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An organocatalyst bound α-aminoalkyl radical intermediate for controlled aerobic oxidation of iminium ion

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A catalyst bound α-aminoalkyl radical intermediate from iminium is developed to control its formation and reactivity with aerobic oxygen. The catalyst influence was demonstrated via ease of radical intermediate formation and its subsequent reactivity, including the first catalyst-controlled enantioselective aerobic oxidation with a chiral phosphite catalyst.

A diverse pathway to α-aminoalkyl radicals is a major focus for mild amine functionalization.[1] Efficient catalyst systems for radical intermediates were developed via C-H activation of both electron rich[1,2] and electron poor amines,[3] defunctionalization of amino acids[4] and α-silylamines,[5] and single electron reduction of imine or iminium.[6] However, its subsequent reactivity remains largely uncontrolled. MacMillan and others developed an elegant dual catalysis approach with transition metal (TM), which transform the initially formed radical to carbon-TM bond for subsequent cross-coupling reactions.[7] Yoon and Ooi group respectively reported a dual Lewis acid and Brønsted acid catalyzed enantioselective coupling of α-aminoalkyl radical.[8]

Our interest in finding catalyst control for radical reactions led us to explore a possible organocatalyst bound α-aminoalkyl radical formation and its reactivity. In this communication, we report facile self-photoredox and anionic auto-oxidation processes for the proposed radical (**5**) formation and its aerobic oxidation. We also demonstrate the first catalyst-controlled enantioselective aerobic oxidation of isoquinolinium with a chiral catalyst.

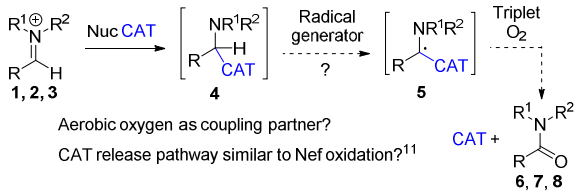

Figure 1: An organocatalyst bound α-aminoalkyl radical for catalyst control: Possible formation and reaction course

We began our study to find a suitable catalyst capable of forming adduct (**4**) with stable and easy to handle methyl isoquinolinium triflate (**1a**). The adduct formation was studied in $CDCl_3$ and analyzed directly by ^{1}H-NMR anticipating its reversible formation and instability. Neutral nucleophiles such as PPh_3, DABCO, DMAP did not add, but DBU led to complex NMR, indicating a possible formation of the unstable cationic adduct. Among anionic nucleophile, sulfite did not add, but phosphites (DMHP and DPHP) and thiophenol with K_2CO_3 led to corresponding adducts, characterized by ^{1}H-NMR.[9]

The next goal is to explore the feasibility of radical intermediate (**5**) formation from the adduct (**4**). We initially chose phosphites as a catalyst since the corresponding radical intermediate should gain synergistic stability via captodative effect.[10] As a result, its formation should be facile and catalyst detachment from radical intermediate less likely.

Aerobic oxygen was chosen as the coupling partner since a catalyst release pathway similar to Nef oxidation is viable.[11] During screening under air atmosphere, we were pleasantly surprised to observe the oxidation product (**6a**),[6b,12] without any radical generation catalyst and specific light (Table 1, entry 1). The reaction under dark did not work (entry 2), indicating daylight or hood light mediated self-photoredox might be operative.[13] Optimization of reaction temperature, base, and solvent led to good yield with 3 equivalent K_2CO_3 base in MTBE at 40 °C (entry 8). With quinolone salt (**2a**), K_2CO_3 did not result in any oxidation, but stronger KOH and KO^{t}Bu led to efficient product formation in acetonitrile solvent entry 11, 12).

