was prepared according to procedure C through the reaction of ethyl glyoxylate and 4-anisidine in 1,3-dioxolane for 12 hours. Compound **4d** was isolated through a silica gel column chromatography (PE: EtOAc from 10:1 to 5:1) as colorless oil (54 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 9.0 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 5.34 (s, 1H), 4.27 – 4.16 (m, 4H), 4.12 – 4.04 (m, 1H), 4.05 – 3.97 (m, 1H), 3.96 – 3.89 (m, 2H), 3.73 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 170.7, 152.9, 141.0, 115.5, 114.8, 103.4, 65.9, 65.6, 61.6, 61.5, 55.7, 14.2; IR ν_{max} (neat)/cm^{-1}: 3373, 3023, 2898, 1739, 1621, 1516, 1240, 1159, 1035, 879; HRMS (ESI/FT-ICR, m/z): calcd for $C_{14}H_{19}NNaO_5$ $[M + Na]^+$ 304.1155, found 304.1159.

Ethyl 2-(1,3-dioxolan-2-yl)-2-((4-fluorophenyl)amino)acetate (**4e**) was prepared according to procedure C through the reaction of ethyl glyoxylate and 4-fluoroaniline in 1,3-dioxolane for 12 hours. Compound **4e** was isolated through a silica gel column chromatography (PE:EtOAc from

10:1 to 5:1) as yellow oil (32 mg, 60% yield) which is a known compound[3h] and the characterization data are in accordance with the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (t, *J* = 8.7 Hz, 2H), 6.65 (dd, *J* = 9.0, 4.3 Hz, 2H), 5.35 (d, *J* = 2.3 Hz, 1H), 4.35 (s, 1H), 4.28 – 4.18 (m, 3H), 4.13 – 4.05 (m, 1H), 4.04 – 3.97 (m, 1H), 3.97 – 3.89 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 170.3, 156.5 (d, *J* = 236.1 Hz), 143.3 (d, *J* = 2.0 Hz), 115.6 (d, *J* = 22.4 Hz), 115.0 (d, *J* = 7.5 Hz), 103.3, 66.0, 65.6, 61.7, 61.0, 14.2; IR ν_{max} (neat)/cm^{-1}: 3378, 3056, 2898, 1739, 1621, 1516, 1369, 1240, 1158, 1035, 825.

Ethyl 2-((4-chlorophenyl)amino)-2-(1,3-dioxolan-2-yl)acetate (**4f**) was prepared according to procedure C through the reaction of ethyl glyoxylate and 4-chloroaniline in 1,3-dioxolane for 12 hours. Compound **4f** was isolated through a silica gel column chromatography (PE: EtOAc from 10:1 to 5:1) as a yellowish solid (48 mg, 85% yield, m.p. 48–49 °C) which is a known compound[3h] and the characterization data are in accordance with the literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 5.36 (d, *J* = 2.3 Hz, 1H), 4.47 (d, *J* = 8.5 Hz, 1H), 4.29 – 4.18 (m, 3H), 4.13 – 4.03 (m, 1H), 4.01 – 3.86 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 170.1, 145.6, 129.0, 123.2, 115.0, 103.3, 66.0, 65.6, 61.8, 60.2, 14.2; IR ν_{max} (neat)/cm^{-1}: 3383, 3036, 2898, 1736, 1620, 1522, 1357, 1242, 1152, 1042, 833.

Ethyl 2-((3-chlorophenyl)amino)-2-(1,3-dioxolan-2-yl)acetate (**4g**) was prepared according to procedure C through the reaction of ethyl glyoxylate and 3-chloroaniline in 1,3-dioxolane for 12 hours. Compound **4g** was isolated through a silica gel column chromatography (PE: EtOAc from 10:1 to 5:1) as colorless oil (35 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.9 Hz, 1H), 6.75 – 6.65 (m, 2H), 6.57 (dd, *J* = 8.1, 2.3 Hz, 1H), 5.37 (d, *J* = 2.3 Hz, 1H), 4.53 (d, *J* = 8.5 Hz, 1H), 4.31 – 4.20 (m, 3H), 4.15 – 4.02 (m, 1H), 4.02 – 3.85 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 169.9, 148.1, 134.9, 130.2, 118.5, 113.7, 112.1, 103.3, 66.0, 65.6, 61.9, 59.9, 14.2; IR ν_{max} (neat)/cm^{-1}: 3388, 3060, 2895, 1738, 1611, 1527, 1355, 1247, 1148, 1047, 837; HRMS (ESI/FT-ICR, m/z): calcd for $C_{13}H_{16}ClNNaO_4$ $[M + Na]^+$ 308.0660, found 308.0667.

