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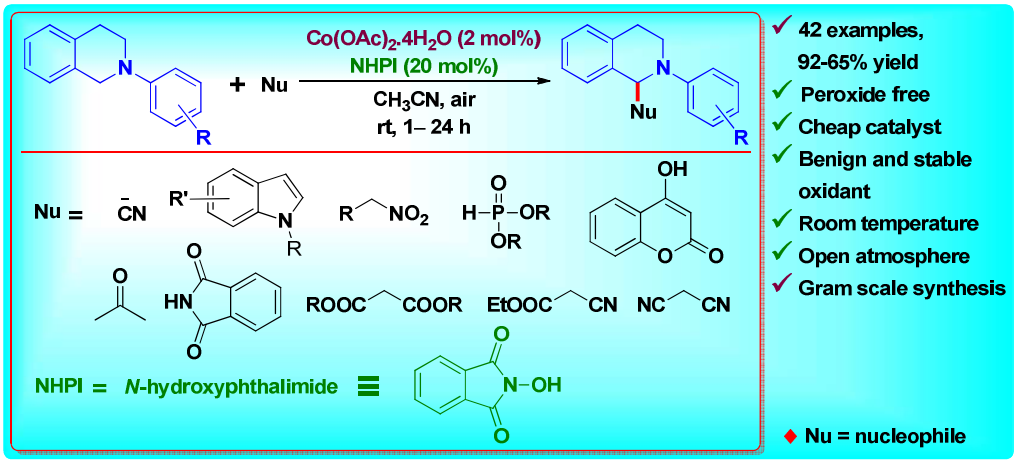
Cobalt(II)/*N*-hydroxyphthalimide Catalyzed Cross-Dehydrogenative Coupling Reaction at Room Temperature Under Aerobic Condition

Mahendra R. Patil, Noopur P. Dedhia, Anant R. Kapdi and A.Vijay Kumar*

Department of Chemistry, Institute of Chemical Technology, Mumbai-400 019, India

E-mail: vijayakki@gmail.com

ABSTRACT: This work reports a Cobalt(II)/*N*-hydroxyphthalimide (NHPI) catalyzed cross-dehydrogenative oxidative coupling of *N*-aryl tetrahydroisoquinolines with various pro-nucleophiles such as indoles, nitroalkanes, trialkylphosphites, active methylene compounds and other nucleophiles such as cyanide (ethyl cyanoformate) at room temperature under aerobic conditions. The present protocol is operationally simple, can be carried out without photoirradiation and under peroxide free conditions even on gram scale to afford the products in good to excellent yields. Based on mass spectrometry and control experiments, a catalytic reaction pathway has been proposed.



TOC Graphic

INTRODUCTION:

In the recent years, C–H bond activation has emerged as a promising ideal synthetic tool for the C–C bond formations. Cross-Dehydrogenative-Coupling (CDC) reaction is an attractive state-of-the-art C-H bond activation process for C-C bond formations, which is deemed beneficial and atom economic from the green chemistry perspective as it precludes the requirement of pre-functionalized substrates.[1] The CDC activation of C-H bonds adjacent to the *N*-atoms in tertiary amines especially the 1, 2, 3, 4-Tetrahydroisoquinolines (THIQs) core *via* oxidation is attractive, as it is commonly found in many natural products including several alkaloids and medicinally active molecules.[2] Many THIQ analogues are of particular interest as they are used as key intermediates/precursors for the synthesis of various bioactive molecules.[3] On account of their importance and wide spread utility, the synthesis of THIQ motifs and scaffolds has gained prominence and significant efforts have been dedicated to synthesize them.

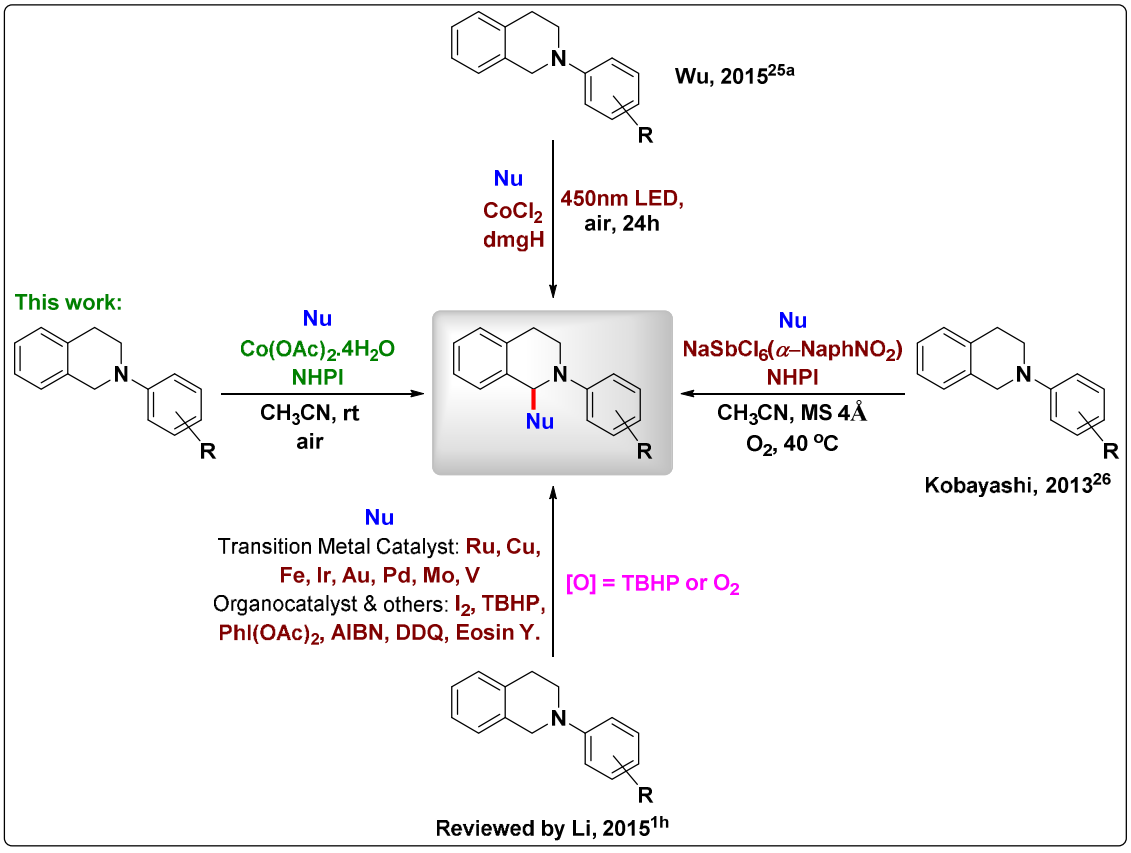
Murahashi and co-workers[4] are the initial pioneers to introduce the C-C bond formation *via* C-H bond activation adjacent to the nitrogen atom in tertiary amines[4] and further break through developments were established by his group,[4a-c,1f] Chao-Jun Li's[5] and others.[6,7] Generally, these CDC reactions rely upon the use of transition metal catalysts such as ruthenium, copper and iron along with oxidants such as H_2O_2, O_2, *tert*-butylhydroperoxide, and 2, 3-dichloro-5,6-dicyanobenzoquinone (DDQ). In addition, CDC is also reported with several other metals such as Ir,[8] Pt,[9] Au,[10] V,[6e,11] Mo,[11b] *etc* and under metal-free conditions.[12,6a] However, most of these catalysts are expensive, suffer from several disadvantages such as complicated synthesis, use of peroxides and other non-benign oxidant systems. Peroxides are corrosive and unstable at room temperature, thus needs to be stored at low temperatures. They are prone to fire and explosive hazards which makes them less suitable for large scale industrial reactions. Besides this, the excess use of hazardous (or)

toxic oxidants such as *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), 2-iodoxybenzoic acid (IBX), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and benzoquinone (BQ) in CDC processes is considered non-benign according to green metrics. These limitations prevent the scope of CDC for further wide applications. However, CDC is well reported with CuBr by using O_2 as the sole oxidant precluding the other oxidants such as TBHP, H_2O_2, DTBP, DDQ, etc.[5g] Therefore, the development of CDC reactions that make use of cheap and abundant oxidants such as air/oxygen which generate water as the sole by product are highly desirable.[13,12a] In this context, to overcome these limitations, our attention was drawn towards *N*-hydroxyphthalimide (NHPI),[14] which is cheap, nontoxic and stable oxidant. In the 1990s, Ishii and coworkers reported the use of NHPI in combination with redox-active metal salts, such as $Co(OAc)_2$ in presence of O_2 to facilitate efficient aliphatic and benzylic C-H oxygenation.[15] Though, this methodology was used in numerous oxidation reactions and industrial applications,[16] majority of the studies have been focused on C-H oxygenation only.[17] Therefore, we envisaged that the use of inexpensive and easily available metal salts in combination with NHPI would be a superior choice and shall meet the requirements of sustainable chemistry. Moreover, Chao-Jun Li and his co-workers reported an interesting CDC reaction catalysed by a bimetallic system using copper & other metal salts in combination with NHPI .[18]

Over the past few years, cobalt has emerged as a good choice to replace precious transition metals for the development of C–H bond functionalizations.[19] It can promote several reactions under milder conditions.[20] Cobalt catalysis is a credible alternative for sustainable processes when compared to the costly rare-earth transition metal catalysed reactions. Due to its economy, low toxicity, and unique reaction mode, cobalt as a catalyst has attracted much attention in the development of applicable transformations in organic synthesis for cross-coupling reactions,[21] hydroformylation,[22] Pauson–Khand reactions,[23] and

other cobalt catalyzed C–C bond formations.[24] To the best of our knowledge, Co metal is less exploited for CDC reactions in the past.[25] Only few reports are known in the literature wherein cobalt metal is used for CDC reactions, but needs the aid of either UV-visible light[25a] or peroxides.[25b-d] However, an elegant CDC method is reported with antimonite salts and NHPI,[26] but, the antimonite salts are toxic and are used in a relatively high loading. Henceforth, considering all the above-aforementioned facts and in the continuation of our previous work, *i.e.* α-cyanation of tertiary amines[27] *via* oxidative CDC reactions, we report a facile and operationally convenient protocol for the oxidative coupling of tertiary amines with various pro-nucleophiles by Co(II) / NHPI in acetonitrile solvent at room temp under aerobic conditions (Scheme 1). To the best of our knowledge, this is a first report to show the use of Co(II)/NHPI system for CDC reaction.

Scheme 1: A Different Catalytic Approach for the α-Substitution of *N*-Aryl-1,2,3,4-Tetrahydroisoquinoline



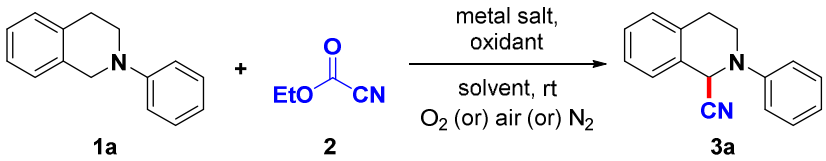
RESULT AND DISCUSSION:

In the preliminary studies, we optimized the reaction conditions, we choose *N*-phenyl THIQ as a model substrate and ethyl cyanoformate as cyanation source for the *α*–cyanation of tertiary amines. The optimized reaction conditions were obtained by screening of different cobalt metal salts, oxidants and solvents by varying atmospheric conditions and stoichiometric amounts (Table 1). Initially, we examined different cobalt metal salts such as $Co(acac)_2$, $CoCl_2.6H_2O$, $Co(NO)_3.6H_2O$ and $Co(OAc)_2.4H_2O$ with NHPI as an oxidant. Among them $Co(OAc)_2.4H_2O$ was proven to be a good catalyst and afforded the desired product (**3a**) in 91% yield (Table 1, entries 1-4). The stoichiometry of the oxidant NHPI was decreased up to as low as 0.1 equivalent (Table 1, entries 5-6), of which 0.2 equivalent was effective to complete the transformation. Moreover, anhydrous $Co(OAc)_2$ showed less catalytic activity (Table 1, entry 7) than hydrated $Co(OAc)_2$. This might be due to the increase in polarity of the catalyst by the hydrated part which alters the electronic environment thereby helping in stabilizing the transition state and thus favoring reaction progress for CDC. Also, literature reports suggest that the presence of water favors CDC reactions and other oxidative coupling reactions.[5g,6e,28] The other oxidants and radical initiator *viz* H_2O_2, TBHP, and BPO in combination with cobalt salt furnished low (70-40%) yields (Table 1, entries 8-10), which showed that among the oxidants, NHPI (Table 1, entry 5) has the best activity as oxidant and as a radical initiator.