Table 1: Optimization for phosphite catalyzed aerobic oxidation of isoquinoline and quinoline salts

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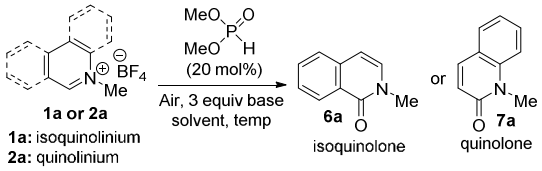
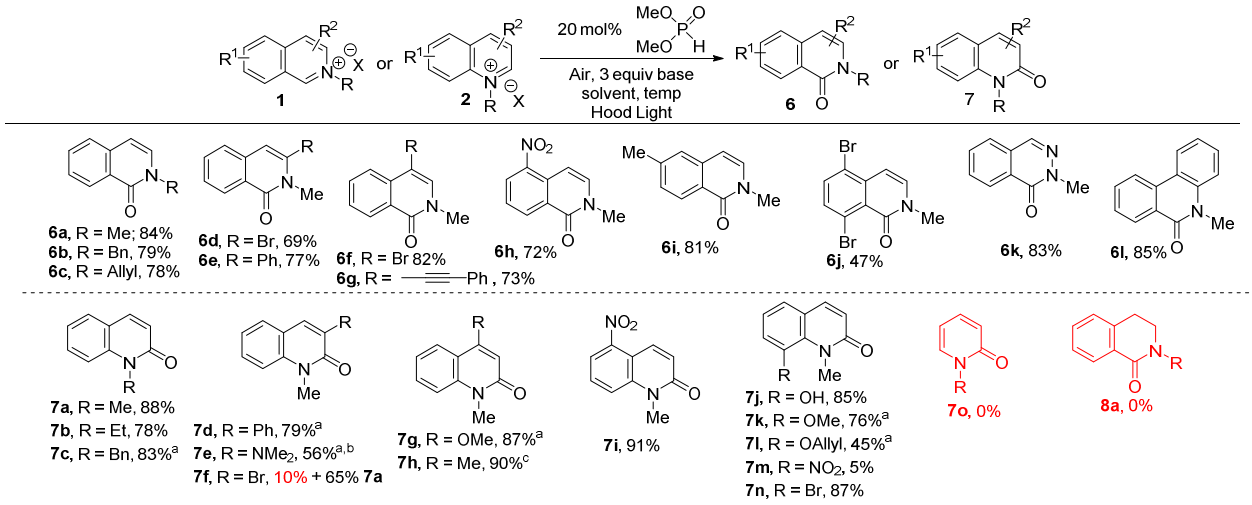


Entry	Starting Material	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	**1a**	K_2CO_3	$CHCl_3$	r.t.	72	62
2	**1a**	K_2CO_3	$CHCl_3$	r.t.	72	<5[b]
3	**1a**	-	$CHCl_3$	r.t.	72	<5
4	**1a**	K_2CO_3	DCM	r.t.	72	60
5	**1a**	K_2CO_3	MeCN	r.t.	72	56
6	**1a**	K_2CO_3	THF	r.t.	72	68
7	**1a**	K_2CO_3	MTBE	r.t.	72	73
8	**1a**	K_2CO_3	MTBE	40	48	84
9	**2a**	K_2CO_3	MTBE	0 - r.t.	48	<5
10	**2a**	KOH	THF	0 - r.t.	48	25
11	**2a**	KOH	MeCN	0 - r.t.	24	88
12	**2a**	KO^{t}Bu	MeCN	0 - r.t.	16	82

[a]isolated yield; under dark.

N-alkyl salt of isoquinoline, quinoline, and other heteraromatic compounds was subjected to the optimized reaction condition to test the generality of our method. A methyl, benzyl, and allyl substituent on isoquinoline nitrogen are all equally effective (**6a-c**). Bromide, phenyl, alkynyl, electron withdrawing nitro, electron rich methyl all are well tolerated on different position (**6d-h**) in moderate to good yields. 5,8-Dibromobo substitution resulted in lower yield (**6j**, 47%). Other isoquinoline type heteroaromatics such as phenanthridinium and dinitrogen phthalazinium salts were also oxidized to the corresponding phenanthridinone (**6k**) and phthazone (**6l**) efficiently.