Ethyl 2-(benzylamino)-2-(1,3-dioxolan-2-yl)acetate (**4h**) was prepared according to procedure D through the reaction of ethyl glyoxylate and benzylamine in 1,3-dioxolane for 4 hours. Compound **4h** was isolated through a silica gel column chromatography (PE: EtOAc from 5:1 to

3:1) as colorless oil (33 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.11 (m, 5H), 5.10 (d, *J* = 3.5 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.01 – 3.90 (m, 2H), 3.87 – 3.77 (m, 3H), 3.66 (d, *J* = 13.2 Hz, 1H), 3.42 (d, *J* = 3.5 Hz, 1H), 2.01 (s, 1H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 171.5, 139.5, 128.4, 128.2, 127.1, 103.8, 65.6, 65.5, 63.6, 61.1, 52.3, 14.3; IR ν_{max} (neat)/cm^{-1}: 3339, 3062, 2893, 1736, 1457, 1190, 1158, 1028, 701; HRMS (ESI/FT-ICR, m/z): calcd for $C_{14}H_{19}NNaO_4$ $[M + Na]^+$ 288.1206, found 288.1217.

Ethyl 2-(1,3-dioxolan-2-yl)-2-((1-phenylethyl)amino)acetate (**4i**) was prepared according to procedure D through the reaction of ethyl glyoxylate and (*R*)-α-methylbenzylamine in 1,3-dioxolane for 4 hours. Compound **4i** was isolated through a silica gel column chromatography (PE: EtOAc from 5:1 to 3:1) as colorless oil (36 mg, 65% yield, *dr* = 1.2:1). ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of 2 diastereomers) δ 6.54 – 6.27 (m, 5H, major+minor), 4.27 (d, *J* = 3.6 Hz, 1H, minor), 4.20 (d, *J* = 3.4 Hz, 1H, major), 3.34 (q, *J* = 7.1 Hz, 2H, major), 3.25 – 2.94 (m, 6H, major+minor), 2.89 (q, *J* = 6.5 Hz, 1H, major), 2.57 (d, *J* = 3.6 Hz, 1H, minor), 2.39 (d, *J* = 3.4 Hz, 1H, major), 0.48 (d, *J* = 6.5 Hz, 3H, major+minor), 0.40 (t, *J* = 7.1 Hz, 3H, major), 0.31 (t, *J* = 7.1 Hz, 3H, minor); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 172.0 (major), 171.6 (minor), 145.1 (minor), 144.5 (major), 128.4 (major), 128.4 (minor), 127.1 (minor), 127.1 (major), 126.9 (major), 126.8 (minor), 104.3 (minor), 103.8 (major), 65.6 (minor), 65.5(major+minor), 65.5 (major), 62.3 (minor), 61.9 (major), 61.0 (minor), 61.0 (major), 57.2 (minor), 56.4 (major), 25.4 (major), 23.4 (minor), 14.3 (major), 14.1 (minor); IR ν_{max} (neat)/cm^{-1}: 3338, 3062, 2891, 1736, 1450, 1190, 1159, 1026, 703; HRMS (ESI/FT-ICR, m/z): calcd for $C_{15}H_{21}NNaO_4$ $[M + Na]^+$ 302.1363, found 302.1369.