To find out the necessity of Co and NHPI combination, individual reaction runs were carried out the in absence of $Co(OAc)_2.4H_2O$ and NHPI (Table 1, entries 11-12). The reaction did not go ~~to~~ for completion and afforded very less ~~yields~~ yield, 30% and 20% ~~yields~~ yield respectively. These results suggest a possible mechanistic synergy between Co (II) and NHPI in the oxidative C-H activation. Additionally, the reactions performed under the N_2

atmosphere were very sluggish and afforded the product (**3a**) in very less yield (Table 1, entry 13). Whereas, under O_2 atmosphere, the reaction was progressive and afforded 91% of

Table 1: Optimization of Reaction Conditions[a]



entry	metal salt	oxidant (equiv.)	solvent	air/O_2 /N_2	time (h)	yield[b] (%)
1	$Co(acac)_2$	NHPI (0.3)	CH_3CN	Air	1	88
2	$CoCl_2.6H_2O$	NHPI (0.3)	CH_3CN	Air	1	85
3	$Co(NO_3)_2.6H_2O$	NHPI (0.3)	CH_3CN	Air	1	82
4	$Co(OAc)_2.4H_2O$	NHPI (0.3)	CH_3CN	Air	1	91
5	**$Co(OAc)_2.4H_2O$**	**NHPI (0.2)**	**CH_3CN**	**Air**	**1**	**91**
6	$Co(OAc)_2.4H_2O$	NHPI (0.1)	CH_3CN	Air	1	80
7	$Co(OAc)_2$	NHPI (0.2)	CH_3CN	Air	1	89[c]
8	$Co(OAc)_2.4H_2O$	H_2O_2 (1.5)	CH_3CN	Air	1	40
9	$Co(OAc)_2.4H_2O$	aq.TBHP (1.2)	CH_3CN	Air	1	65
10	$Co(OAc)_2.4H_2O$	BPO (0.3)	CH_3CN	Air	24	70
11	$Co(OAc)_2.4H_2O$	-	CH_3CN	O_2	24	30
12	-	NHPI (0.2)	CH_3CN	Air	24	20
13	$Co(OAc)_2.4H_2O$	NHPI (0.2)	CH_3CN	N_2	24	15
14	$Co(OAc)_2.4H_2O$	NHPI (0.2)	CH_3CN	O_2	0.75[d]	91
15	$Co(OAc)_2.4H_2O$	NHPI (0.2)	$CHCl_3$	Air	1	65
16	$Co(OAc)_2.4H_2O$	NHPI (0.2)	EtOH	Air	1	75
17	$Co(OAc)_2.4H_2O$	NHPI (0.2)	MeOH	Air	1	87
18	$Co(OAc)_2.4H_2O$	NHPI (0.2)	Toluene	Air	1	45
19	$Co(OAc)_2.4H_2O$	NHPI (0.2)	EtOAc	Air	1	60
20	$Co(OAc)_2.4H_2O$	NHPI (0.2)	H_2O	Air	24	NR[e]

[a]Reaction conditions: **1a** (0.35 mmol), **2** (0.7 mmol), cobalt salt (2 mol %), solvent (1.6 mL) at room temperature. [b]Isolated yield. [c]anhydrous $Co(OAc)_2$ (obtained by vacuum oven drying at 100°C) and reaction under dry air. [d]45 minutes. [e]β-cyclodextrin as a phase transfer catalyst, NR: no reaction

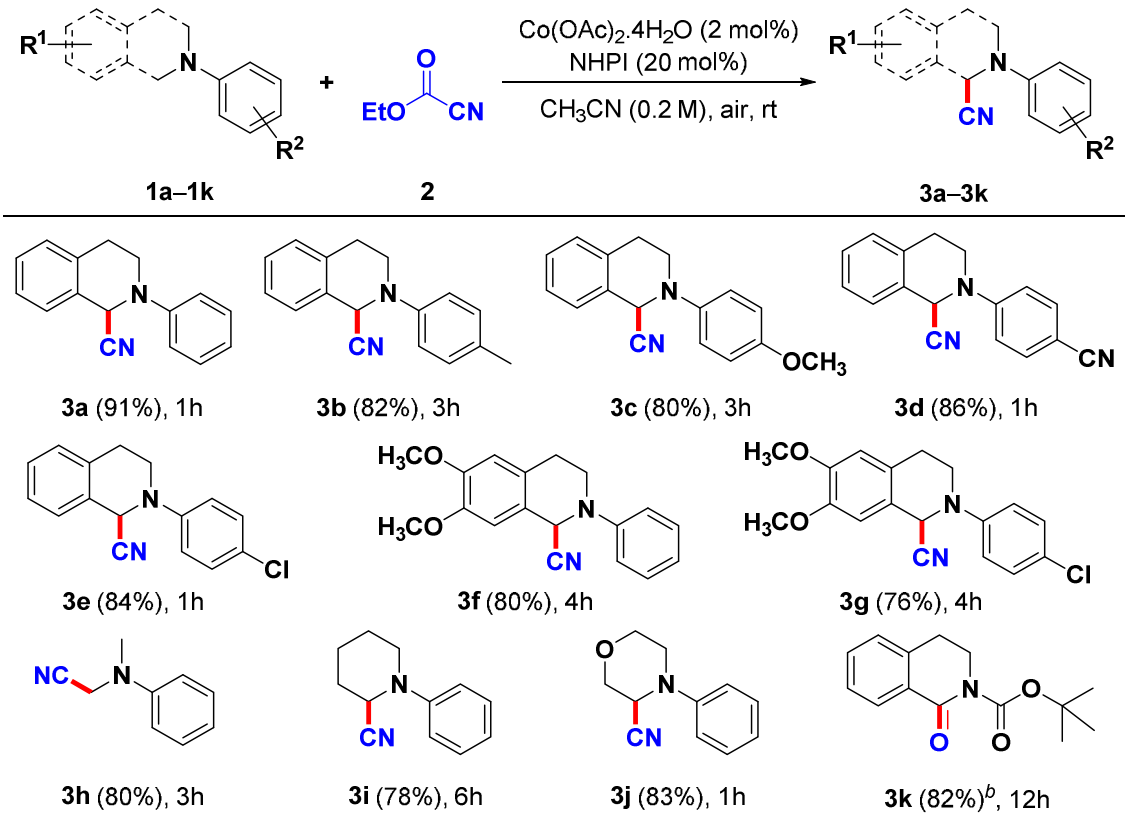
the product yield (Table 1, entry 14). This suggests that the reaction is predominantly driven by oxygen thus confirming an oxidative CDC pathway. In case of solvent study, the different solvents such as $CHCl_3$, EtOH, MeOH, acetonitrile, toluene, EtOAc, H_2O were screened (Table 1, entry 15-20), which revealed CH_3CN as the best choice of the reaction solvent. In the case of MeOH as reaction solvent, the product yield was comparatively less than the reaction in CH_3CN, which might be because of the solvent molecules competing as nucleophiles. We also examined other metal salts in combination with NHPI as oxidant (ref. supporting information, Table S1), of which desired product (**3a**) was obtained in excellent yield in the case of $Co(OAc)_2.4H_2O$ and it was identified as a most effective redox metal catalyst of all.

With the optimized reaction conditions in our hand, we studied the substrate scope by using various pro-nucleophiles to check the versatility of the developed protocol. Initially, the α-cyanation of tertiary amines was tried as they provide access to a variety of α-amino nitriles which are key intermediates of natural products and drug molecules.[27,29] The CDC reaction of ethyl cyanoformate (**2**), a user-friendly cyanide source with THIQs **1a-1k** under optimized conditions furnished α-amino nitriles (**3a-3k**) in good to excellent yields (Scheme 2). Among all the substrates (**1a-1k**), the model substrate **1a** afforded the highest yield of the product **3a** in 91%. Later, the effect of electron-donating and electron-withdrawing substituents on the phenyl group attached to nitrogen of the THIQs was studied. Electron donating group (*p*-Me, *p*-OMe) substituted THIQs, **1b** and **1c** furnished the product **3b** and **3c** in 82% and 80% yield respectively, which was comparatively less than the electron withdrawing group (*p*-CN) substituted THIQ, **1d** which gave the product **3d** in 88% yield. Whereas, *p*-Cl substrate **1e** afforded the product **3e** in comparatively good yield. This might be because of the influence of substituents on the intermediate formed during the progress of the reaction and product stability. Moreover, the effect of the substituent, on the aromatic part of THIQ was studied.

The reaction in the case of **1f** and **1g** furnished good yields, but were comparatively lower than the simple *N*-phenyl THIQ analogs. The product (**3f**) was obtained from corresponding 6, 7-dimethoxy-*N*-phenyl THIQ (**1f**) in 80% yield which was better than the product (**3g**) obtained from **1g**, which can be due to substituent effect.

With the optimised reaction conditions, we also tried *α*-cyanation of *N,N*-dimethyl aniline (**1h**), *N*-phenyl piperidine (**1i**) and *N*-phenyl morpholine (**1j**). The products **3h, 3i** and **3j** were obtained in good to excellent yields. Unfortunately, the *N*-BOC THIQ (**1k)** substrate did not furnish the expected cyanation coupled product even under prolonged heating conditions, rather it formed C-H oxygenation amide product **3k** in 82% yield.

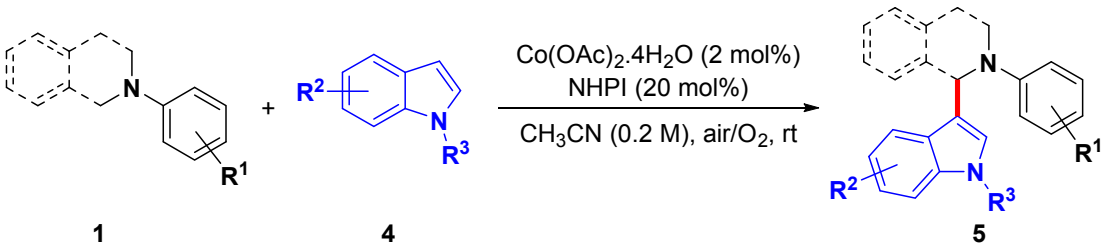
Scheme 2: Reaction Scope for *α*-Cyanation[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), CH_3CN (2.3 mL), $Co(OAc)_2.4H_2O$ (2 mol%), NHPI (20 mol%) at room temperature and open to air. [b]50°C and O_2 atmosphere, isolated yields in parenthesis.

Further the study was extended to the synthesis of indolyl tetrahydroisoquinoline derivatives owing to the importance of various bioactive indoles substituted THIQs.[30]

Scheme 3: Reaction Scope for Indolation[a]



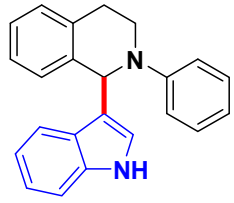
1

1a: R^1 = H
1b: R^1 = CH_3
1c: R^1 = OCH_3
1h: *N*,*N*-dimethyl aniline

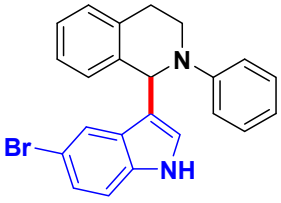
4

4a: R^2 = H; R^3 = H
4b: R^2 = *5*-Br; R^3 = H
4c: R^2 = *5*-CN; R^3 = H
4d: R^2 = H; R^3 = CH_3
4e: R^2 = *5*-Br; R^3 = CH_3
4f: R^2 = *5*-CN; R^3 = CH_3

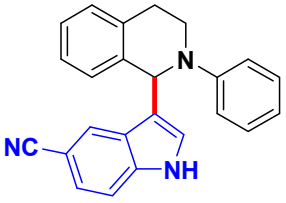
5



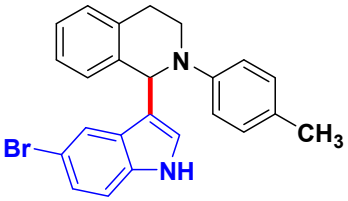
5aa (82%)[b], 1h; (67%)[c], 24h



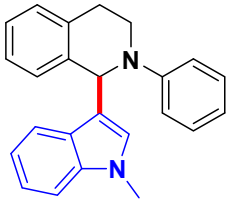
5ab (78%)[b], 1h



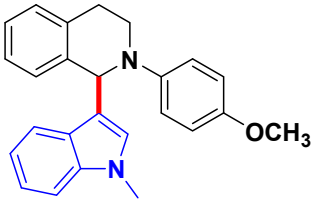
5ac (69%)[b], 3h



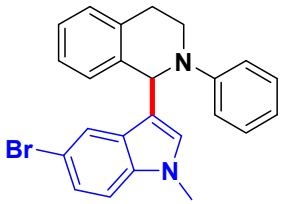
5bb (74%)[b], 1h



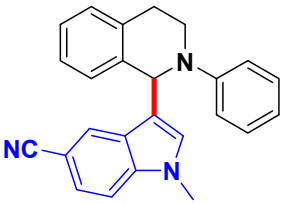
5ad (84%)[c], 15 min



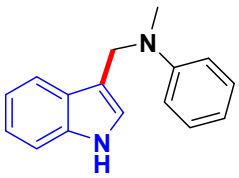
5cd (78%)[c], 1h



5ae (83%)[c], 30 min



5af (73%)[c], 3h



5ha (NR)[b,d], 24h

[a]Reaction conditions: **1** (0.45 mmol), **4** (0.5 mmol), CH_3CN (2 mL), $Co(OAc)_2.4H_2O$ (2 mol %), NHPI (20 mol%) at room temperature , [b]O_2 atmosphere. [c]open air, [d]50 °C, isolated yields in parenthesis.