Table2: Substrate scope for household light mediated self-photoredox aerobic oxidation of N-heteroaromatic salts



Conditions: 0.3 mmol scale, for **1** to **6**, 2 ml MTBE, K_2CO_3 base, 40 °C, 16h; for **2** to **7**, 2 ml MeCN, KOH or KO^{t}Bu base, 16-48 h. [a]KO^{t}Bu as base; [b]50 °C; [c]1.5 equiv dimethyl hydrogen phosphite (DMHP) catalyst

Different N-alkyl substitution on quinoline is also compatible, but KO^{t}Bu base results in better yield for benzyl substitution (**7c**). Phenyl at 3-position works well with KO^{t}Bu base, but electron rich NMe_2 substitution led to a very slow reaction. Raising the temperature to 50 °C led to moderate yield (**7e**, 54%). A major debrominated product obtained along with the minor required product (**7f**) for 3-bromo substitution. Photoredox debromination of aryl bromides are known, which might be operating here.[14] Change of base and reaction temperature did not improve the result. 4-Methoxy substitution works well with KO^{t}Bu (**7g**), but 4-methyl quinolinium gave poor yield (<10%) under standard reaction condition. We suspect possible deprotonation of the 4-methyl proton in starting salt under basic reaction condition could be a problem. To circumvent, 1.5 equivalent DMHP was added to convert all the salt to the intermediate before base mediated oxidation, which led to 92% yield (**7h**). Aryl, electron withdrawing as well as electron donating groups on other ring were well tolerated, including free hydroxyl group at C-8 (**7k**). Surprisingly, the 8-Br substrate gave required **7n** (56%), along with minor 4-oxo product (23%). A sterically bulky **9a** catalyst yielded the **7n** selectively with good yield (87%). A pyridinium and non-aromatic cyclic iminium salt did not oxidize in our optimized photoredox reaction condition.

With the successful aerobic oxidation of N-alkyl salts of isoquinoline in hand, we eagerly explored the possibility of catalyst controlled oxidative kinetic resolution (Table 2). 1-Phenylethy salt of isoquinoline (**1m**) with an α-stereogenic center to nitrogen was chosen,[15] along with TADDOL based phosphite (**9a**) as a chiral catalyst.[16] Analysis of product at ~50% conversion with 10 mol% tetramethyl catalyst **9a** did not result in any enantioenrichment (entry 1), but tetraphenyl catalyst (**9b**) showed promise (entry 2). Screening of other tetra-aryl catalysts and reaction condition (entry 3-11) led to 70% ee at 45% conversion (s factor = 12.3) with α-naphthyl substituted catalyst (**9e**). The recovered enantioenriched SM was also oxidized under photoredox condition with 20 mol%

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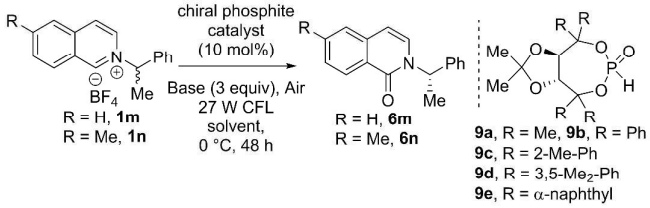
DMHP catalyst in good yield (entry 13). Optically pure **1m** was oxidized with complete retention of absolute configuration to establish the stability of chiral center under reaction condition (entry 12).[17] 6-Methyl substituted salt (**1n**) also resulted in 64% ee at 40% conversion (s factor = 9.6, entry 14). These initial results suggest that a suitable catalyst for high kinetic resolution with isoquinoline salt is viable.

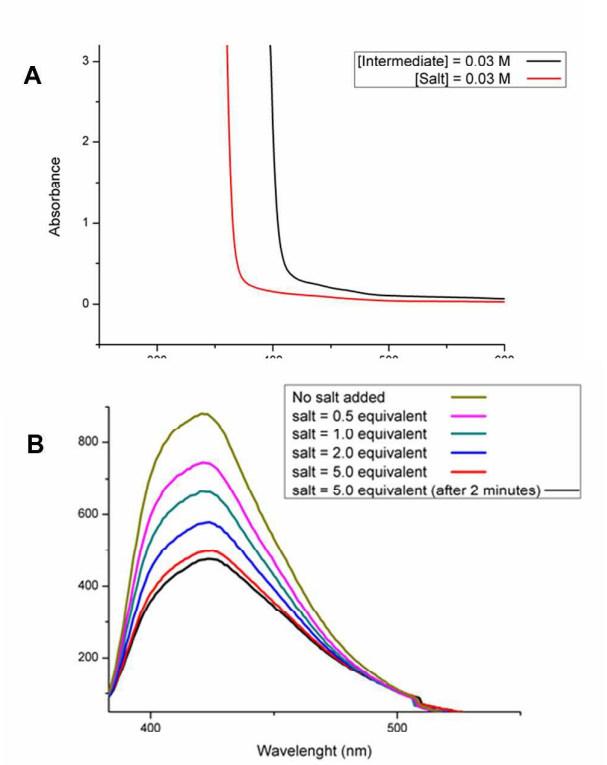
Table 3: Oxidative kinetic resolution studies with chiral phosphites



