Platinum-catalyzed cross-dehydrogenative coupling reaction in the absence of oxidant†

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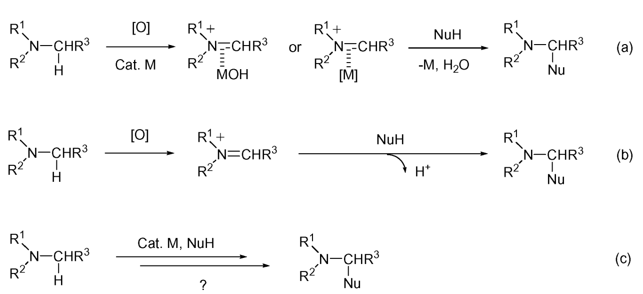
A third strategy for cross-dehydrogenative coupling reaction has been reported *via* platinum-catalyzed sp^3 C–H and sp^3 C–H coupling reaction in the absence of oxidant. Nitroalkanes as well as dialkyl malonate derivatives, β-keto esters and malononitrile are active participants in this coupling reaction. Both cyclic and acyclic non-activated simple ketones are good reactants in this reaction.

The development of catalytic reactions which involve the cleavage of C–H bonds is one of the most challenging projects in organic synthesis.[1] Despite significant progress in this area, catalytic intermolecular transformations of sp^3 C–H bonds to C–C bonds still remain rare.[2] Based on a recent literature survey, sp^3 C–H bonds adjacent to a nitrogen atom are more reactive, and their functionalization catalyzed by transition metals has attracted great attention.[3] These reactions always involve α-C–H activation and subsequent carbon–carbon bond formation. Among these reactions, the oxidative cross-dehydrogenative coupling (CDC) reaction is an attractive strategy. In this case, generation of iminium ion intermediates followed by reactions with carbon pronucleophiles would give α-substituted products.

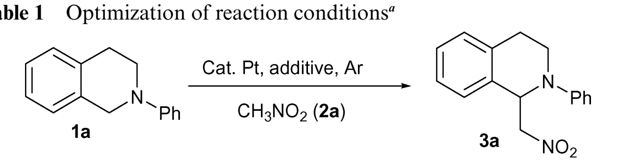
Based on recent literature precedent regarding CDC reactions, the two pathways have been developed to achieve this transformation: (i) the route using treatment with metal catalysts in the presence of oxidants (Scheme 1a);[4] (ii) the route using treatment with oxidants (Scheme 1b).[5] The former pathway was started by Murahashi using a Ru(III) catalyst with O_2 or H_2O_2 as oxidants.[4a–c] Copper-catalyzed oxidative CDC reactions were reported by Li and others, where ^{t}BuOOH, O_2, NBS and diethyl azodicarboxylate (DEAD) are good oxidants.[4d–p] When rhodium was used, a strong oxidant such as T-HYDRO (70% ^{t}BuOOH in water) was needed.[4q] Iron–(^{t}BuO)$_2$[4r] and vanadium–^{t}BuOOH[4s] systems also showed high catalytic activity in CDC reactions. On the other hand, due to the high reactivity of the iminium intermediate, such a complex could react with nucleophiles in the absence of metal catalyst. Todd's[5a] and our[5b] recent works have shown this interesting transformation by using DDQ and PhI(OAc)$_2$, respectively. However, for the above two pathways, an oxidant is always needed. Such a protocol is not ideal from the viewpoint of atom efficiency and safety of the reaction. Herein we report a third way *via* platinum-catalyzed CDC reaction in the absence of oxidant (Scheme 1c).



Scheme 1 General pathways for CDC reaction.