Ethyl 2-(cyclohexylamino)-2-(1,3-dioxolan-2-yl)acetate (**4j)** was prepared according to procedure D through the reaction of ethyl glyoxylate and cyclohexylamine in 1,3-dioxolane for 8 hours. Compound **4j** was isolated through a silica gel column chromatography (PE:EtOAc from 5:1 to 3:1) as colorless oil (32 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, *J* = 3.8 Hz, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 4.07 – 3.94 (m, 2H), 3.94 – 3.83 (m, 2H), 3.55 (d, *J* = 3.8 Hz, 1H), 2.44 – 2.33 (m, 1H), 1.91 – 1.51 (m, 4H), 1.28 (t, *J* = 7.3 Hz, 3H), 1.27 – 0.97 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 104.0, 65.4, 61.7, 61.0, 55.4, 34.0, 32.8, 26.0, 25.0, 24.7, 14.3; IR ν_{max} (neat)/cm^{-1}: 3329, 2935, 2893, 1736, 1471, 1371, 1190, 1159, 1032, 947; HRMS (ESI/FT-ICR, m/z): calcd for $C_{13}H_{23}NNaO_4$ $[M + Na]^+$ 280.1519, found 280.1526.

Ethyl-2-adamantan-1-yl)amino)-2-(1,3-dioxolan-2-yl)acetate (**4k**) was prepared according to procedure C through the reaction of ethyl glyoxylate and amantadine in 1,3-dioxolane for 12 hours. Compound **4k** was isolated through a silica gel column chromatography (PE:EtOAc from 8:1 to 5:1) as colorless oil (46 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, *J* = 4.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.07 – 3.92 (m, 2H), 3.91 – 3.81 (m, 2H), 3.57 (d, *J* = 4.0 Hz, 1H), 2.02 (s, 3H), 1.80 (s, 1H), 1.66 – 1.45 (m, 12H), 1.28 (t, *J* = 7.1 Hz, 3H).; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 173.6, 104.9, 65.5, 65.4, 61.1, 56.9, 50.7, 42.9, 36.5, 29.5, 14.2; IR ν_{max} (neat)/cm^{-1}: 3330, 2905, 2850, 1738, 1451, 1247, 1164, 1144, 1027, 946; HRMS (ESI/FT-ICR, m/z): calcd for $C_{17}H_{27}NNaO_4$ $[M + Na]^+$ 332.1832, found 332.1836.

Ethyl 2-(1,3-dioxolan-2-yl)-2-((3-hydroxypropyl)amino)acetate (**4l**) was prepared according to procedure C through the reaction of ethyl glyoxylate and 3-aminopropanol in 1,3-dioxolane for 12 hours. Compound **4k** was isolated through a silica gel column chromatography (PE:EtOAc from 1:1 to 1:5) as colorless oil (21 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (d, *J* = 3.0 Hz, 1H), 4.23 (q, *J* = 7.1, 2H), 4.04 – 3.94 (m, 2H), 3.94 – 3.83 (m, 2H), 3.79 (t, *J* = 5.4 Hz, 2H), 3.50 (d, *J* = 3.0 Hz, 1H), 3.07 – 2.95 (m, 1H), 2.74 – 2.62 (m, 1H), 1.75 – 1.60 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 171.2, 103.2, 65.7, 65.6, 63.8, 63.7, 61.3, 48.1, 30.9, 14.2; IR ν_{max} (neat)/cm^{-1}: 3418, 2957, 2889, 1730, 1593, 1497, 1314, 1147, 1073, 1027, 813; HRMS (ESI/FT-ICR, m/z): calcd for $C_{10}H_{19}NNaO_5$ $[M + Na]^+$ 256.1155, found 256.1163.