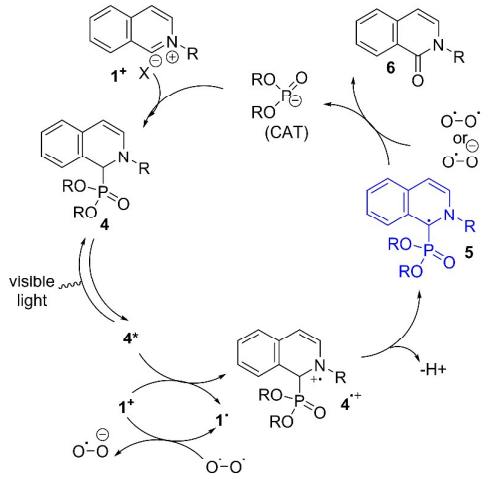
Entry	SM	Cat.	Base	Solv.	% conv.[a]/ % yield[b]	er (R:S)	s factor
1	**1m**	**9a**	K_2CO_3	DCE	55/40	50:50	0
2	**1m**	**9b**	K_2CO_3	DCE	50/30	40:60	ND
3	**1m**	**-**	K_2CO_3	DCE	10/7	-	-
4	**1m**	**9b**	DABCO	DCE	45/30	36:64	ND
5	**1m**	-	DABCO	DCE	<5/-	-	-
6	**1m**	**9c**	DABCO	DCE	45/15	34:66	ND
7	**1m**	**9d**	DABCO	DCE	60/43	42:58	ND
8[c]	**1m**	**9e**	**DABCO**	**DCE**	**45/32**	**15:85**	**12.3**
9	**1m**	**9e**	DABCO	DCM	50/35	15:85	ND
10	**1m**	**9e**	DABCO	MTBE	55/26	45:55	ND
11	**1m**	**9e**	DABCO	$PhCF_3$	50/25	39:61	ND
12[d]	**1m**	DMHP	DABCO	DCE	100/82	1:99	-
13[e]	**1m**	DMHP	DABCO	DCE	100/76	66:33	ND
14[c]	**1n**	**9e**	**9e**	**DCE**	**40/29**	**18:82**	**9.6**

Conditions: 0.2 mmol; 2 ml solvent. [a]based on recovered SM; [b]isolated yield; [c]% conversion was calculated (CHPLC = $ee_{SM}/e_P + ee_{SM}$); [d]with chiral **1m** and 20 mol% cat; [e]with recovered **1m** from entry 9 and 20 mol% cat.

To explore the probable mechanistic path, we first check the UV-vis absorption of isoqunoline salt (**1m**) and its adduct with catalyst **9a**. The salt itself does not absorb visible light, but the adduct (**4**) absorb with fluorescence emission. The Stern – Volmer quenching study showed a concentration and time-dependent decrease in fluorescence in the presence of **1m**. It indicates a light mediated excitation of the adduct, followed by single electron transfer to starting iminium salt (**1**).[13] The α C-H acidity of the one-electron oxidized intermediate (**4**$^{\cdot+}$) would increase greatly,[18] and deprotonation via base led to our proposed catalyst bound α-aminoalkyl radical intermediate (**5**). On the other hand, the reduced salt (**1**$^{\cdot}$) can transfer one electron to oxygen to regenerate the salt and superoxide anion ($O_2^{\cdot-}$). The reaction of radical **5** with either O_2 or $O_2^{\cdot-}$ can lead to the product formation via alternative pathways.[6b,12] Direct oxidation of reduced α-aminoalkyl radical (**1**$^{\cdot}$) and oxygen or $O_2^{\cdot-}$ is either not operating or a minor path at best since we achieved catalyst control kinetic resolution.