We started by using the tetrahydroisoquinoline **1a** (0.2 mmol) with 10 mol% of $PtCl_2$ under argon in CH_3NO_2 (1 mL) at 85 °C, and the coupling product **3a** was obtained in 34% yield after 24 h (Table 1, entry 1). To our delight, the mixed solvent CH_3NO_2–H_2O (10 : 1) afforded a good yield of the desired product (Table 1, entry 2). Addition of hexafluoroisopropanol (HFIP) improved the reaction efficiency and product yield (Table 1, entry 3). Further investigation of the effect of acids indicated that weakly acidic 5 Å molecular sieves in water gave the best result (Table 1, entries 3–7). After this, studies were conducted on the amount of water added and catalyst loading as well as other platinum catalytic

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Additive	Time/h	Yield of **3a** (%)
1[b]	$PtCl_2$ (10%)	—	24	34
2	$PtCl_2$ (10%)	—	16	72
3	$PtCl_2$ (10%)	HFIP (1 equiv)[d]	9	75
4	$PtCl_2$ (10%)	TsOH (1 equiv)	24	*NR*[f]
5	$PtCl_2$ (10%)	AcOH (1 equiv)	16	53
6	$PtCl_2$ (10%)	silica gel (50 mg)[e]	10	73
7	$PtCl_2$ (10%)	5 Å MS (50 mg)	10	80
8[c]	$PtCl_2$ (10%)	5 Å MS (50 mg)	10	74
9	$PtCl_2$ (5%)	5 Å MS (50 mg)	48	76
10	$PtCl_2$ (15%)	5 Å MS (50 mg)	8	81
11	$PtCl_2$ (10%), COD (20%)	5 Å MS (50 mg)	18	71
12	$PtCl_2$ (10%), CO (1 atm)	5 Å MS (50 mg)	16	65
13	K_2PtCl_4 (10%)	5 Å MS (50 mg)	24	64
14	$PtCl_4$ (10%)	5 Å MS (50 mg)	16	49
15	no	5 Å MS (50 mg)	24	0

[a] The reaction was run with tetrahydroisoquinoline **1a** (0.2 mmol) and additive in 1 mL of CH_3NO_2/H_2O (10 : 1) under argon at 85 °C. [b] The reaction was run in 1 mL of CH_3NO_2. [c] The reaction was run in 1 mL of CH_3NO_2/H_2O (5 : 1). [d] HFIP is hexafluoroisopropanol. [e] Acidic silica gel was used. [f] No reaction.

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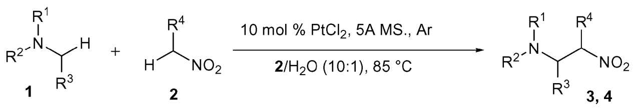
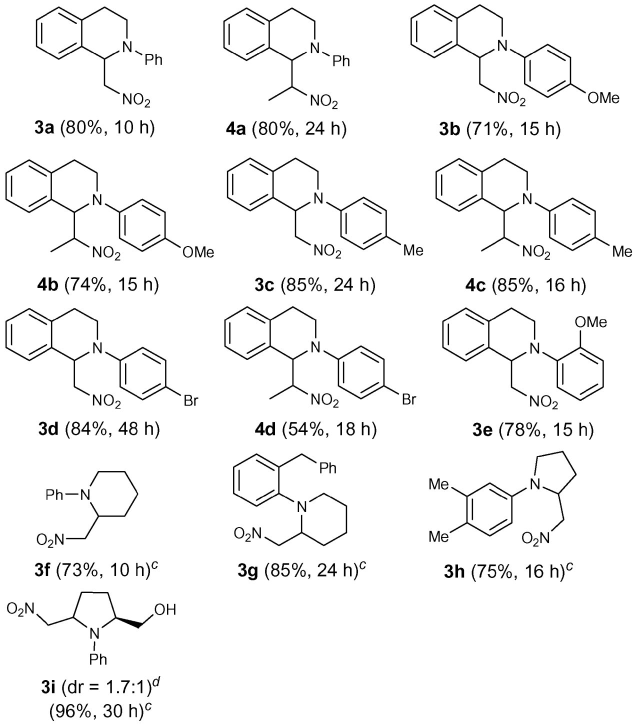
Table 2 Coupling reaction of amines with nitroalkanes[a]

