

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

Xing-Zhong Shu, Yan-Fang Yang, Xiao-Feng Xia, Ke-Gong Ji, Xue-Yuan Liu and Yong-Min Liang\*

Received 15th June 2010, Accepted 8th July 2010

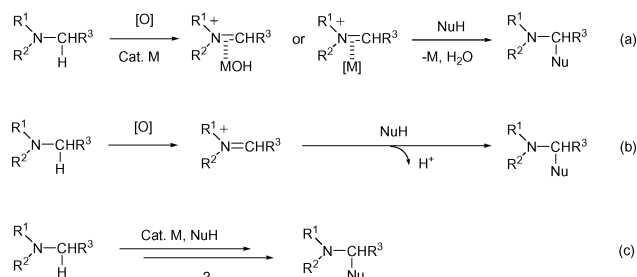
First published as an Advance Article on the web 28th July 2010

DOI: 10.1039/c0ob00261e

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,  $\beta$ -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.<sup>1</sup> Despite significant progress in this area, catalytic intermolecular transformations of  $sp^3$  C–H bonds to C–C bonds still remain rare.<sup>2</sup> 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.<sup>3</sup> These reactions always involve  $\alpha$ -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  $\alpha$ -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);<sup>4</sup> (ii) the route using treatment with oxidants (Scheme 1b).<sup>5</sup> The former pathway was started by Murahashi using a Ru(III) catalyst with  $O_2$  or  $H_2O_2$  as oxidants.<sup>4a–c</sup> Copper-catalyzed oxidative CDC reactions were reported by Li and others, where  $t$ -BuOOH,  $O_2$ , NBS and diethyl azodicarboxylate (DEAD) are good oxidants.<sup>4d–p</sup> When rhodium was used, a strong oxidant such as T-HYDRO (70%  $t$ -BuOOH



**Scheme 1** General pathways for CDC reaction.

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, P. R. China. E-mail: liangym@lzu.edu.cn; Fax: 0086-931-8912582

† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/c0ob00261e

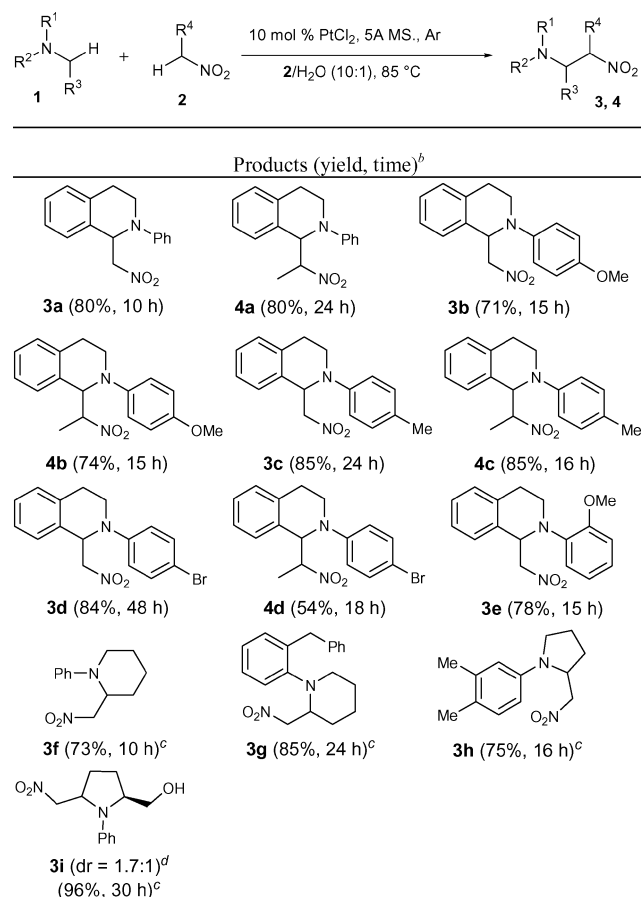
**Table 1** Optimization of reaction conditions<sup>a</sup>