(a) UV-vis absorption spectrum of **1m** and corresponding adduct with **9a** at reaction concentration (0.1 M solution in DCM); (b) Emission spectra of adduct (2x10^{-5} M in DCM, λ_{ex} = 380 nm) and its quenching with **1m**



Scheme 2: Proposed catalytic cycle

No reaction without the presence of iminium salt excludes a direct oxygen activation by the adduct. The oxidation also proceeds in the presence of singlet oxygen quencher DABCO, suggesting photo-excitation of oxygen is unlikely.

Next, we aim to develop a general method which is not only limited to heteroaromatic iminium salts (**1**, **2**; Table 2). Unsuccessful oxidation of non-aromatic iminium (**8a**) is expected since the salt, or

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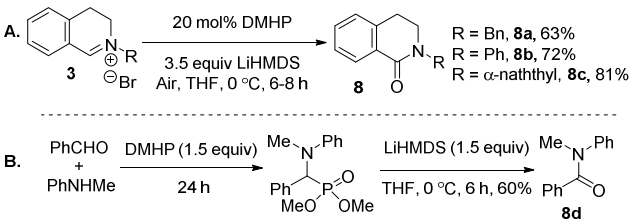
the corresponding phosphite adduct do not absorb visible light. An external photoredox catalyst can oxidize the adduct to initiate the process,[2] but it has to be compatible with nucleophile phosphite catalyst. Instead, we check a possible Nef type anionic auto-oxidation first to avoid compatibility of dual catalysis.[11,12,19] Hydrolytically stable cyclic salts were synthesized (**3a-c**),[20] which were subjected to DMHP catalyzed reaction condition with a strong LiHMDS base to deprotonate the α C-H. To our delight, the corresponding lactams formed in moderate to good yields (Scheme 6A). Acyclic iminium salts were difficult to handle and resulted in poor yield. To check the efficiency of aerobic auto-oxidation, we synthesized dimethyl hydrogen phosphite adduct for acylic systems (Scheme 6B),[21] and upon treatment with LiHMDS under air atmosphere led to a good yield of the corresponding amide.



Scheme 3: (a) Aerobic auto-oxidation of non-aromatic cyclic iminium salt to lactam; (b) Stepwise oxidation to amide

In conclusion, an organocatalyst bound α-aminoalkyl radical formation and its aerobic oxidation was achieved without any other radical generation catalyst. N-alkyl salts of a variety of heteroaromatic compounds were oxidized in presence of household light. The catalyst bound α-radical was utilized successfully for an unprecedented oxidative kinetic resolution with racemic isoquinolinium salts. Cyclic and acyclic iminiums were oxidized via an alternative strong base mediated aerobic auto-oxidation. Full mechanistic studies and catalyst controlled stereoselective oxidation is currently underway.

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Conflicts of interest

There are no conflicts to declare.

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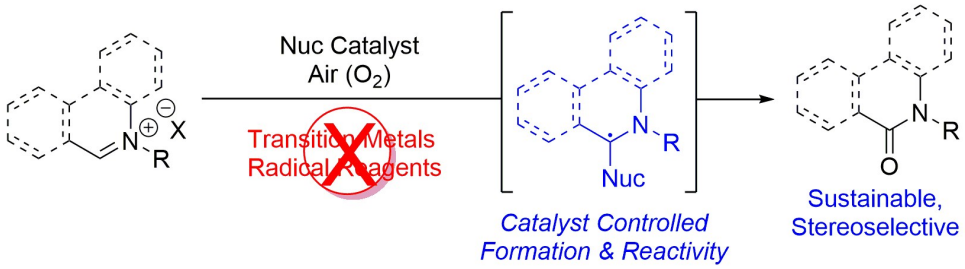

A nucleophile catalyst is introduced for facile radical formation and its catalyst controlled aerobic oxidation