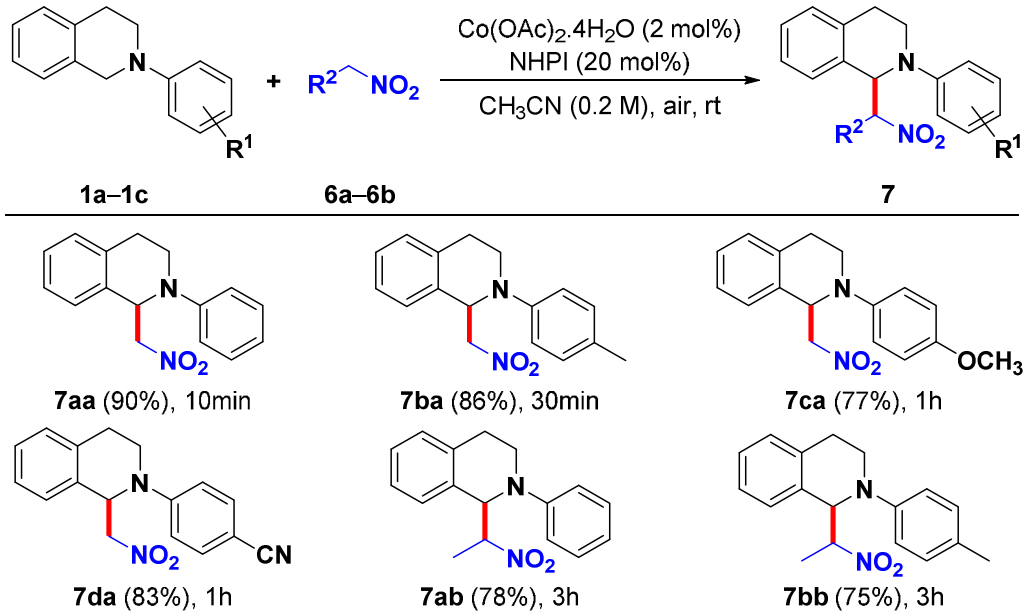
The indolation of *N*-aryl THIQs through dehydrogenative pathway is aza-Friedel-Crafts/CDC reaction. To the best of our knowledge, coupling between *N*-aryl THIQs and NH-unprotected indole derivatives are either reported in photo-irradiation or in peroxide condition.[1d-e,1h, 25a] But in this report, we have successfully overcome these challenges and as well extended the

substrate scope of the indolation CDC methodology. The *N*-aryl THIQs **1a**, **1b**, **1c** and **1h** reaction with various indole derivatives **4a**, **4b**, **4c**, **4d**, **4e** and **4f** under the optimized reaction conditions afforded the coupled products **5aa**, **5bc**, **5ad**, **5ab**, **5cb**, **5db**, **5ae** and **5af** in good to excellent yields (Scheme 3). Both the electron-donating and electron-withdrawing substituents on indole ring and *N*-aryl THIQs worked well under optimized conditions. In the case of THIQs with an electron-donating group, the yield of the product decreased slightly due to the decreased electrophillicity. Similarly, the electron-withdrawing substituent on indole ring (**4c, 4f**) furnished coupled products in lesser yields than those with a strongly or a weakly electron-donating group substituted indoles (**4b**, **4e**). This can be explained by the fact that the electron-withdrawing substituents could profoundly decrease the nucleophilicity of the indoles. Moreover, the coupling of *N*-aryl THIQs **1a** and **1b** with free (NH) indoles **4a**, **4b** and **4c** in open to air atmosphere, afforded the desired products in comparatively less yield and also required longer reaction times. When the same reactions were carried out in O_2 atmosphere, a significant increase in the yields of the desired products (**5aa**, **5ab 5ac** and **5bb**) (82-72%) along with decreased reaction times was observed. However, it was observed that *N*-methyl indole derivatives **4d**, **4e** and **4f** worked well in open to air atmosphere and afforded coupled product in good yields with a shorter reaction times. This might be due to the increased nucleophilicity of *N*-methyl indole than free indoles (-NH). Unfortunately, the reaction of *N,N*-dimethyl aniline **1h** with indole **4a** did not furnish the coupled product **5ha** even after prolonged heating for 24h.

Further, to extend the study we chose to investigate nitroalkylation of THIQs. Literature reports of the coupling of nitroalkanes with *N*-phenyl THIQ derivatives were successfully demonstrated *via* CDC reactions in several studies.[1d,1h] The nitroalkyalation of THIQ derivatives through iminium ion intermediate is nitro-mannich /Aza-Henry type of CDC reaction. Also, the reduction products of *β*–nitroamine derivatives generated by

nitroalkylation furnish *vicinal* diamines, which are important structural motifs to synthesize the pharmaceutically important molecules[3a] and are also used as chiral auxiliaries in asymmetric catalysis.[31] Hence considering the potential benefits of these compounds, nitro methane (**6a**) and nitro ethane (**6b**) were tested for their reaction with *N*-Phenyl THIQs **1a**, **1b**, **1c** and **1d,** which furnished the products **7aa**, **7ba**, **7ca**, **7da**, **7ab** and **7bb** in excellent yields (90-75%) with shorter reaction timings (Scheme 4). However, the nitro methylation reactions were more facile than nitro ethylations, which can be attributed to the steric effects.

Scheme 4: Reaction Scope for Nitroalkylation[a]

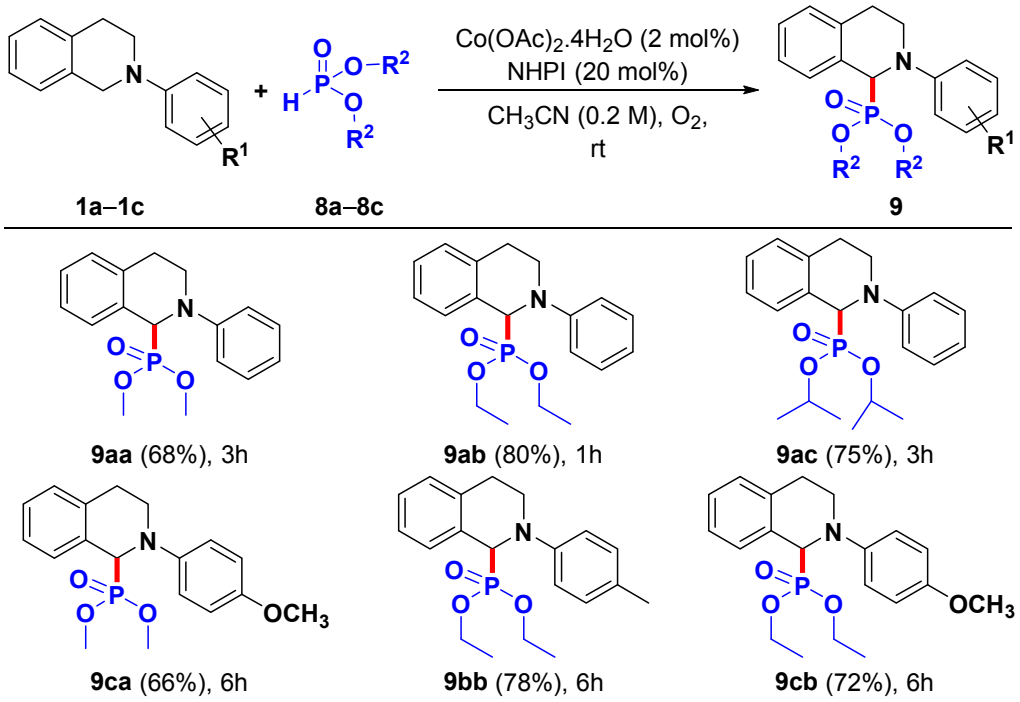


[a]Reaction conditions: **1** (0.5 mmol), **6** (0.5 mL), CH_3CN (2.3 mL), $Co(OAc)_2.4H_2O$ (2 mol%), NHPI (20 mol%) at room temperature open to air, isolated yields in parenthesis.

After successful establishment of CDC reaction for cyanation, indolation and nitro alkylation, our attention was focused on to investigate the C-P bond formation reactions. The phosphonation of tertiary amines is a promising route to synthesize α-amino-phosphonates. These compounds have been known to show a broad range of biological activities such as antifungal, antibacterial, and enzyme inhibitor activity.[32] Therefore we attempted the

synthesis of various α-amino-phosphonates under the developed conditions. The reaction of **1a**, **1b** and **1c** was tried with various dialkyl phosphites such as dimethyl phosphite (**8a**), diethyl phosphite (**8b**) and diisopropyl phosphite (**8c**). The coupled products **9aa**, **9ab**, **9ac**, **9ca**, **9bb** and **9cb** were obtained in 80-68% yield (isolated yield). In the phosphonation study, the coupling reactions of diethyl phosphite (**8b**) were more efficient when compared to other dialkyl phosphite reactions wherein the corresponding products **9ab**, **9bb,** and **9cb** were obtained in good to moderate yields (80-72%). Surprisingly, it is also noteworthy to mention that the stoichiometric amount of dialkyl phosphonates was sufficient for phosphonation of tertiary amines (Scheme 5).

Scheme 5: Reaction Scope for Phosphonation[a]

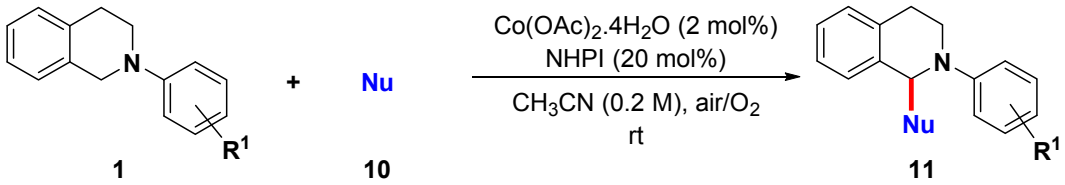


[a]Reaction conditions: **1** (0.45 mmol), **8** (0.5 mmol), CH_3CN (2 mL), $Co(OAc)_2.4H_2O$ (2 mol%), NHPI (20 mol%) at room temperature in O_2 atmosphere, isolated yields in parenthesis.

After successful establishment of CDC reaction with various pro-nucleophiles, we decided to explore the developed protocol with active methylene compounds and other

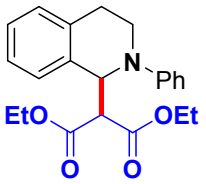
nucleophiles. The oxidative coupling of active methylene compounds with tertiary amines is also called as the oxidative-Mannich type CDC reaction. The Co(II)/ NHPI mediated reaction

Scheme 6: Reaction Scope for Oxidative Coupling of Tetrahydroisoquinolines with Active Methylene Compound and other Nucleophiles[a]

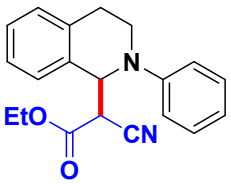


1a: R^1 = H
1b: R^1 = CH_3
1c: R^1 = OCH_3

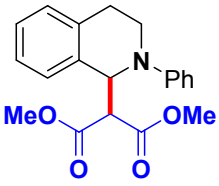
10a: Diethylmalonate
10b: Ethylcyanoacetate
10c: Dimethylmalonate
10d: Malanonitrile
10e: Acetone
10f: Phenol
10g: 4-Hydroxycoumarin
10h: Phthalimide



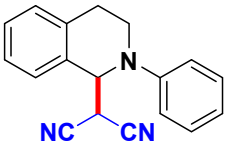
11aa (76%)[b], 24h



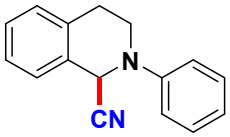
11ab (83%)[b],12h



11ac (80%)[b],12h

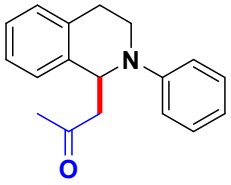


11ad (52%)

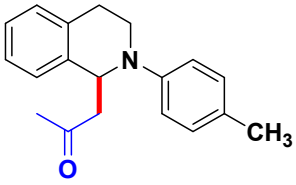


3a (27%)

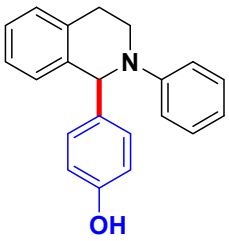
11ad Mixture (71%)[b], 24h



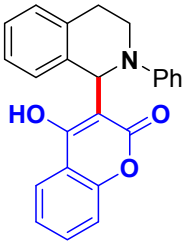
11ae (81%)[b,c],18h



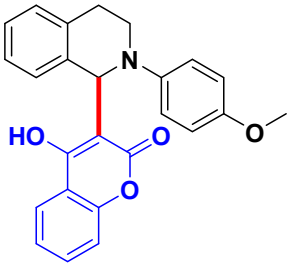
11be (79%)[b,c],18h



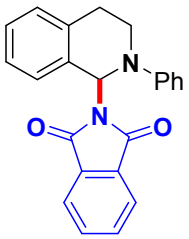
11af (60%)[d], 6h



11ag (90%)[d],1h



11cg (68%)[d], 3h



11ah (55%)[d], 6h

[a]Reaction conditions: **1** (0.5 mmol), [**10a-10c** (0.85 mmol), **10d** (0.6 mL), **10e-10g** (0.58 mmol)], CH_3CN (2.3 mL), $Co(OAc)_2.4H_2O$ (0.02 mmol), NHPI (0.2 mmol%) at room temperature, [b]O_2 atmosphere, [c]L-proline (35 mol%), [d]open air, isolated yields in parenthesis.