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

<sup>a</sup> 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. <sup>b</sup> The reaction was run in 1 mL of  $CH_3NO_2$ . <sup>c</sup> The reaction was run in 1 mL of  $CH_3NO_2/H_2O$  (5 : 1). <sup>d</sup> HFIP is hexafluoroisopropanol. <sup>e</sup> Acidic silica gel was used. <sup>f</sup> No reaction.

in water) was needed.<sup>4a</sup> Iron-( $t$ -BuO)<sub>2</sub><sup>4r</sup> and vanadium- $t$ -BuOOH<sup>4s</sup> 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<sup>5a</sup> and our<sup>5b</sup> recent works have shown this interesting transformation by using DDQ and PhI(OAc)<sub>2</sub>, 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).

We started by using the tetrahydroisoquinoline **1a** (0.2 mmol) with 10 mol% of PtCl<sub>2</sub> 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

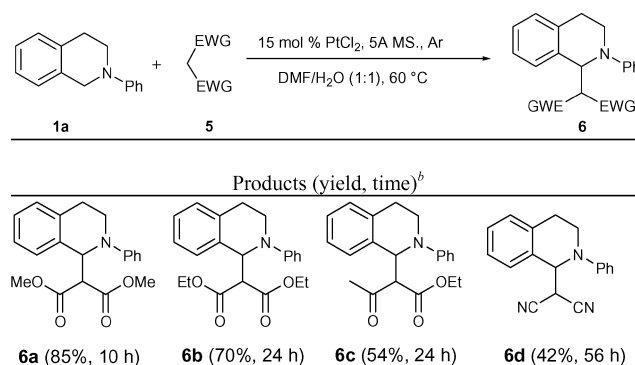
**Table 2** Coupling reaction of amines with nitroalkanes<sup>a</sup>

<sup>a</sup> The reaction was run with PtCl<sub>2</sub> (10 mol%), tetrahydroisoquinoline **1** (0.2 mmol) in 1 mL of 2-H<sub>2</sub>O (10:1) under argon in the presence of powdered 5 Å MS (50 mg). <sup>b</sup> Isolated yield. <sup>c</sup> The reaction was run at 80 °C and CH<sub>3</sub>NO<sub>2</sub>-H<sub>2</sub>O (5:1) was used. <sup>d</sup> Diastereomeric ratio (dr) was determined by HPLC (OD-H), hexane-*i*-PrOH (80:20), flow rate (1.0 mL min<sup>-1</sup>).

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<sup>3</sup> C–H bond in piperidine still remains one of the more challenging areas of research.<sup>3c</sup> 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.

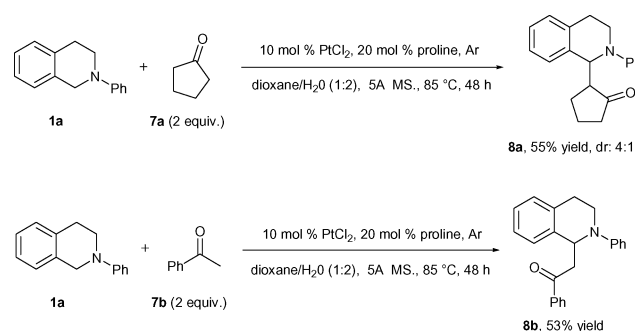
In addition to nitroalkanes, this oxidant-free CDC reaction was also applicable to activated methylene compounds (Table 3). Dialkyl malonate derivatives and malononitrile reacted smoothly with tertiary amines in the presence of water, affording the desired products in moderate to good yield. β-Keto esters,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

**Table 3** Coupling reaction of tertiary amines with activated methylene compounds<sup>a</sup>

<sup>a</sup> The reaction was run with PtCl<sub>2</sub> (15 mol%), **1a** (0.2 mmol), **5** (2 equiv.) in 1 mL of DMF-H<sub>2</sub>O (1:1) under argon in the presence of powdered 5 Å MS (50 mg). <sup>b</sup> Isolated yield.