Ethyl 2-(((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)amino)-2-(1,3-dioxolan-2-yl)acetate (**4m**): was prepared according to procedure C through the reaction of ethyl glyoxylate and 2,2-dimethyl-1,3-dioxolane-4-methanamine in 1,3-dioxolane for 12 hours. Compound **4m** was isolated through a silica gel column chromatography (PE:EtOAc from 5:1 to 3:1) as colorless oil (38 mg, 66% yield, mixture of 2 diastereomers, *dr* = 1.5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, *J* = 3.4 Hz, 1H, major), 5.12 (d, *J* = 3.6 Hz, 1H, minor), 4.30 – 4.15 (m, 3H, major+minor), 4.08 – 3.93 (m, 3H, major+minor), 3.95 – 3.81 (m, 2H, major+minor), 3.75 – 3.61 (m, 1H, major+minor), 3.50 (d, *J* = 3.5 Hz, 1H, major), 3.45 (d, *J* = 3.6 Hz, 1H, minor), 2.87 – 2.76 (m, 1H, major+minor), 2.70 (dd, *J* = 12.1, 6.0 Hz, 1H, major), 2.62 (dd, *J* = 11.8, 4.5 Hz, 1H, minor), 2.00 (brs, 1H, major+minor), 1.40 (s, 3H, minor), 1.39 (s, 3H, major), 1.33 (s, 3H, major+minor), 1.28 (t, *J* = 7.2 Hz, 3H, major+minor); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 170.3 (minor), 170.2 (major), 108.2 (minor), 108.1 (major), 102.7 (major), 102.6 (minor), 74.7 (minor), 74.5 (major), 66.5

(minor), 66.4 (major), 64.6 (major), 64.6 (minor), 64.5 (major+minor), 63.8 (minor), 63.5 (major), 60.13 (major), 60.09 (minor), 50.5 (minor), 49.7 (major), 26.0 (minor), 25.8 (major), 24.5 (minor), 24.4 (major), 13.2 (major+minor); IR ν_{max} (neat)/cm^{-1}: 3341, 2985, 2893, 1737, 1467, 1375, 1212, 1191, 1159, 1033, 798; HRMS (ESI/FT-ICR, m/z): calcd for $C_{13}H_{23}NNaO_6$ $[M + Na]^+$ 312.1418, found 312.1422.

Gram-scale preparation of 4d: To an oven-dried sealable flask charged with a stir bar were added ethyl glyoxylate (2.0 mL, 10.0 mmol, ~50% in toluene), anisidine (1.23 g, 10.0 mmol) and freshly activated 4 Å molecular sieves (4 g). The flask was sealed with a septum and freshly distilled 1,3-dioxolane (70 mL) was added through a syringe. The mixture was stirred for 1 hour at room temperature before the addition of AIBN (41 mg, 0.25 mmol for each) and TDM (59 μL, 0.25 mmol for each). The reaction mixture was then heated up to 80 °C. Another three portions of AIBN (41 mg, 0.25 mmol) and TDM (59 μL, 0.25 mmol) were added every 12 hours. After totally 48 hours, the reaction mixture was cooled down to room temperature, filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo*, and the residue was purified through a silica gel column chromatography (PE:EtOAc from 10:1 to 5:1) to afford product **4d** as colorless oil (2.52 g, 90% yield).

Gram-scale preparation of 4h: To an oven-dried sealable flask charged with a stir bar were added ethyl glyoxylate (2.0 mL, 10.0 mmol, ~50% in toluene), benzylamine (1.09 mL, 10.0 mmol) and freshly activated 4 Å molecular sieves (4 g). The flask was sealed with a septum and freshly distilled 1,3-dioxolane (70 mL) was added through a syringe. The mixture was stirred for 1 hour at room temperature before the addition of AIBN (41 mg, 0.25 mmol). The reaction mixture was then heated up to 65 °C. Another three portions of AIBN (41 mg, 0.25 mmol for each) were added every 12 hours. After totally 48 hours, the reaction mixture was cooled down to room temperature, filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo*, and the residue was purified through a silica gel column chromatography (PE:EtOAc from 5:1 to 3:1) to afford product **4h** as colorless oil (1.37g, 55% yield).

vii. Product derivatization (Scheme 2)