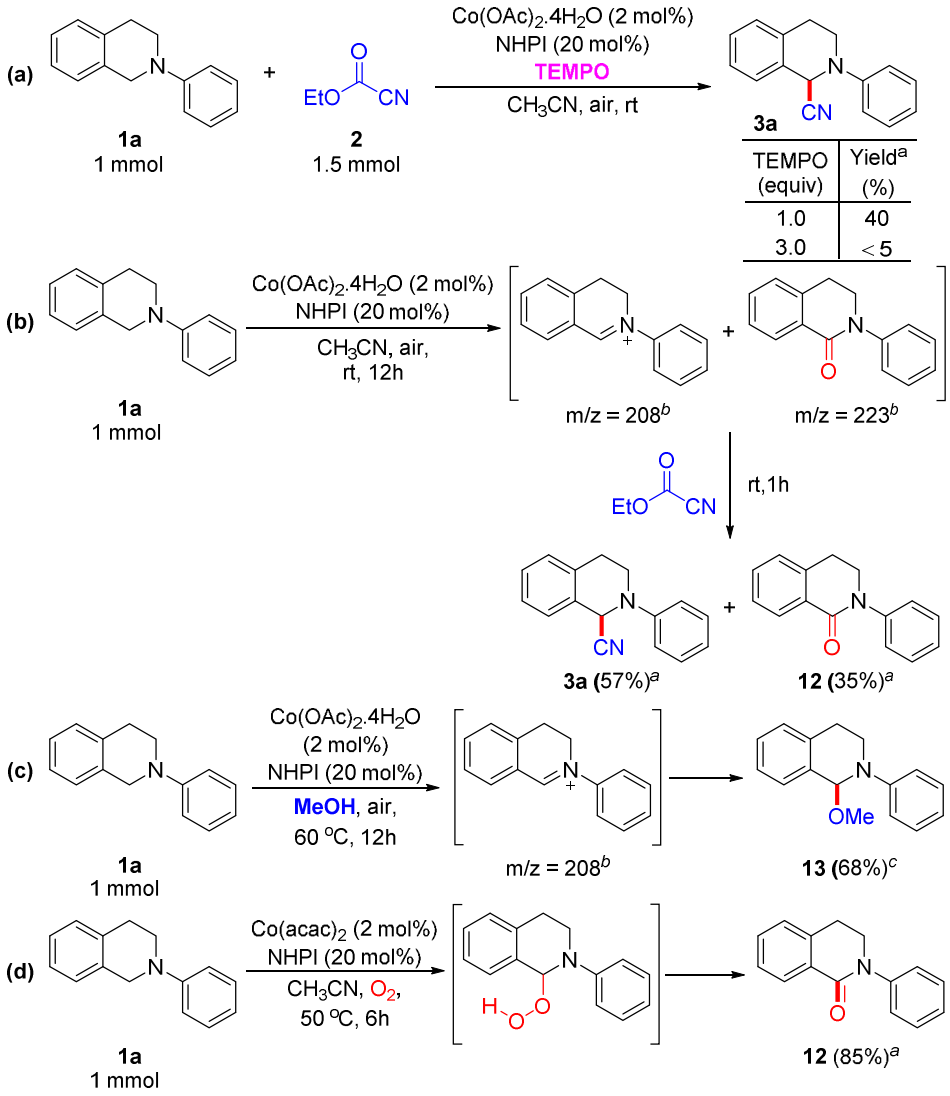
was also found to be amenable to several active methylene compounds such as diethylmalonate (**10a**), ethyl cyanoacetate (**10b**), dimethylmalonate (**10c**) with *N*-phenyl THIQ (**1a**). All these substrates underwent smooth reactions to afford desired products **11aa**, **11ab** and **11ac** in good yields (Scheme 6).

However, the reaction of malononitrile **10d** with **1a** under the established conditions afforded a mixture of **11ad** (malononitrile adduct) as the major product along with an *α*-cyanated *N*-phenyl THIQ (**3a**) in minor quantity. It is noteworthy to mention that, under the optimized conditions we obtained **11ad** as the major product, as opposed to previous literature reports wherein **3a** was the major product in CDC reaction of malononitrile with **1a**. However oxidative coupling between *N*-aryl THIQs (**1a** and **1b**) and unactivated ketone (acetone, **10e**) did not proceed under optimized conditions, but after the addition of L-proline as additive (*via* enamine), underwent reaction smoothly to afford the corresponding products (**11ae**, **11be**) in good yields. Next, the other nucleophiles such as phenol (**10f**), 4-hydroxy coumarin (**10g**) and phthalimide (**10h**) were also tested as coupling partners for CDC reaction with tertiary amine **1a** and **1c** (Scheme 6). In case of **10f** and **10h** as coupling partners the coupled products **11af** and **11ah** were obtained in moderate to good yields. To our delight, the oxidative coupling of **1a** and **1c** with 4-hydroxy coumarin (**10g**) has successfully furnished the desired products **11ag** and **11cg** in good to excellent yield.

Having studied the substrate scope, with the intention to gain insight into the mechanism of the developed CDC protocol, some control experiments were performed (Scheme 7). To find out whether the reaction proceeds through a radical pathway, the stable free radical TEMPO was deliberately added to the reaction at the beginning, as the nitroxide radicals are widely used as radical scavenging agents due to their radical inhibition activity. In scheme 7a, the employment of 1 equivalent of TEMPO decreased the product yield to 41%

and when 3 equivalents was added, only a slight amount of product (**3a**) was formed. These results suggest that the reaction might go through a radical pathway.

Scheme 7: Control experiments



[a]Isolated yield, [b]GC-MS analysis of reaction mixture, [c]GC yield and confirmed by mass spectrometry

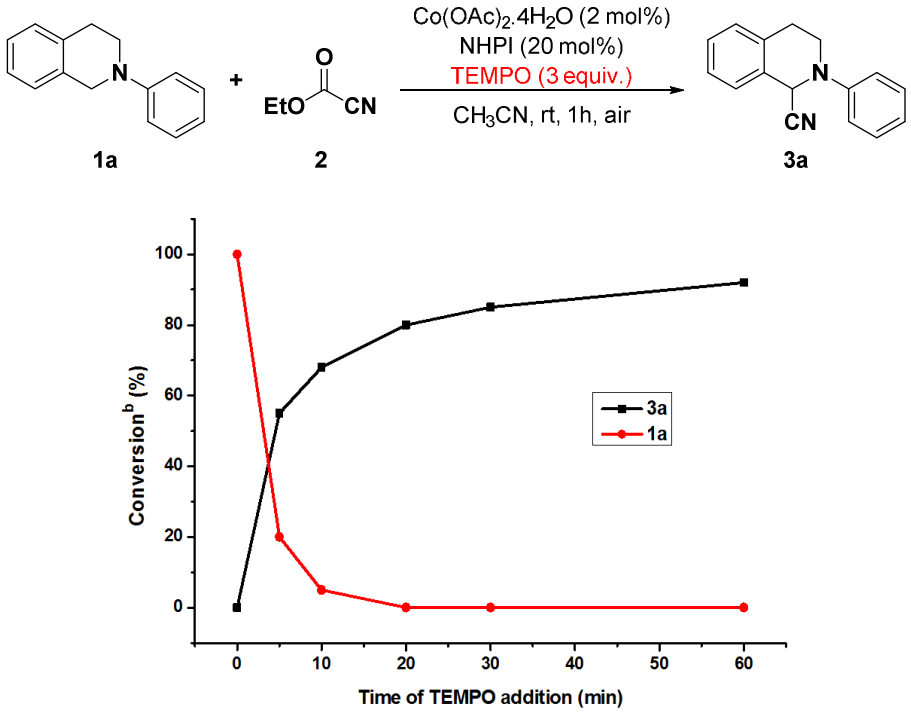
Another control experiment was performed wherein the reaction was carried out in the absence of nucleophile to check for the formation of the iminium ion, which is reported to be the intermediate of many CDC reactions (Scheme 7b). To our delight, the ESI mass spectrometry analysis of this reaction mixture after **12** h showed the presence of the

corresponding iminium ion along with an amide side product. To quantify the ratio of imine and amide, the imine was trapped by adding ethyl cyanoformate (cyanide source) to convert it into an α-cyanated product. The product **3a** was isolated in 57% yield along with the amide in 35% yield. These results strongly support that the reaction goes through an iminium ion intermediate, which in the absence of nucleophile forms the amide side product. The generation of iminium ion as intermediate was also confirmed by performing the reaction in methanol, which furnished the methoxy substituted *N*-phenyl THIQ **13** in 68% yield (Scheme 7c). To our fortune, serendipitously we were able to observe the amide formation from tertiary amine in absence of nucleophile at room temperature using Co/NHPI catalytic protocol after 48 h. To understand the origin of oxygenation process for formation of amide **12,** we performed another control experiment wherein **1a** was stirred in acetonitrile with $Co(acac)_2$/NHPI under oxygen atmosphere (in which oxygen was bubbled through a dreschel bottle filled with concentrated sulphuric acid). The amide **12** was isolated in 85% yield. This result shows that the oxygen atom originated from molecular dioxygen, but not the traces of water present in the reaction.

Further in continuation to understand the mechanism of the reaction, we examined the conversion of oxidative coupling reaction of **1a** with ethyl cyanoformate under the standard reaction conditions by terminating the reaction with a radical quencher after a specific time interval (Figure 1). As seen in radical trapping experiments, the reaction was completely terminated upon the addition of 3 equivalents of TEMPO. Hence, to observe how quickly the imine formation takes place from the substrate, we added the 3 equivalents of TEMPO at a specific time interval (0 min, 5min, 10min, 20min, 30 min) in separate experiments under same conditions followed by isolation of **1a** and the product by flash chromatography. A plot of the substrate/product concentration *versus* time of TEMPO addition as shown in Figure 1

suggests that both product formation and reactant consumption traverse an exponential trace, where the reactant consumption path was more exponential than the product formation.

Figure 1: Conversion study of the oxidative coupling reaction[a]



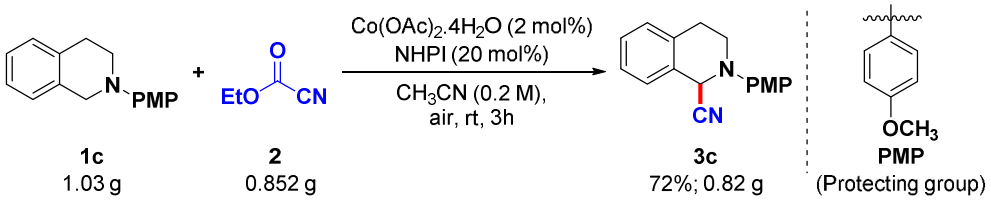
[a]Reaction conditions: **1a** (1mmol), **2** (2.5 mmol), $Co(OAc)_2.4H_2O$ (0.02 mmol), NHPI (0.2 mmol), CH_3CN (3 mL), rt, 1h and 3 mmol of TEMPO added at specific time interval. [b]conversions on basis of yield obtained by flash chromatography of crude reaction mixture.

It is clearly evident from the profile, that much of the substrate conversion to imine (or) iminium ion takes place within 10-15 minutes of the reaction initiation. This suggests that the generation of intermediate iminium ion may be the rate determining step. However, within first 5 minutes, the reaction shows more than 50% conversion indicating that the rate of the reaction is initially faster and then further steadily progresses to form the product.