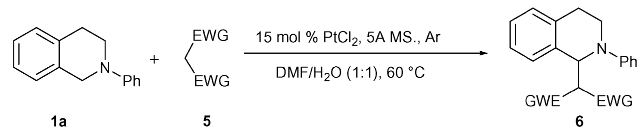


Products (yield, time)[b]

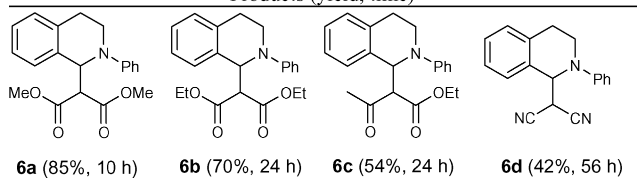


[a] The reaction was run with $PtCl_2$ (10 mol%), tetrahydroisoquinoline **1** (0.2 mmol) in 1 mL of **2**–H_2O (10 : 1) under argon in the presence of powdered 5 Å MS (50 mg). [b] Isolated yield. [c] The reaction was run at 80 °C and CH_3NO_2–H_2O (5 : 1) was used. [d] Diastereomeric ratio (dr) was determined by HPLC (OD–H), hexane–*i*-PrOH (80 : 20), flow rate (1.0 mL min^{-1}).

Table 3 Coupling reaction of tertiary amines with activated methylene compounds[a]



Products (yield, time)[b]



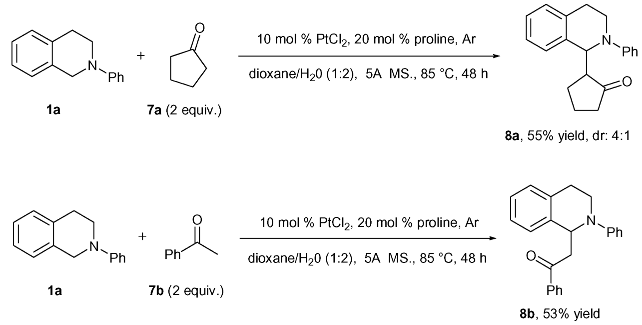
[a] The reaction was run with $PtCl_2$ (15 mol%), **1a** (0.2 mmol), **5** (2 equiv.) in 1 mL of DMF–H_2O (1 : 1) under argon in the presence of powdered 5 Å MS (50 mg). [b] Isolated yield.

systems but no better result obtained (Table 1, entries 8–14). No reaction was observed in the absence of platinum catalyst (Table 1, entry 15).

Under the optimized conditions, various β-nitroamine derivatives were generated, as shown in Table 2. Tetrahydroisoquinoline derivatives always gave moderate to high yields of the desired products, both from nitromethane and nitroethane (**3a–3e**, **4a–4d**). 1-Arylpiperidines generated the desired products **3f** and **3g** in 73% and 85% yields, respectively, although direct functionalization of the sp^3 C–H bond in piperidine still remains one of the more challenging areas of research.[3c] A 1-arylpyrrolidine also gave the desired compound **3h** in good yield. In these cases, bis-CDC products were not observed. When a substituted five-membered ring was used, the coupling reaction was observed at the 5-position of *N*-phenyl-L-prolinol and the desired product **3i** was isolated in 96% yield with alcoholic group remaining intact.

In addition to nitroalkanes, this oxidant-free CDC reaction was also applicable to activated methylene compounds (Table 3). Dialkyl malonate derivatives and malononitrile reacted smoothly with tertiary amines in the presence of water, affording the desired products in moderate to good yield. β-Keto esters, such as ethyl acetoacetate, also gave a moderate yield of coupling compound **6c**.