Ethyl (E)-2-(N-benzylacetamido)-3-hydroxyacrylate **(5):** To a stirred solution of **4h** (1.06 g, 4 mmol) and Et_3N (835 μL, 6 mmol) in dry 1,2-dichloroethane (50 mL) was added freshly distilled acetyl chloride (427 uL, 6 mmol) drop-wise at 0 °C. The reaction mixture was warmed up to

room temperature and stirred for 4h. Upon completion of the reaction, the insolubles were removed by filtration and washed with ether. The filtrate is concentrated under reduced pressure to afford the crude acetylated product which is subjected in next step without further purification. The obtained crude product is dissolved in acetic acid (10 mL) in a 25 mL flask, followed by the addition of hydriodic acid (45 mg, 57%, 0.2 mmol). After being stirred at 65 °C for 2 hours, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (30 mL). The resulting solution was washed with water (3 × 30 mL), dried with Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified through a silica gel column chromatography (PE:acetone from 4:1 to 1:1) to give product **5** as a major isomer (725 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (d, *J* = 13.0 Hz, 1H), 7.36 – 7.21 (m, 5H), 6.82 (d, *J* = 13.0 Hz, 1H), 5.28 (d, *J* = 14.2 Hz, 1H), 4.34 – 4.18 (m, 2H), 3.98 (d, *J* = 14.2 Hz, 1H), 2.01 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 172.4, 169.6, 164.2, 136.9, 129.3, 128.5, 127.6, 110.7, 61.5, 51.7, 21.9, 14.2; IR ν_{max} (neat)/cm^{-1}: 3349, 3064, 2983, 1744, 1710, 1637, 1413, 1219, 1148, 1039, 700; HRMS (ESI/FT-ICR, m/z): calcd for $C_{14}H_{17}NNaO_4$ [M + Na]$^+$ 286.1050, found 286.1054. The double bond geometry of **5** was tentatively assigned to be (*E*) by NOE analysis based on the correlation between the olefinic proton and the acetyl group. This preferred geometry is presumably ascribed to the intramolecular hydrogen bonding. The NOE spectrum was presented in the supporting information.

Ethyl (E)-2-(N-benzylacetamido)-3-(butylamino)acrylate (**6**): A mixture of **5** (53 mg, 0.2 mmol) and butylamine (22 mg, 0.3 mmol) in EtOH (2 mL) was heated under reflux for 12 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified through a silica gel column chromatography (PE:EtOAc 5:1) to give the product **6** (55 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.31 – 7.23 (m, 4H), 5.38 (d, *J* = 13.7 Hz, 1H), 4.21 – 4.03 (m, 3H), 3.78 (d, *J* = 13.7 Hz, 1H), 2.96 – 2.81 (m, 1H), 2.81 – 2.64 (m, 1H), 1.94 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.12 – 1.00 (m, 4H), 0.84 – 0.80 (m, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 172.9, 166.1, 146.9, 139.0, 129.4, 128.5, 127.6, 102.9, 76.7, 59.8, 50.5, 47.8, 32.8, 21.3, 19.4, 14.6, 13.6; IR ν_{max} (neat)/cm^{-1}: 3305, 3031, 2930, 2869, 1683, 1639, 1408, 1279, 1171, 1052, 731; HRMS (ESI/FT-ICR, m/z): calcd for $C_{18}H_{26}N_2NaO_3$ [M + Na]$^+$ 341.1836, found 341.1840.

Diethyl (E)-2-(N-benzylacetamido)pent-2-enedioate (**7**): A solution of **5** (53.0 mg, 0.2 mmol) and ethyl 2-(triphenylphosphanylidene) acetate (69 mg, 0.2 mmol) in dry 1,2-dichloroethane (2 mL)

was stirred at 80 °C for 6 hours. The resulting mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified through a silica gel column chromatography (PE:EtOAc from 10:1 to 5:1) to give product **7** as colorless oil (60 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 5H), 7.08 (t, *J* = 7.5 Hz, 1H), 5.26 (d, *J* = 14.1 Hz, 1H), 4.32 – 4.15 (m, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.98 (d, *J* = 14.1 Hz, 1H), 2.81 (dd, *J* = 18.0, 8.1 Hz, 1H), 2.46 (dd, *J* = 18.0, 6.9 Hz, 1H), 1.92 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 170.4, 168.9, 163.6, 136.9, 136.5, 133.8, 129.8, 128.5, 127.8, 61.8, 61.2, 50.2, 33.1, 21.6, 14.2, 14.1; IR ν_{max} (neat)/cm^{-1}: 3064, 2983, 2906, 1724, 1672, 1655, 1444, 1393, 1254, 1184, 1030, 704; HRMS (ESI/FT-ICR, m/z): calcd for $C_{18}H_{23}NNaO_5$ [M + Na]$^+$ 356.1468, found 356.1473. Compound **7** is also isolated as a single isomer. However, the geometry of the double bond seemed difficult to determine through NOE analysis.