Further next, to demonstrate the synthetic utility of the developed protocol, a gram scale synthesis of **3c** was carried out wherein *N*-(4-methoxyphenyl)-tetrahydroisoquinoline

(**1c**) (4.3 mmol, 1.03 g) was reacted with 850 μL (8.6 mmol) of ethyl cyanoformate **2** under the standard reaction conditions (Scheme 8).

Scheme 8: Gram Scale Synthesis of 3c

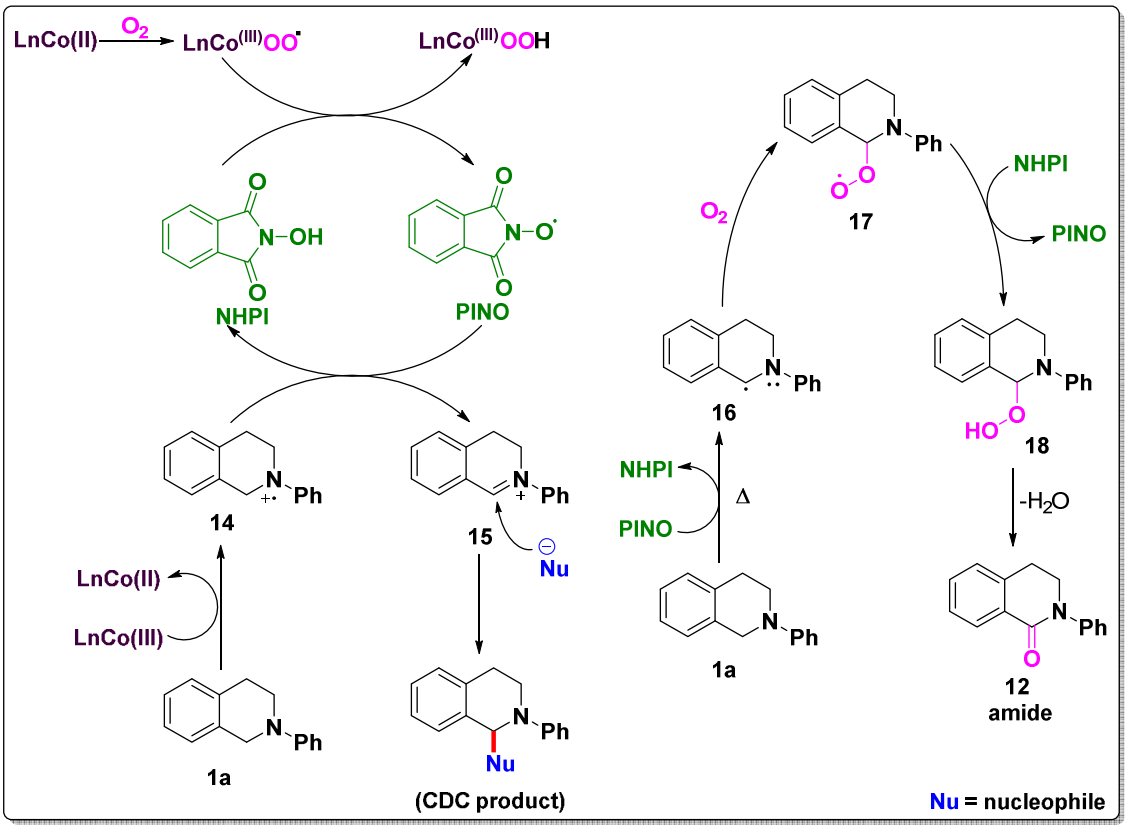


1c 1.03 g | **2** 0.852 g | **3c** 72%; 0.82 g | **PMP** (Protecting group)

The reaction proceeded smoothly to afford 0.82 g (72%) of the product **3c**. To illustrate the utility of the developed methodology, we purposefully used **1c**, a *p*-methoxyphenyl (PMP) protected amine instead of a simple *N*-phenyl derivative **1a**, as the deprotection of PMP provides ready access to the secondary amines, which are important key intermediates of bioactive molecules.[2g,33] Additionally, this feature assists the reaction by stabilizing the oxidized form of the tertiary amine.[34]

On the basis of the above results and previous reports,[16a,19b,6b] the mechanism of this transformation is proposed (Scheme 9). According to Ishii and co-workers, Co(II) salt in combination with oxygen produces a Co(III) peroxy radical complex, which thereby generates PINO radical from NHPI at room temperature.[15] The PINO radical abstracts a hydrogen radical from the cationic radical **14** to furnish the iminium ion **15.** The formation of the cationic radical **14** may be by a single electron oxidation of **1a** by the high valent Co(III) complex which causes the regeneration of Co(II) complex. Next, the attack of the nucleophile on the iminium ion forms the α-substituted CDC product.[6b] Interestingly, in absence of the nucleophile at ambient temperature under O_2 atmosphere, the hydrogen radical abstraction from **1a** can form radical **16,** which upon reaction with oxygen forms a peroxy radical complex **17.** After which, an NHPI mediated formation of a hydroperoxide moiety **18,** followed by a subsequent dehydration affords the amide compound **12**.

Scheme 9: Proposed Reaction Mechanism.



CONCLUSION:

In conclusion, we developed an efficient protocol for cross dehydrogenative coupling reaction by using Co(II)/NHPI system at room temperature under peroxide-free aerobic conditions and without photo irradiation. In which, a very cheap and less toxic transition metal catalyst such as $Co(OAc)_2.4H_2O$ is required in a low sub stoichiometric amounts along with a sub stoichiometric amount of stable and cheap oxidant NHPI. The undertaken mechanistic study suggested that the reaction proceeds through a radical pathway with iminium ion as intermediate. A diverse substrate scope for the developed protocol using different pro-nucleophiles was demonstrated along with a gram scale synthesis. Furthermore, we anticipate such approaches to increase the CDC reactions viability for large scale utility, thereby paving way for the development of green and safe protocols at ambient conditions.

EXPERIMENTAL SECTION:

General Methods.

All starting materials and reagents and metal salts were purchased from commercial sources and used without further purification. All reactions were performed in oven-dried glassware. Solvents were purchased with high purity and used without purification. The *N*-aryl-1,2,3,4-tetrahydroisoquinoline derivatives were synthesized by reported procedures from their respective precursors and purified by flash chromatography on *neutral silica* gel (mesh 60–120) . All the reactions were monitored by using thin layer chromatography (TLC) which was silica (Silica Gel 60 F254) pre-coated aluminum plates and the products were visualized by UV lamp (PHILIPS TUV 8W lamp) and I_2 stain. Most of the reactions were performed at room temperature which could be varied between 25-29 ^{o}C. Products were purified by flash column chromatography on *neutral* silica gel (100-200 mesh and 60–120 mesh). The characterization of products were done by ^{1}H and ^{13}C-NMR spectroscopy recorded in $CDCl_3$ and TMS as reference slandered on an Avance III and Bruker NMR spectrophotometer at 400 MHz and 101 MHz respectively. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as internal standard. The *J* (coupling constant) values are expressed in Hz. Splitting patterns of the proton are represented as s (singlet), d (doublet), t (triplet), and m (multiplet).

Neutral silica gel preparation: Triethylamine (3-4 mL) was added to 150 g 100-200 silica gel and made into slurry by addition of petroleum ether for the even distribution of the amine. The solvent was removed under reduced pressure on a rotary evaporator and dried under vacuum overnight.

Typical procedure for α-cyanation of tertiary amines

In a typical experiment, a 15 mL round bottom flask was equipped with a teflon coated magnetic stirring bar. A weighed quantity of THIQ derivative (0.5 mmol, 1 equiv) and ethyl

cyanoformate (1 mmol, 2 equiv) was added followed by addition of 2.3 mL of acetonitrile. To the stirring reaction mixture $Co(OAc)_2.4H_2O$ (0.01 mmol, 0.02 equiv) and NHPI (0.1 mmol, 0.2 equiv) was added successively. The reaction mixture was stirred at room temperature in open to air atmosphere and the reaction progress was monitored by thin layer chromatography (TLC) visualized in UV or I_2 chamber. After the reaction completion, the mixture was passed through the celite bed and the organic layer evaporated under reduced pressure. The product was isolated by flash column chromatography on neutral silica gel (mesh 100–200).

Typical procedure for *α*-indolation of *N*-aryl THIQ derivatives

In a typical experiment, a 15 mL round bottom flask was equipped with a teflon coated magnetic stirring bar. A weighed quantity of THIQ derivative (0.45 mmol) and indole derivative (0.5 mmol, 1.1 equiv) were added followed by addition of 2 mL of acetonitrile. To the stirring reaction mixture $Co(OAc)_2.4H_2O$ (0.009 mmol, 0.02 equiv) and NHPI (0.09 mmol, 0.2 equiv) were added successively. The reaction mixture was stirred at room temperature in open atmosphere and the reaction progress was monitored by TLC visualized in UV or I_2 chamber. After the reaction completion, the mixture was passed through the celite bed and the organic layer evaporated under reduced pressure. The product was isolated by flash column chromatography on neutral silica gel (mesh 100–200). (Note: in case of NH free indole, reaction kept in the O_2 atmosphere.)

Procedure for *α*-nitroalkylation of *N*-aryl THIQ derivatives

In a typical experiment, a 15 mL round bottom flask was equipped with a teflon coated magnetic stirring bar. A weighed quantity of THIQ derivative (0.5 mmol) and nitroalkane (0.5 mL) were added followed by addition of 2.3 mL of acetonitrile. To the stirring reaction mixture $Co(OAc)_2.4H_2O$ (0.01 mmol, 0.02 equiv) and NHPI (0.1 mmol, 0.2 equiv) was added

successively. The reaction mixture was stirred at room temperature in open air atmosphere and the reaction progress was monitored by TLC visualized in UV or I_2 chamber. After the reaction completion, the mixture was passed through the celite bed and the organic layer evaporated under reduced pressure. The product was isolated by flash column chromatography on neutral silica gel

Procedure for phosphonation of *N*-aryl THIQ derivatives

In a typical experiment, a 15 mL round bottom flask was equipped with a teflon coated magnetic stirring bar. A weighed quantity of THIQ derivative (0.45 mmol) and dialkyl phosphite (0.5 mmol, 1.1 equiv) were added followed by addition of 2 mL of acetonitrile. To the stirring reaction mixture $Co(OAc)_2.4H_2O$ (0.009 mmol, 0.02 equiv) and NHPI (0.09 mmol, 0.2 equiv) was added successively. The reaction mixture was stirred at room temperature in the O_2 atmosphere and the reaction progress was monitored by TLC visualized in UV or I_2 chamber. After the reaction completion, the mixture was passed through the celite bed and the organic layer evaporated under reduced pressure. The product was isolated by flash column chromatography on silica gel (mesh 100–200).

Procedure for oxidative coupling of *N*-aryl THIQ derivatives with active methylene compound and other nucleophiles

In a typical experiment, a 15 mL round bottom flask was equipped with a teflon coated magnetic stirring bar. A weighed quantity of THIQ derivative (0.5 mmol) and pronucleophile [diethyl malonate or dimethyl malonate or ethyl cyanoacetate or malononitrile (0.85 mmol, 1.7 equiv) and phenol or 4-hydroxycoumarin or phthalimide (0.58 mmol, 1.16 equiv)] was added followed by addition of 2.3 mL of acetonitrile. To the stirring reaction mixture $Co(OAc)_2.4H_2O$ (0.01 mmol, 0.02 equiv) and NHPI (0.1 mmol, 0.2 equiv) was added successively. The reaction mixture was stirred at room temperature in the O_2 atmosphere or open to air and the reaction progress was monitored by TLC visualized in UV or I_2 chamber.

After that reaction mixture pass through the celite bed and the organic layer evaporated under reduced pressure. The product was isolated by flash column chromatography on neutral silica gel (mesh 100–200).

Procedure for the synthesis of 3c on gram scale

In 50 mL round bottom flask equipped with a teflon coated magnetic stirring bar, a 1.03 g of *N*-(4-methoxy phenyl)-1,2,3,4-tetrahydroisoquinoline (4.3 mmol) and 850 μL of ethyl cyanoformate (8.6 mmol) were added followed by addition of 25 mL of acetonitrile. To the stirred uniform reaction mixture, 21.5 mg of $Co(OAc)_2.4H_2O$ (0.086 mmol) and 140 mg of NHPI (0.86 mmol) were added successively. The reaction mixture was stirred at room temperature in the O_2 atmosphere (oxygen balloon used) and the reaction progress was monitored by TLC (mobile phase: petroleum ether/ ethyl acetate = 8:2). After that, the reaction mass was passed through the celite bed and the organic layer evaporated under reduced pressure. The product 3c was eluted in 4% ethyl acetate in petroleum ether from column chromatography on neutral silica gel (mesh 60–120) and afforded 0.82 g in 72% yield.