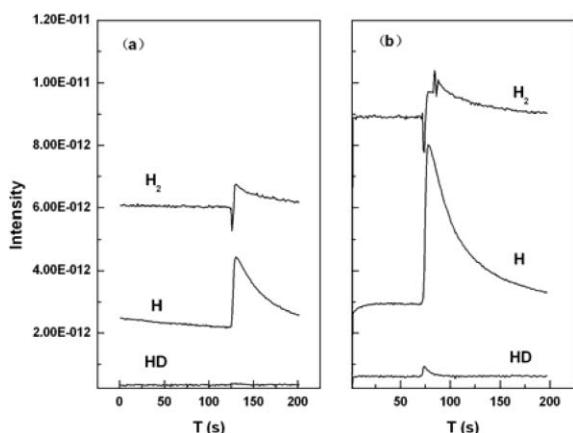
acetoacetate, also gave a moderate yield of coupling compound **6c**.

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.<sup>6</sup> After treating **1a** with 2 equiv of cyclic ketone **7a** in the presence of PtCl<sub>2</sub> (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.

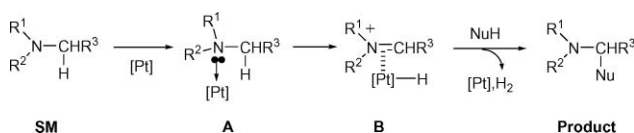
**Scheme 2** Direct coupling of amine with non-activated simple ketones.

To further study the mechanism, we conducted an experiment to detect hydrogen evolution by using an Inficon Transpector 2.<sup>7</sup> Fortunately we detected the presence of H<sub>2</sub> in the reaction. The results are shown in Fig. 1. When D<sub>2</sub>O was added instead of H<sub>2</sub>O, DH was also formed besides the formation of H<sub>2</sub> (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**.<sup>4c</sup> 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<sub>2</sub>. Weak acid in the reaction system promotes this process, whereas more H<sub>3</sub>O<sup>+</sup> blocks the step from **SM** to **A** (Table 1, entries 3, 6, 7 vs.



**Fig. 1** Results of  $\text{H}_2$  detection by using an Inficon Transceptor 2. H is the fraction of  $\text{H}_2$  and HD during the detection. (a) Spectra were obtained when  $\text{CH}_3\text{NO}_2\text{-H}_2\text{O}$  (10:1) was used. (b) Spectra were obtained when  $\text{CH}_3\text{NO}_2\text{-D}_2\text{O}$  (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  $\text{D}_2\text{O-H}^+$  and  $\text{HDO-D}^+$ , also  $\text{NuH-D}_2\text{O-NuD}$ .

In conclusion, we have reported a third strategy for cross-dehydrogenative coupling *via* platinum-catalyzed  $\text{sp}^3$  C-H and  $\text{sp}^3$  C-H coupling reaction in the absence of oxidant. Nitroalkanes as well as dialkyl malonate derivatives,  $\beta$ -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.

## Acknowledgements

We thank the the National Natural Science Foundation of China (NSF-20732002, NSF-20872052, NSF-20921120404) for financial support.