The direct coupling of amines with non-activated simple ketones was also tested (Scheme 2). To achieve this coupling, a secondary amine, L-proline, was used as an organic co-catalyst to activate the ketones in the form of a nucleophilic enamine intermediate.[6] After treating **1a** with 2 equiv of cyclic ketone **7a** in the presence of $PtCl_2$ (10 mol%) and L-proline (20 mol%) at 85 °C, desired product **8a** was isolated in 55% yield after 48 h. When an acyclic phenyl ketone was used, the reaction also proceeded smoothly to afford a 53% yield of coupling product **8b**. No enantiomeric excess was observed in either example.



Scheme 2 Direct coupling of amine with non-activated simple ketones.

To further study the mechanism, we conducted an experiment to detect hydrogen evolution by using an Inficon Transpector 2.[7] Fortunately we detected the presence of H_2 in the reaction. The results are shown in Fig. 1. When D_2O was added instead of H_2O, DH was also formed besides the formation of H_2 (Fig. 1b).

On the basis of the above observations, a possible reaction mechanism is proposed in Scheme 3. The tertiary amine is activated by coordination with platinum and then platinum mediated H-abstraction generates the intermediate **B**.[4c] Subsequent reaction of iminium intermediate **B** with a nucleophile affords the CDC product, where the [Pt]–H bond is cleaved by the formation of H_2. Weak acid in the reaction system promotes this process, whereas more H_3O^+ blocks the step from **SM** to **A** (Table 1, entries 3, 6, 7 *vs.*

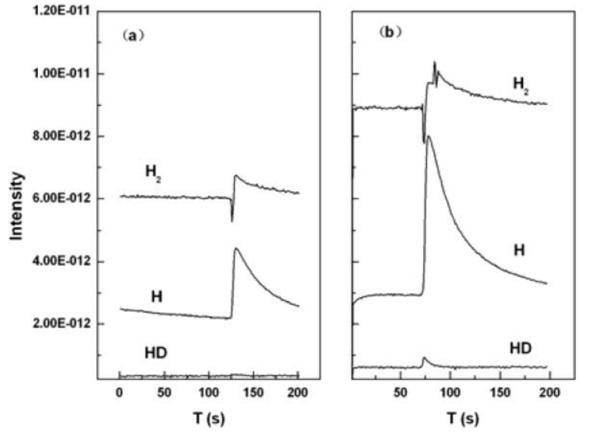
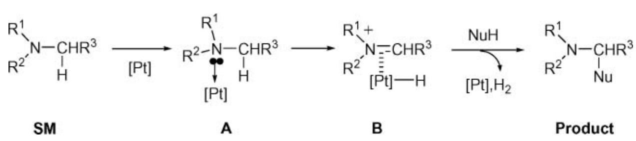


Fig. 1 Results of H_2 detection by using an Inficon Transpector 2. H is the fraction of H_2 and HD during the detection. (a) Spectra were obtained when CH_3NO_2–H_2O (10 : 1) was used. (b) Spectra were obtained when CH_3NO_2–D_2O (10 : 1) was used.



Scheme 3 Proposed mechanism.

4, 5). The detection of HD in the hydrogen evolution experiment might be ascribed to the equilibrium of hydride-acceptors D_2O–H^+ and HDO–D^+, also NuH–D_2O–NuD.

In conclusion, we have reported a third strategy for cross-dehydrogenative coupling *via* platinum-catalyzed sp^3 C–H and sp^3 C–H coupling reaction in the absence of oxidant. Nitroalkanes as well as dialkyl malonate derivatives, β-keto esters and malononitrile are active participants in this coupling reaction. Both cyclic and acyclic non-activated simple ketones are good reactants in this reaction.

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7 Although it is difficult to detect the evolution of H_2 in this reaction, we still carried out a qualitative experiment using the Inficon Transpector 2: The reaction was carried out by using tetrahydroisoquinoline **1a** (0.5 mmol), $PtCl_2$ (10% mol) and 5 Å MS (100 mg) in CH_3NO_2–H_2O or CH_3NO_2–D_2O (2 mL) under argon in a sealed tube. When the mixture was stirred at 85 °C for 6 h, the gas (2 mL) over the solution was injected into the Hydrogen Detector Inficon Transpector 2.