General procedure for the preparation of *N*-aryl-1,2,3,4-tetrahydroisoquinoline derivatives

Copper (I) Iodide (1.2 mmol, 10 mol%) and potassium phosphate (24 mmol, 2 equiv) were taken into the 100 mL two neck round bottomed flask with a condenser and filled with nitrogen gas. 2-propanol (25 mL) and ethylene glycol (24 mmol, 2 equiv) were added by syringe and allowed to stir for 5-10 min at room temperature. Aryl iodides (12 mmol, 1 equiv) and secondary amine (14.4 mmol, 1.2 equiv) were added successively at room temperature. The reaction mixture was heated up to reflux temperature for 30 hrs and then allowed to cool to room temperature. The solvent was removed under *vacuo*, water *ca* 10mL was added and

extracted with dichloromethane/diethyl ether. The organic layer was dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure and purified by column chromatography on neutral silica gel (hexane/ethyl acetate = 95:5) to give the desired product.

General procedure for *N*-methylation of indole derivatives

In 100 mL round bottom flask equipped with a teflon coated magnetic stirring bar, a solution of indole derivative (10 mmol) in THF (30 mL) was prepared. To the stirring reaction mixture NaH (600 mg, 60 % dispersed in mineral oil, 15 mmol) was added at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 20 minutes and 1.5h at room temperature. After the stirring at room temperature, it was cooled to 0 ^{o}C and iodomethane (834 μL, 13.5 mmol) was added slowly within 5-10 min. After the complete addition of iodomethane, the reaction mixture was allowed to cool room temperature and further stirred till reaction completion as monitored by TLC. The reaction mixture was cooled to 0 ^{o}C and quenched with saturated NH_4Cl (50 mL), and extracted with diethyl ether (3 x 15 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude mass was purified by flash chromatography (eluent: petroleum ether/EtOAc 10:1). The products were charactarized by NMR spectroscopy.

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (3a)[37]

White solid; mp: 95–96 ^{o}C, 107 mg, 91% yield, R_f = 0.5 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.32 – 7.20 (m, 4H), 7.11 – 7.05 (m, 2H), 7.04 – 6.98 (m, 1H), 5.50 (s, 1H), 3.75 (m, 1H), 3.46 (m, 1H), 3.14 (m, 1H), 2.94 (dt, J = 16.3, 3.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 134.6, 129.6, 129.6, 129.4, 128.8, 127.1, 126.7, 121.9, 117.8, 117.6, 53.2, 44.2, 28.5

2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (3b)[38]

White solid; mp: 94–96 °C, 102 mg, 82% yield, R_f = 0.5 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.09 (m, 6H), 7.00 (d, J = 8.3 Hz, 2H), 5.45 (s, 1H), 3.69 (dd, J = 11.5, 5.4 Hz, 1H), 3.51 – 3.36 (m, 1H), 3.23 – 3.06 (m, 1H), 2.93 (d, J = 16.3 Hz, 1H), 2.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.25, 134.5, 131.8, 130.1, 129.6, 129.4, 128.7, 127.1, 126.75, 118.3, 117.7, 54.1, 44.4, 28.6, 20.6

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (3c)[37]

Pale yellow solid; mp: 107–108 °C, 106 mg, 80% yield, R_f = 0.45 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 4H), 7.09 – 7.03 (m, 2H), 6.92 – 6.86 (m, 2H), 5.34 (s, 1H), 3.76 (s, 3H), 3.55 (dd, J = 12.1, 6.0 Hz, 1H), 3.40 (td, J = 11.7, 3.9 Hz, 1H), 3.13 (m, 1H), 2.89 (d, J = 16.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7, 142.6, 134.4, 129.7, 129.5, 128.7, 127.1, 126.7, 121.0, 117.65, 114.8, 55.6, 44.9, 28.7

2-(4-Cyanophenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (3d)[39]

Yellow solid; mp: 151–152 °C, 112 mg, 86% yield, R_f =0.45 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2H), 7.29 (dd, J = 25.5, 9.4 Hz, 4H), 7.00 (d, J = 8.2 Hz, 2H), 5.58 (s, 1H), 3.99 – 3.70 (m, 1H), 3.57 (s, 1H), 3.08 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5, 134.6, 133.8, 129.3, 129.1, 128.7, 127.4, 127.0, 119.4, 117.4, 114.7, 102.5, 50.05, 43.7, 28.2

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (3e)[10a]

White solid; mp: 152–153 °C, 113 mg, 84% yield, R_f = 0.45 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 15.3, 6.4 Hz, 5H), 7.24 – 7.20 (m, 1H), 7.02 – 6.95 (m, 2H), 5.43 (s, 1H), 3.74 – 3.64 (m, 1H), 3.44 (m, 1H), 3.13 (m, 1H), 2.95 (dt, J = 16.3, 3.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.34, 134.73, 129.87, 129.71, 129.57, 129.25, 127.39, 127.32, 119.23, 117.79, 53.49, 44.66, 28.78

6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (3f)[11b]

Yellow solid; mp: 137–138 °C, 118 mg, 80% yield, R_f = 0.35 (mobile phase: petroleum ether/ ethyl acetate = 8:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.7 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 7.3 Hz, 1H), 6.68 (d, J = 26.9 Hz, 2H), 5.41 (s, 1H), 3.85 (s, 6H), 3.73 (dd, J = 12.0, 4.6 Hz, 1H), 3.40 (td, J = 11.9, 3.6 Hz, 1H), 3.11 – 2.98 (m, 1H), 2.81 (d, J = 16.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.37, 148.43, 148.06, 129.53, 126.87, 121.90, 121.08, 117.88, 117.71, 111.52, 109.32, 56.07, 55.94, 53.05, 44.18, 28.09

2-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (3g)[27]

White crystalline solid; mp 153–155 °C; 125 mg, 76% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 7:3). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.9 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 6.69 (d, J = 23.2 Hz, 2H), 5.37 (s, 1H), 3.85 (d, J = 2.1 Hz, 6H), 3.68 (dd, J = 12.3, 4.2 Hz, 1H), 3.44 – 3.33 (m, 1H), 3.04 (m, 1H), 2.82 (dt, J = 16.1, 3.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.37, 148.03, 146.94, 129.35, 126.86, 126.55, 120.59, 118.85, 117.51, 111.41, 109.18, 55.97, 55.85, 52.82, 44.19, 27.86

2-(Methyl(phenyl)amino)acetonitrile (3h)[37]

Colorless oil; 58 mg, 80% yield, R_f = 0.6 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 6.88 (tt, J = 7.5, 1.0 Hz, 1H), 6.83 – 6.78 (m, 2H), 4.04 (s, 2H), 2.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.74, 129.40, 119.97, 115.62, 114.70, 42.03, 39.08

1-Phenylpiperidine-2-carbonitrile (3i)[37]

Light brown oil; 73 mg, 78% yield, R_f = 0.55 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H), 7.05 – 6.97 (m, 3H), 4.64 (t, J = 3.5 Hz, 1H), 3.51 – 3.42 (m, 1H), 3.05 (td, J = 12.0, 2.6 Hz, 1H), 2.10 – 1.96 (m, 2H), 1.92 –

1.81 (m, 2H), 1.78 – 1.65 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7, 129.3, 122.1, 118.3, 117.1, 52.0, 46.5, 29.2, 25.1, 20.15

4-Phenylmorpholine-3-carbonitrile (3j)[40]

Colourless viscous Oil; 78 mg, 83% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H), 7.09 – 7.03 (m, 1H), 7.03 – 6.97 (m, 2H), 4.47 – 4.41 (m, 1H), 4.20 – 4.15 (m, 1H), 4.14 – 4.08 (m, 1H), 3.93 (dd, J = 11.5, 2.8 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.30 (dd, J = 8.1, 2.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.3, 129.7, 122.7, 117.3, 116.0, 68.1, 67.0, 51.1, 45.5

***tert*-Butyl 1-*oxo*-3,4-dihydroisoquinoline-2(*1H*)-carboxylate (3k)[41]**

White solid; mp: 70–73 ^{o}C, 101 mg, 82% yield, R_f = 0.45 (mobile phase: petroleum ether/ ethyl acetate = 8:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H), 3.99 (dd, J = 8.8, 3.3 Hz, 2H), 3.00 (t, J = 6.0 Hz, 2H), 1.59 (d, J = 1.0 Hz, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9, 153.1, 139.5, 132.8, 129.6, 129.3, 127.2, 127.1, 83.2, 44.4, 28.3, 28.1

1-(*1H*-Indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5aa)[42]

White solid; mp: 167–169 ^{o}C, 120 mg, 82% yield, R_f = 0.25 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.23 (m, 8H), 7.02 (d, J = 8.0 Hz, 3H), 6.77 (t, J = 7.2 Hz, 1H), 6.63 (s, 1H), 6.17 (s, 1H), 3.62 (dd, J = 7.4, 4.6 Hz, 2H), 3.07 (dt, J = 15.6, 7.7 Hz, 1H), 2.80 (dt, J = 16.1, 4.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.8, 137.4, 136.6, 135.6, 129.2, 128.8, 128.0, 126.7, 126.5, 125.7, 124.15, 122.1, 120.1, 119.6, 119.3, 118.1, 115.9, 111.0, 56.7, 42.3, 26.65

1-(5-Bromo-*1H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5ab)[25a]

Yellow solid; mp: 186–188 ^{o}C, 142 mg, 78% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 8:2). **^{1}H NMR** (400 MHz, DMSO) δ 11.08 (s, 1H), 7.55 (s, 1H), 7.29 (dd, J =

11.4, 7.1 Hz, 2H), 7.20 – 7.07 (m, 6H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.79 (s, 1H), 6.65 (t, *J* = 7.2 Hz, 1H), 6.21 (s, 1H), 3.59 – 3.43 (m, 2H), 3.02 – 2.91 (m, 1H), 2.82 (dd, *J* = 11.7, 4.7 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO) δ 149.6, 137.9, 135.6, 135.3, 129.5, 128.9, 128.2, 128.2, 127.0, 126.5, 126.1, 123.9, 121.9, 117.9, 117.75, 115.3, 114.0, 111.65, 55.7, 42.0, 26.7

3-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-*1H*-indole-5-carbonitrile (5ac)

Light brown solid; mp: 215–217 ^{o}C, 109 mg, 69% yield, R_f = 0.32 (mobile phase: petroleum ether/ ethyl acetate = 7:3). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.47 – 7.30 (m, 3H), 7.27 – 7.14 (m, 6H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.76 (s, 1H), 6.10 (s, 1H), 3.67 – 3.43 (m, 2H), 3.14 – 2.97 (m, 1H), 2.80 (dt, *J* = 16.3, 4.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.8, 138.3, 136.6, 135.4, 129.3, 127.9, 125.9, 119.3, 116.9, 116.8, 112.1, 112.0, 56.8, 42.8, 26.7 **FTIR-ATR** (neat, cm^{-1}): 3401, 3309, 2921, 2218, 1593, 1498, 1468, 1425, 1349, 1282, 1213, 1129, 1095, 1031, 937, 882, 806, 750, 684, 642, 610, 521, 495 **HRESI-MS** (m/z): calculated for $C_{24}H_{20}N_3^+$ (M + H): 350.1652, Found (M + H): 350.1646

1-(5-Bromo-*1H*-indol-3-yl)-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline (5bb)

Off white solid; mp: 143–145 ^{o}C, 139 mg, 74% yield, R_f = 0.37 (mobile phase: petroleum ether/ ethyl acetate = 8:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.51 (s, 1H), 7.16 (td, *J* = 20.6, 11.2 Hz, 6H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.50 (s, 1H), 5.98 (s, 1H), 3.50 (d, *J* = 4.5 Hz, 2H), 3.03 (dt, *J* = 15.7, 7.9 Hz, 1H), 2.75 (d, *J* = 16.5 Hz, 1H), 2.26 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.8, 137.05, 135.3, 135.05, 129.7, 128.9, 128.65, 128.3, 128.0, 126.7, 125.7, 125.6, 124.9, 122.7, 118.9, 117.55, 112.9, 112.4, 57.1, 42.8, 26.5, 20.5. **FTIR-ATR** (neat, cm^{-1}) 3144, 3023, 2919, 1512, 1451, 1423, 1338, 1210, 1118, 1041, 1012, 918, 870, 840, 813, 792, 764, 732, 671, 613, 561, 529, 513, 488. **HRESI-MS** (m/z): calculated for $C_{24}H_{22}BrN_2^+$ (M + H): 417.0961, Found (M + H): 417.0956

1-(1-Methyl-*1H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5ad)[42]

White solid; mp: 126–128 ^{o}C, 128 mg, 84% yield, R_f = 0.25 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.41 – 6.89 (m, 11H), 6.75 (t, J = 7.3 Hz, 1H), 6.48 (s, 1H), 6.17 (s, 1H), 3.59 (s, 5H), 3.04 (m, 1H), 2.78 (dt, J = 16.2, 4.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.8, 137.65, 137.4, 135.6, 129.3, 128.8, 128.8, 128.1, 126.9, 126.7, 125.75, 121.7, 120.2, 119.2, 118.0, 117.7, 115.65, 109.2, 56.6, 42.2, 32.7, 26.7