## Notes and references

- (a) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013; (b) Y. J. Park, J. W. Park and C. H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222; (c) B. J. Li, S. D. Yang and Z. J. Shi, *Synlett*, 2008, 949; (d) C. I. Herreras, X. Q. Yao, Z. P. Li and C. J. Li, *Chem. Rev.*, 2007, **107**, 2546; (e) C. J. Li and Z. P. Li, *Pure Appl. Chem.*, 2006, **78**, 935; (f) G. Dyker, *Handbook of C-H Transformations*, Wiley-VCH, Weinheim, 2005; (g) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077; (h) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731.
- For select reviews on  $\text{C}(\text{sp}^3)\text{-H}$  functionalization, see: (a) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (b) P. Thansandote and M. Lautens, *Chem.-Eur. J.*, 2009, **15**, 5874; (c) M. M. Diaz-Requejo and P. J. Pérez, *Chem. Rev.*, 2008, **108**, 3379; (d) M. Tobisu and N. Chatani, *Angew. Chem., Int. Ed.*, 2006, **45**, 1683; (e) S. Doye, *Angew. Chem., Int. Ed.*, 2001, **40**, 3351.
- For recent reviews, see: (a) C. J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (b) S.-I. Murahashi and D. Zhang, *Chem. Soc. Rev.*, 2008, **37**, 1490; (c) K. R. Campos, *Chem. Soc. Rev.*, 2007, **36**, 1069; (d) S.-I. Murahashi, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2443.
- For ruthenium catalysis: (a) S.-I. Murahashi, T. Nakae, H. Terai and N. Komiya, *J. Am. Chem. Soc.*, 2008, **130**, 11005; (b) S.-I. Murahashi, N. Komiya and H. Terai, *Angew. Chem., Int. Ed.*, 2005, **44**, 6931; (c) S.-I. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312; (d) For copper catalysis: X. Xu and X. Li, *Org. Lett.*, 2009, **11**, 1027; (e) Y.-M. Shen, M. Li, S.-Z. Wang, T.-G. Zhan, Z. Tan and C.-C. Guo, *Chem. Commun.*, 2009, (8), 953; (f) L. L. Chu, X. G. Zhang and F.-L. Qing, *Org. Lett.*, 2009, **11**, 2197; (g) M. Niu, Z. Yin, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2008, **73**, 3961; (h) O. Basle and C.-J. Li, *Org. Lett.*, 2008, **10**, 3661; (i) Y. Zhang, H. Fu, Y. Jiang and Y.-F. Zhao, *Org. Lett.*, 2007, **9**(19), 3813; (j) O. Basle and C.-J. Li, *Green Chem.*, 2007, **9**, 1047; (k) Z. Li, D. S. Bohle and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 8928; (l) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 6968; (m) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3672; (n) Z. Li and C.-J. Li, *Eur. J. Org. Chem.*, 2005, (15), 3173; (o) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810; (p) Z. Li and C.-J. Li, *Org. Lett.*, 2004, **6**, 4997; (q) For rhodium catalysis: A. J. Catino, J. M. Nichols, B. J. Nettles and M. P. Doyle, *J. Am. Chem. Soc.*, 2006, **128**, 5648; (r) For iron catalysis: C. M. R. Volla and P. Vogel, *Org. Lett.*, 2009, **11**, 1701; (s) For vanadium catalysis: A. Sud, D. Sureshkumar and M. Klusmann, *Chem. Commun.*, 2009, 3169.
- For metal-free CDC reactions, see: (a) A. S.-K. Tsang and M. H. Todd, *Tetrahedron Lett.*, 2009, **50**, 1199; (b) X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu and Y.-M. Liang, *J. Org. Chem.*, 2009, **74**, 7464.
- For recent overviews on enamine catalysis, see: (a) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138; (b) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471.
- Although it is difficult to detect the evolution of  $\text{H}_2$  in this reaction, we still carried out a qualitative experiment using the Inficon Transceptor 2: The reaction was carried out by using tetrahydroisoquinoline **1a** (0.5 mmol),  $\text{PtCl}_2$  (10% mol) and 5 Å MS (100 mg) in  $\text{CH}_3\text{NO}_2\text{-H}_2\text{O}$  or  $\text{CH}_3\text{NO}_2\text{-D}_2\text{O}$  (2 mL) under argon in a sealed tube. When the mixture was stirred at  $85^\circ\text{C}$  for 6 h, the gas (2 mL) over the solution was injected into the Hydrogen Detector Inficon Transceptor 2.