Diethyl acetylglutamate (**8**): To a 20 mL sealable tube equipped with a stir bar were added compound **7** (33.3 mg, 0.1 mmol) and 10% palladium on charcoal (10 mg). The vial was evacuated *in vacuo* and refilled with N_2 three times and then was added ethanol (2 mL). The tube was evacuated again and refilled with an H_2 balloon, three times. The reaction mixture was warmed up to 60 °C and stirred under H_2 atmosphere for 24 h. The resulting mixture was cooled to room temperature, filtered through a Celite® pad and concentrated *in vacuo*. The residue was purified through a silica gel column chromatography (PE:EtOAc from 5:1 to 2:1) to give compound **8** (18.4 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, *J* = 7.3 Hz, 1H), 4.59 (td, *J* = 7.3, 5.1 Hz, 1H), 4.25 – 4.13 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.48 – 2.27 (m, 2H), 2.25 – 2.12 (m, 1H), 2.01 (s, 3H), 1.99 – 1.89 (m, 1H), 1.32 – 1.20 (m, 6H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 172.9, 172.0, 170.0, 61.7, 60.7, 51.7, 30.3, 27.4, 23.1, 14.2, 14.1; IR ν_{max} (neat)/cm^{-1}: 3288, 2983, 2935, 1737, 1658, 1543, 1376, 1259, 1200, 1026, 859; HRMS (ESI/FT-ICR, m/z): calcd for $C_{11}H_{19}NNaO_5$ [M + Na]$^+$ 268.1155, found 268.1158.

viii. **Mechanistic related experiments (Scheme 3)**

The inhibiting effect of TEMPO: To an oven-dried 20 mL sealable tube charged with a stir bar were added 2,4-dichlorobenzaldehyde **1i** (35 mg, 0.2 mmol), aniline **2a** (18.6 mg, 0.2 mmol), AIBN (3.3 mg, 0.02 mmol) and freshly activated 4 Å molecular sieves (80 mg). The tube was sealed with a septum and 1,3-dioxolane (2 mL, freshly distilled) was added through a syringe, followed by the addition of TDM (5 μL, 0.02 mmol). The reaction mixture was stirred at 80 °C

for 10 hours and then cooled down. After concentrated *in vacuo*, the resulting residue was submitted for ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. By comparing the spectrum to authentic sample **3ia**, no desired product was detected in this case (<5%, Scheme 3a).

Kinetic study with different thiol loadings: To an oven-dried 20 mL sealable tube charged with a stir bar were added (*E*)-1-(2,4-dichlorophenyl)-*N*-phenylmethanimine (50 mg, 0.2 mmol), AIBN (3.3 mg, 0.02 mmol), methyl benzoate (25 μL, 0.2 mmol, as an internal standard) and freshly activated 4 Å molecular sieves (80 mg). The tube was sealed with a septum and 1,3-dioxolane (2 mL, freshly distilled) was added through a syringe, followed by the addition of TDM (0, 0.02, 0.06, and 0.1 mmol). The reaction mixture was stirred at 80 °C and 50 μL of reaction mixture was taken by a syringe at 0.5 h, 1.0 h, 1.5 h, 2.0 h, 3.0 h, 4.0 h, 6.0 h, 8.0 h and 10 h, respectively. The sample was diluted with 2 mL hexanes/^{i}PrOH (9:1 mixture) and filtered through a 0.45 μm nylon membrane before submitted for HPLC analysis (Note: the response factors of imine/internal standard and product/internal standard were determined first by mixing specific amount of samples). The results are depicted in Scheme 3b.