2-(4-Methoxyphenyl)-1-(1-methyl-*1H*-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (5cd)[43]

White solid; mp: 142–143 ^{o}C, 129 mg, 78% yield, R_f = 0.2 (mobile phase: petroleum ether/ ethyl acetate = 9:1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.0 Hz, 1H), 7.27 – 7.06 (m, 6H), 7.04 – 6.87 (m, 3H), 6.84 – 6.68 (m, 2H), 6.40 (s, 1H), 5.97 (s, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 3.57 – 3.39 (m, 2H), 3.01 (m, Hz, 1H), 2.76 (dt, J = 16.4, 3.8 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 144.7, 137.7, 137.2, 135.4, 129.0, 128.9, 128.2, 127.25, 126.4, 125.7, 121.5, 120.3, 119.3, 119.0, 117.6, 114.45, 109.1, 57.7, 55.6, 43.5, 32.7, 26.7

1-(5-Bromo-1-methyl-*1H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5ae)

Pale yellow solid; mp: 127–129 ^{o}C, 156 mg, 83% yield, R_f = 0.5 (mobile phase: petroleum ether/ ethyl acetate = 6:1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 1.5 Hz, 1H), 7.17 (m, 7H), 7.05 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 7.9 Hz, 2H), 6.77 (t, J = 7.3 Hz, 1H), 6.44 (s, 1H), 6.04 (s, 1H), 3.56 (s, 5H), 3.01 (dt, J = 15.7, 7.7 Hz, 1H), 2.76 (dt, J = 16.3, 4.3 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.8, 137.2, 136.0, 135.4, 130.0, 129.2, 128.9, 128.4, 127.9, 126.8, 125.8, 124.5, 122.7, 118.6, 117.3, 116.3, 112.6, 110.7, 56.6, 42.4, 32.9, 26.6. **FTIR-ATR** (neat, cm^{-1}) 3017, 2942, 2899, 1594, 1500, 1472, 1387, 1285, 1217, 1139, 1108, 1030, 993, 938, 864, 779, 794, 761, 745, 692, 648, 626, 587 **HRESI-MS** (m/z): calculated for $C_{24}H_{21}BrKN_2^+$ (M + K): 455.0520, Found (M + K): 455.0523

1-Methyl-3-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-*1H*-indole-5-carbonitrile (5af)

Brown solid; mp: 149–152 °C, 119 mg, 73% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 8:3). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.32 – 7.13 (m, 7H), 7.00 (d, J = 8.0 Hz, 2H), 6.84 (t, J = 7.3 Hz, 1H), 6.61 (s, 1H), 6.10 (s, 1H), 3.69 (s, 3H), 3.64 – 3.48 (m, 2H), 3.13 – 3.00 (m, 1H), 2.80 (d, J = 16.4 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7, 138.7, 136.7, 135.4, 130.9, 129.3, 129.0, 127.8, 126.95, 126.5, 126.0, 125.9, 124.6, 120.9, 119.1, 118.8, 116.6, 110.0, 102.1, 56.7, 42.6, 32.9, 26.6. **FTIR-ATR** (neat, cm^{-1}) 1317, 2937, 2887, 2215, 1595, 1500, 1386, 1285, 1220, 1139, 1109, 938, 886, 844, 808, 745, 692, 630, 522 **HRESI-MS** (m/z): calculated for $C_{25}H_{21}N_3Na_+$ (M + Na): 386.1628, Found (M + Na): 386.1615

1-(Nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (7aa)[12a]

Yellow solid; mp: 90-91 °C, 121 mg, 90% yield, R_f = 0.7 (mobile phase: petroleum ether/ ethyl acetate = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.07 (m, 6H), 6.98 (d, J = 8.2 Hz, 2H), 6.85 (t, J = 7.1 Hz, 1H), 5.55 (t, J = 7.1 Hz, 1H), 4.87 (dd, J = 11.7, 7.9 Hz, 1H), 4.56 (dd, J = 11.8, 6.6 Hz, 1H), 3.75 – 3.53 (m, 2H), 3.18 – 2.99 (m, 1H), 2.79 (dt, J = 16.2, 4.7 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 135.3, 132.9, 129.5, 129.2, 128.1, 127.0, 126.7, 119.4, 115.1, 78.8, 58.2, 42.05, 26.4

1-(Nitromethyl)-2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline (7ba)[12a]

Off white solid; mp: 93-94 °C, 121 mg, 86% yield, R_f = 0.6 (mobile phase: petroleum ether/ ethyl acetate = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 6.88 (m, 6H), 6.79 (d, J = 8.5 Hz, 2H), 5.39 (t, J = 7.2 Hz, 1H), 4.73 (dd, J = 11.8, 8.2 Hz, 1H), 4.44 (dd, J = 11.8, 6.3 Hz, 1H), 3.62 – 3.38 (m, 2H), 3.05 – 2.86 (m, 1H), 2.63 (dt, J = 16.4, 4.4 Hz, 1H), 2.16 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.4, 135.4, 132.9, 130.0, 129.3, 129.1, 128.0, 127.0, 126.6, 115.9, 78.8, 58.4, 42.3, 26.2, 20.4

2-(4-Methoxyphenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (7ca)[44]

Yellow Oil; 115 mg, 77% yield, R_f = 0.21 (mobile phase: petroleum ether/ ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.09 (m, 4H), 6.91 (d, J = 9.1 Hz, 2H), 6.81 (d, J = 9.1 Hz, 2H), 5.38 (dd, J = 8.4, 6.0 Hz, 1H), 4.81 (dd, J = 11.9, 8.7 Hz, 1H), 4.55 (dd, J = 11.9, 5.8 Hz, 1H), 3.74 (s, 1H), 3.55 (td, J = 6.1, 3.6 Hz, 1H), 3.00 (m, 1H), 2.68 (dt, J = 16.5, 3.8 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.9, 143.0, 135.4, 132.8, 129.45, 127.9, 126.9, 126.6, 118.8, 114.7, 78.9, 58.9, 55.55, 43.1, 25.7

4-(1-(Nitromethyl)-3,4-dihydrisoquinolin-2(*1H*)-yl)benzonitrile (7da)[44]

Pale yellow solid; mp: 125–127 ^{o}C, 122 mg, 83% yield, R_f = 0.45 (mobile phase: petroleum ether/ ethyl acetate = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, J = 9.0 Hz, 2H), 7.24 (m, 3H), 7.13 (t, J = 6.3 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 5.61 (t, J = 7.2 Hz, 1H), 4.83 (dd, J = 12.0, 7.5 Hz, 1H), 4.58 (dd, J = 12.0, 6.9 Hz, 1H), 3.66 (t, J = 6.1 Hz, 2H), 3.11 (m, 1H), 2.88 (dt, J = 16.2, 5.7 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.55, 137.3, 136.5, 134.8, 131.8, 131.4, 129.8, 129.7, 122.55, 115.9, 103.15, 80.9, 60.1, 44.4, 29.45

1-(1-Nitroethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (7ab)[12a]

Yellow oil; 110 mg, 78% yield, R_f = 0.8 (mobile phase: petroleum ether/ ethyl acetate = 9:1).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 6.90 (m, 8H), 6.80 (dt, J = 7.2, 2.9 Hz, 1H), 5.23 (t, J = 9.4 Hz, 1H), 5.12 – 4.78 (m, 1H), 3.92 – 3.42 (m, 2H), 3.03 (dt, J = 13.8, 6.8 Hz, 1H), 2.87 (ddd, J = 20.9, 13.6, 6.0 Hz, 1H), 1.59 (dd, J = 64.6, 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.1, 148.9, 135.6, 134.8, 133.8, 132.0, 129.4, 129.3, 129.1, 128.7, 128.4, 128.2, 127.25, 126.6, 126.1, 119.3, 118.8, 115.4, 114.45, 89.0, 85.4, 62.7, 61.15, 43.5, 42.6, 26.7, 26.4, 17.4, 16.4

1-(1-Nitroethyl)-2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline (7bb)[44]

Viscous red oil; 111 mg, 75% yield, R_f = 0.7 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 6.90 (m, 6H), 6.82 (d, J = 8.4 Hz, 2H), 5.14 – 5.05 (m, 1H), 5.01 – 4.74 (m, 1H), 3.82 – 3.37 (m, 2H), 3.82 – 3.37 (m, 2H), 2.17 (d, J = 9.7 Hz, 3H), 1.54 (dd, J = 63.2, 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1, 146.7, 135.7, 134.8, 133.7, 132.0, 129.9, 129.8, 129.1, 128.9, 128.75, 128.3, 128.1, 127.2, 126.5, 126.0, 116.0, 115.1, 88.9, 85.5, 62.9, 61.4, 43.85, 43.0, 26.5, 26.2, 20.3, 17.35, 16.4

Dimethyl (2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (9aa)[45]

Pale yellow liquid; 97 mg, 68% yield, R_f = 0.5 (mobile phase: petroleum ether/ ethyl acetate = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 1H), 7.27 – 7.13 (m, 5H), 6.97 (d, J = 8.2 Hz, 2H), 6.80 (t, J = 7.3 Hz, 1H), 5.20 (d, J = 20.0 Hz, 1H), 4.03 – 3.97 (m, 1H), 3.64 (dd, J = 10.4, 7.1 Hz, 7H), 3.13 – 2.92 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 149.2 (d, J = 6.0 Hz), 136.4 (d, J = 5.6 Hz), 130.4, 129.25, 128.8 (d, J = 2.6 Hz), 127.9 (d, J = 4.6 Hz), 127.55 (d, J = 3.5 Hz), 126.1 (d, J = 2.8 Hz), 118.7, 114.7, 58.7 (d, J = 159.6 Hz), 54.0 (d, J = 7.2 Hz), 52.95 (d, J = 7.7 Hz), 43.5, 26.7

Diethyl (2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (9ab)[46]

Pale yellow liquid; 124 mg, 80% yield, R_f = 0.5 (mobile phase: petroleum ether/ ethyl acetate = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, J = 6.5 Hz, 1H), 7.23 – 7.00 (m, 5H), 6.90 (d, J = 8.2 Hz, 2H), 6.71 (t, J = 7.2 Hz, 1H), 5.11 (d, J = 20.0 Hz, 1H), 4.20 – 3.71 (m, 5H), 3.63 – 3.45 (m, 1H), 3.09 – 2.82 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.35 (d, J = 5.8 Hz), 136.4 (d, J = 5.6 Hz), 130.6 (s), 129.1 (s), 128.7 (d, J = 2.6 Hz), 128.1 (d, J = 4.6 Hz), 127.4 (d, J = 3.5 Hz), 125.85 (d, J = 2.8 Hz), 118.4 (s), 114.7 (s), 63.3 (d, J = 7.3 Hz), 62.3 (d, J = 7.7 Hz), 58.8 (d, J = 159.3 Hz), 43.45 (s), 26.7 (s), 16.45 (d, J = 5.5 Hz), 16.36 (d, J = 5.9 Hz)

Diisopropyl (2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (9ac)[46]

Pale yellow liquid; 126 mg, 75% yield, R_f = 0.5 (mobile phase: petroleum ether/ ethyl acetate = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, J = 5.7 Hz, 1H), 7.25 – 7.07 (m, 4H), 6.94 (d, J = 8.2 Hz, 2H), 6.75 (t, J = 7.2 Hz, 1H), 5.14 (d, J = 21.1 Hz, 1H), 4.62 (ddd, J = 12.6, 6.3, 2.7 Hz, 2H), 4.09 – 3.99 (m, 1H), 3.69 – 3.59 (m, 1H), 2.99 (dt, J = 11.9, 10.9 Hz, 2H), 1.28 (t, J = 6.4 Hz, 7H), 1.15 (d, J = 6.1 Hz, 3H), 0.94 (d, J = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 149.5 (d, J = 6.6 Hz), 136.4 (d, J = 5.5 Hz), 130.9 (d, J = 1.2 Hz), 129.0, 128.7 (d, J = 2.5 Hz), 127.3 (d, J = 3.4 Hz), 125.6 (d, J = 2.8 Hz), 118.3, 115.0, 72.25 (d, J = 7.8 Hz), 70.8 (d, J = 8.2 Hz), 58.75 (d, J = 161.1 Hz), 43.5, 26.6, 24.61 (d, J = 2.8 Hz), 24.15 (d, J = 3.2 Hz), 23.75 (d, J = 5.7 Hz), 23.31 (d, J = 5.6 Hz)

Dimethyl (2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonates (9ca)[12a]

Red oily liquid; 103 mg, 66% yield, R_f =0.2 (mobile phase: petroleum ether/ ethyl acetate = 7:3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 (d, J = 3.1 Hz, 1H), 7.19 – 7.08 (m, 3H), 6.91 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.1 Hz, 2H), 5.04 (d, J = 21.4 Hz, 1H), 4.06 – 3.93 (m, 1H), 3.73 (s, 3H), 3.66 (dd, J = 10.4, 4.8 Hz, 6H), 3.58 – 3.48 (m, 1H), 2.90 (d, J = 2.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.2, 143.9 (d, J = 8.5 Hz), 136.3 (d, J = 5.9 Hz), 130.1, 129.0 (d, J = 2.6 Hz), 127.9 (d, J = 4.5 Hz), 126.0 (d, J = 3.0 Hz), 117.7, 114.5, 59.3 (d, J = 159.1 Hz), 55.6, 54.1 (d, J = 7.2 Hz), 53.0 (d, J = 7.7 Hz), 44.7, 26.0

Diethyl (2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (9bb)[46]

Yellow oily liquid; 126 mg, 78% yield, R_f =0.2 (mobile phase: petroleum ether/ ethyl acetate = 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, J = 4.6 Hz, 1H), 7.18 (t, J = 24.6 Hz, 3H), 7.04 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 7.9 Hz, 2H), 5.12 (d, J = 20.8 Hz, 1H), 3.83 – 4.20 (m, 5H), 3.69 – 3.47 (m, 1H), 2.97 (s, 2H), 2.24 (s, 3H), 1.25 (t, J = 6.1 Hz, 3H), 1.14 (t, J = 6.8

Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.4 (d, J = 7.0 Hz), 136.4 (d, J = 5.6 Hz), 130.6 (s), 129.6 (s), 128.8 (d, J = 2.5 Hz), 128.1 (d, J = 4.5 Hz), 127.9 (s), 127.3 (d, J = 3.4 Hz), 125.8 (d, J = 2.8 Hz), 115.3 (s), 63.35 (d, J = 7.2 Hz), 62.3 (d, J = 7.6 Hz), 59.0 (d, J = 159.5 Hz), 43.8 (s), 26.4 (s), 20.3 (s), 16.46 (d, J = 5.5 Hz), 16.36 (d, J = 5.8 Hz)

Diethyl (2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (9cb)[46]

Red oily liquid; 122 mg, 72% yield, R_f =0.2 (mobile phase: petroleum ether/ ethyl acetate = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 – 7.33 (m, 1H), 7.25 – 7.06 (m, 3H), 6.92 (d, J = 9.1 Hz, 2H), 6.81 (dd, J = 9.8, 2.8 Hz, 2H), 5.02 (d, J = 21.5 Hz, 1H), 4.17 – 3.90 (m, 5H), 3.74 (s, 3H), 3.54 (dt, J = 10.2, 4.8 Hz, 1H), 2.99 – 2.85 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.0, 144.1 (d, J = 8.3 Hz), 136.4 (d, J = 5.7 Hz), 130.4, 128.9 (d, J = 2.5 Hz), 128.1 (d, J = 4.4 Hz), 127.25 (d, J = 3.6 Hz), 125.8 (d, J = 2.9 Hz), 117.5, 114.4, 63.4 (d, J = 7.3 Hz), 62.2 (d, J = 7.6 Hz), 59.4 (d, J = 158.8 Hz), 55.6, 44.6, 26.1, 16.46 (d, J = 5.5 Hz), 16.36 (d, J = 5.8 Hz)

Diethyl-2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate (11aa)[46]

Orange oil; 140 mg, 76% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32 – 7.05 (m, 6H), 6.97 (d, J = 8.2 Hz, 2H), 6.74 (t, J = 7.2 Hz, 1H), 5.72 (d, J = 9.2 Hz, 1H), 4.24 – 3.93 (m, 4H), 3.90 (d, J = 9.2 Hz, 1H), 3.75 – 3.57 (m, 2H), 3.05 (ddd, J = 15.5, 8.8, 6.3 Hz, 1H), 2.87 (dt, J = 16.3, 5.0 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.95, 167.1, 148.8, 135.9, 134.8, 129.05, 128.9, 127.5, 127.15, 126.0, 118.4, 115.05, 61.6, 59.5, 57.9, 42.3, 26.1, 13.9, 13.9

Ethyl 2-cyano-2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (11ab)

Yellow viscous oil, 133 mg, 83% yield, R_f = 0.3 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32 – 7.11 (m, 6H), 6.98 (dd, J = 7.9, 4.4 Hz, 2H),

6.88 – 6.81 (m, 1H), 5.52 (dd, *J* = 8.9, 6.0 Hz, 1H), 4.18 (qd, *J* = 7.1, 3.3 Hz, 1H), 4.11 – 3.90 (m, 2H), 3.71 (m, *J* = 18.4, 13.6, 8.6, 5.1 Hz, 1H), 3.52 (dt, *J* = 12.3, 5.9 Hz, 1H), 3.21 – 2.91 (m, 2H), 1.24 – 1.06 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.9, 149.3, 147.9, 129.6, 129.3, 129.1, 128.5, 127.0, 126.6, 126.5, 120.2, 119.6, 117.15, 115.9, 115.1, 63.0, 62.8, 60.0, 59.8, 45.9, 44.2, 43.1, 42.35, 27.3, 26.0, 13.94, 13.84. **FTIR-ATR** (neat, cm^{-1}): 2982, 2936, 2249, 1739, 1598, 1495, 1394, 1369, 1254, 1214, 1157, 1027, 1114, 937, 853, 749, 692, 522. **HRESI-MS** (m/z): calculated for $C_{20}H_{21}N_2O_2^+$ (M + H): 321.1598, Found (M + H): 321.1602

Dimethyl 2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate (11ac)[46]

Yellow thick oil, 136 mg, 80% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 – 7.14 (m, 4H), 7.14 – 7.06 (m, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 5.71 (d, *J* = 9.4 Hz, 1H), 3.95 (d, *J* = 9.4 Hz, 1H), 3.71 – 3.59 (m, 5H), 3.54 (d, *J* = 1.0 Hz, 3H), 3.13 – 2.99 (m, 1H), 2.86 (dt, *J* = 16.5, 4.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.28, 167.4, 148.75, 135.6, 134.8, 129.11, 128.99, 127.6, 127.0, 126.0, 118.6, 115.2, 59.1, 58.2, 52.6, 42.15, 26.0

2-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)malononitrile (11ad)[12a]

Brown oil, 71 mg, 52% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 7:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 – 7.19 (m, 6H), 6.98 (dd, *J* = 11.7, 7.8 Hz, 3H), 5.35 (d, *J* = 4.5 Hz, 1H), 4.18 (d, *J* = 4.6 Hz, 1H), 3.80 (ddd, *J* = 12.3, 7.4, 5.0 Hz, 1H), 3.50 (dt, *J* = 12.2, 6.2 Hz, 1H), 3.17 – 2.95 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.7, 135.6, 130.6, 129.9, 129.3, 129.2, 127.4, 127.0, 121.1, 116.4, 112.2, 111.9, 61.5, 43.4, 29.55, 27.6

1-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (11ae)[47]

Grey solid; mp: 79-80 °C, 107 mg, 81% yield -, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.14 (dd,

J = 12.4, 5.4 Hz, 4H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 7.7 Hz, 1H), 5.39 (t, *J* = 6.3 Hz, 1H), 3.66 – 3.60 (m, 1H), 3.54 – 3.49 (m, 1H), 3.07 – 3.00 (m, 2H), 2.86 – 2.75 (m, 2H), 2.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 207.3, 148.9, 138.3, 134.5, 129.4, 128.7, 126.9, 126.9, 126.3, 118.3, 114.8, 54.8, 50.25, 42.1, 31.15, 27.3

1-(2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (11be)[47]

Grey off white solid; mp: 80-82 °C, 110 mg, 79% yield, R_f = 0.5 (mobile phase: petroleum ether/ ethyl acetate = 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 – 7.07 (m, 4H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 5.33 (t, *J* = 6.4 Hz, 1H), 3.61 (dt, *J* = 12.6, 5.0 Hz, 1H), 3.52 – 3.42 (m, 1H), 3.01 (dd, *J* = 16.0, 6.2 Hz, 2H), 2.82 – 2.71 (m, 2H), 2.24 (s, 3H), 2.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.4, 147.0, 134.45, 129.9, 128.85, 128.0, 126.9, 126.8, 126.25, 115.7, 55.2, 50.1, 42.2, 31.05, 27.0, 20.4

4-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenol (11af)[12a]

Brown thick oil: 90 mg, 60% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 8:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (ddd, *J* = 16.2, 13.2, 6.0 Hz, 6H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 5.77 (s, 1H), 3.67 (dt, *J* = 11.2, 5.6 Hz, 1H), 3.54 – 3.42 (m, 1H), 3.00 – 2.81 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.5, 149.6, 138.0, 135.6, 135.1, 129.1, 128.65, 128.1, 126.9, 117.5, 115.0, 114.1, 62.25, 43.5, 27.9

4-Hydroxy-3-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-*2H*-chromen-2-one (11ag)[12a]

Pale yellow solid; *mp*: 137-139 °C, 166 mg, 90% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.46 – 7.36 (m, 4H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.24 – 7.09 (m, 6H), 6.16 (s, 1H), 3.69 (dd, *J* = 11.8, 3.5 Hz, 1H), 3.60 – 3.46 (m, 1H), 3.25 (td, *J* = 12.1, 2.8 Hz, 1H), 2.95 (d, *J* = 16.4 Hz,

1H), 1.97 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.1, 164.0, 153.3, 148.5, 132.7, 132.0, 129.6, 128.25, 127.4, 127.0, 126.2, 123.6, 123.25, 122.35, 116.4, 104.7, 58.2, 54.9, 30.3

4-Hydroxy-3-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-*2H*-chromen-2-one (11cg)[12a]

Yellow solid; *mp*: 144–146 °C, 136 mg, 68% yield, R_f = 0.3 (mobile phase: petroleum ether/ ethyl acetate = 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 (d, J = 6.4 Hz, 1H), 7.41 (d, J = 35.0 Hz, 4H), 7.23 (dd, J = 22.7, 14.2 Hz, 5H), 6.85 (d, J = 6.3 Hz, 2H), 6.08 (s, 1H), 3.75 (s, 3H), 3.56 (d, J = 13.5 Hz, 2H), 3.28 (s, 1H), 2.96 (d, J = 14.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.9, 164.1, 157.9, 153.4, 140.9, 135.6, 132.4, 131.9, 128.2, 127.4, 127.0, 123.5, 123.3, 116.8, 116.4, 114.8, 104.0, 59.4, 55.4, 54.95, 30.1

2-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)isoindoline-1,3-dione (11ah)[12a]

Brownish yellow viscous oil; 97 mg, 55% yield, R_f = 0.4 (mobile phase: petroleum ether/ ethyl acetate = 8:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 5.1, 3.0 Hz, 2H), 7.63 (dd, J = 5.2, 3.0 Hz, 2H), 7.24 (t, J = 7.0 Hz, 4H), 7.12 (d, J = 5.3 Hz, 5H), 6.81 (t, J = 7.2 Hz, 1H), 4.17 – 4.05 (m, 1H), 3.81 (dd, J = 7.4, 4.4 Hz, 1H), 3.10 (d, J = 4.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6, 147.8, 135.8, 134.3, 134.0, 132.55, 131.75, 129.15, 128.5, 127.95, 126.4, 126.4, 123.5, 123.3, 119.8, 116.4, 63.7, 42.15, 29.0

2-phenyl-3,4-dihydroisoquinolin-1(*2H*)-one (12)[48]

White solid; mp: 118-121 ^{o}C, 190 mg, 85% yield, R_f = 0.5 (mobile phase: petroleum ether/ ethyl acetate =7:3). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.5 Hz, 1H), 7.51 – 7.34 (m, 6H), 7.25 (td, J = 6.8, 2.2 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H), 3.14 (t, J = 6.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2, 143.1, 138.3, 132.0, 129.7, 128.9, 128.7, 127.2, 126.9, 126.2, 125.3, 49.4, 28.6

5-Bromo-1-methyl-1*H*-indole[49]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 0.4 Hz, 1H), 7.24 (dd, J = 8.7, 1.1 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 3.0 Hz, 1H), 6.37 (d, J = 3.0 Hz, 1H), 3.66 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.35, 130.1, 130.03, 124.25, 123.2, 112.6, 110.7, 100.5, 33.0

1-Methyl-1*H* -indole-5-carbonitrile[50]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 0.7 Hz, 1H), 7.37 (dd, J = 8.5, 1.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 3.1 Hz, 1H), 6.52 (d, J = 3.1 Hz, 1H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 131.2, 128.1, 126.3, 124.2, 121.0, 110.1, 102.05, 102.0, 33.0

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SUPPORTING INFORMATION

Screening study of other Metal Salts for CDC Reaction, mass spectrometry data of control experiments and the copies of ^{1}H and ^{13}C NMR spectra.

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