Thiyl radical capturing through thiol-ene reaction: To an oven-dried sealable tube charged with a stir bar were added allyl benzoate (32.4 mg, 0.2 mmol) and AIBN (3.3 mg, 0.02 mmol). The tube was evacuated *in vacuo* and refilled with N_2 three times. Then, 1,3-dioxolane (2 mL, freshly distilled) was added through a syringe, followed by the addition of TDM (50 μL, 0.2 mmol). The sealed tubes were then heated up to 80 °C and kept stirring for 12 hours. After concentrated *in vacuo*, the resulting residue was purified through a silica gel column chromatography (PE: Et_2O from 100:1 to 50:1) to afford the corresponding product **9** as colorless oil (23 mg, 31% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 4.41 (t, J = 6.4 Hz, 2H), 2.63 (q, J = 7.4 Hz, 1H), 2.57 (q, J = 6.9 Hz, 1H), 2.03 (m, 1H), 1.50 – 1.07 (m, 13H), 1.00 – 0.71 (m, 12H); ^{13}C{^{1}H}NMR (151 MHz, $CDCl_3$) δ 166.5, 132.9, 130.3, 129.6, 128.4, 63.9, 45.6, 29.7, 29.1, 28.8, 24.3, 23.7, 23.7, 22.7, 17.5, 16.1, 14.5, 14.1, 12.2, 8.7.; HRMS (ESI/FT-ICR, m/z): calcd for $C_{22}H_{36}NaO_2S$ $[M + Na]^+$ 387.2328, found 387.2329.

The oxygen effects: To an oven-dried 20 mL sealable tube (22-24 mL gas space) charged with a stir bar were added (*E*)-1-(2,4-dichlorophenyl)-*N*-phenylmethanimine (50 mg, 0.2 mmol), AIBN

(3.3 mg, 0.02 mmol) and freshly activated 4 Å molecular sieves (80 mg). The tube was evacuated *in vacuo* and refilled with N_2 three times. Then, certain volume of N_2 (1 mL, 2 mL, 5 mL, 10 mL, respectively) was withdrawn from the reaction tubes (with a syringe) and they were refilled with an O_2 balloon immediately. 1,3-Dioxolane (2 mL, freshly distilled) was added through a syringe, followed by the addition of TDM (5 μL, 0.02 mmol). The sealed tubes were then heated up to 80 °C and kept stirring for 3 hours. After concentrated *in vacuo*, the resulting residue was submitted for ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. The reaction results are presented in Scheme 3d.

The **intermolecular competition kinetic isotope effect** was studied with a 1:1 mixture of THF and THF-*d*8. To an oven-dried 20 mL sealable tube charged with a stir bar were added 2,4-dichlorobenzaldehyde (17.5 mg, 0.1 mmol), aniline (9.1 μL, 0.1 mmol), AIBN (1.6 mg, 0.01 mmol) and freshly activated 4 Å molecular sieves (80 mg). The tube was sealed with a septum and THF/THF-*d8* (1 mL, 1:1 v/v) was added through a syringe, followed by the addition of TDM (2.4 μL, 0.01 mmol). The reaction mixture was stirred at 80 °C for 12 hours and then cooled down. After concentrated *in vacuo*, the resulting residue was submitted for ^{1}H NMR analysis. The k_H/k_D (**11** + **11**-*d1*)/(**11**-*d7* + **11**-*d8*) was determined to be 6.3. (Detailed spectrum analysis is presented in the Supporting Information)

The **parallel kinetic isotope effect** was studied through parallel reactions with THF and THF-*d*8 as solvent, respectively. To an oven-dried 20 mL sealable tube charged with a stir bar were added 2,4-dichlorobenzaldehyde (17.5 mg, 0.1 mmol), aniline (9.1 μL, 0.1 mmol), AIBN (1.6 mg, 0.01 mmol) and freshly activated 4 Å molecular sieves (80 mg). The tube was sealed with a septum and THF or THF-*d8* (1 mL) was added through syringes, followed by the addition of TDM (2.4 μL, 0.01 mmol). The reaction mixture was stirred at 80 °C for 4 or 8 hours and then cooled down. After concentrated *in vacuo*, the resulting residue was submitted for ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. The product ratio **11**/**11**-*d8* are in good agreement at different time point and the k_H/k_D was determined to be 3.6±0.1.

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Supporting Information

NMR spectra and for all compounds. (PDF) This file is available free of charge on the ACS Publications website.

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