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Authors: Iris Martín-García and Francisco Alonso

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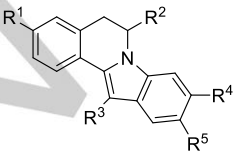
Synthesis of Dihydroindoloisoquinolines through the Copper-Catalyzed Cross-Dehydrogenative Coupling of Tetrahydroisoquinolines and Nitroalkanes

Iris Martín-García[a] and Francisco Alonso*[a]

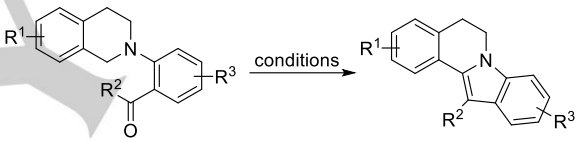
Abstract: Lately, the cross-dehydrogenative coupling of tetrahydroisoquinolines and nitroalkanes has become a widely studied reaction in organic chemistry; the corresponding β-nitroamines are generally formed irrespective of the catalysis and activation mode utilized. A quite distinct behavior has been observed when the reaction is catalyzed by copper nanoparticles supported on titania, leading to the formation of 5,6-dihydroindolo[2,1-*a*]isoquinolines with high selectivity and good yields. A meticulous reaction mechanism is proposed, based on experimentation, and discussed along with a key chemical modification of these compounds. Apparently, the catalyst effectiveness resides in its nanostructured character, outperforming the activity of the commercial copper catalysts.

There is a necessity for novel organic reactions that enable unconventional disconnections, C-H activation and late-stage functionalization in order to overcome synthetic challenges and offer more opportunities in drug discovery research.[1] In this vein, studies on the biological activity of 5,6-dihydroindolo[2,1-*a*]isoquinolines have revealed promising results to advance in the treatment of manifold diseases. For instance, compounds **1a** and **1b** strongly inhibit tubulin polymerization and the growth of human breast cancer cells in vitro,[2a,b] whereas compound **1c** is a melatonin agonist (Chart 1).[2c] Modern synthetic methods toward the 5,6-dihydroindolo[2,1-*a*]isoquinoline skeleton rely on the intramolecular cyclization of *N*-aryl-1,2,3,4-tetrahydroisoquinolines.[3] However, the installation of an *ortho* acyl group on the *N*-aryl moiety is mandatory to accomplish the corresponding dehydrative coupling (Chart 1). This transformation has been promoted by stoichiometric amounts of a base[3a] or catalyzed by iridium complexes under thermal[3b] of photoredox conditions.[3c,d]

On the other hand, the cross dehydrogenative coupling (CDC) aza-Henry reaction[4] allows the coupling of the acidic α C–H bond of nitroalkanes with the α C–H bond of tertiary amines, furnishing β-nitroamines in a straight manner. This reaction was pioneered by Li's group using CuBr (5 mol%) and a stoichiometric amount of *tert*-butylhydroperoxide (TBHP)[5a] or oxygen.[5b] Thereafter, a plethora of procedures have emerged around this reaction involving thermal, photochemical or electrochemical activation in the presence or absence of transition metals, oxidants or organocatalysts.[6] In all cases, the outcome of the reaction was the same irrespective of the primary nitroalkane deployed: the 1-(nitroalkyl)-2-aryl-1,2,3,4-tetrahydroisoquinolines were the only products reported (Scheme 1a).[7] Another common property in these reactions is the use of the nitrocompound in a great excess and/or as the solvent,[8] what increases the E factor and the laboratory hazards, particularly, for larger scale preparations.[9] As the only exception, Brasholz et al. described the anomalous formation of 12-nitro-5,6-dihydroindolo[2,1-*a*]isoquinolines when the starting tetrahydroisoquinolines and nitromethane were subjected to irradiation in the presence of a base and an organic photocatalyst (Scheme 1b).[10]



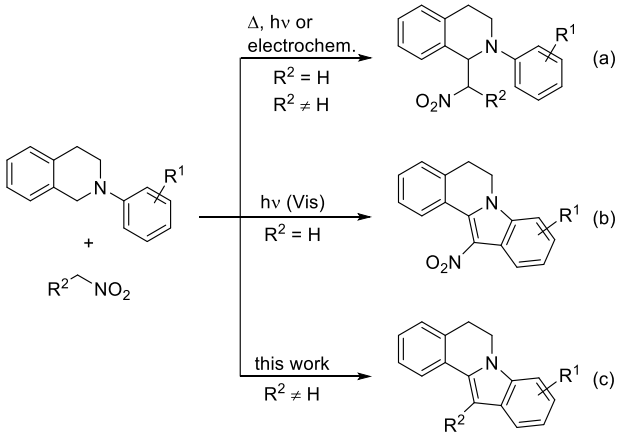
1a R^1 = OAc; R^2 = Bu; R^3 = CHO; R^4 = OAc; R^5 = H
1b R^1 = OMe; R^2 = Pr, Bu; R^3 = CHO; R^4 = OH; R^5 = H
1c R^1 = H; R^2 = H; R^3 = CH_2CH_2NHCOR; R^4 = H; R^5 = OMe



ref. 2a: KO*t*-Bu (1.2 equiv.), DMF, 90 ºC, 3 h, Ar
ref. 2b: $[Ir(cod)Cl]_2$ (2.5 mol%), dppe (5 mol%), HOAc, reflux, 24 h
ref. 2c: $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol%), K_2HPO_4 (0.5 equiv.), methyl 2-mercaptoacetate (0.5 equiv.), 5 W blue LED, rt, MeCN, Ar, 48 h
ref. 2d: $Ir(ppy)_2(dtbbpy)PF_6$ (3 mol%), $(PhO)_2PO_2H$ (40 mol%), 23 W CFL, rt, DMF, N_2, 8-48 h

Chart 1. Biologically active 5,6-dihydroindolo[2,1-*a*]isoquinolines and synthetic approaches.

In recent years, the synthesis and modification of nitrogen heterocycles via transition-metal catalyzed sp^2 functionalization has attracted a great deal of attention.[11] As part of our interest on the application of copper nanoparticles (CuNPs) in coupling reactions,[12] herein, we want to put forward the unparalleled



Scheme 1. Reaction of tetrahydroisoquinolines and nitroalkanes through CDC.

[a] I. Martín-García, Prof. Dr. Francisco Alonso
Instituto de Síntesis Orgánica (ISO) and Departamento de Química Orgánica, Facultad de Ciencias
Universidad de Alicante, Apdo. 99, E 03080 Alicante, Spain
E-mail: falonso@ua.es
Supporting information for this article can be found at: XXXXXXX.

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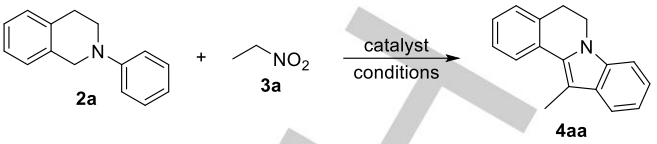
reaction of tetrahydroisoquinolines and nitrocompounds leading to 5,6-dihydroindolo[2,1-*a*]isoquinolines catalyzed by supported CuNPs through CDC under aerobic conditions[13] (Scheme 1c).

We first optimized the catalytic system and reaction conditions using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**2a**) and nitroethane (**3a**) as the model substrates (Table 1). A control experiment in the absence of catalyst led to the unreacted starting materials (entry 1). The catalyst composed of CuNPs/TiO_2 was found to be the best one among a range of supported catalysts at 70 ºC under solvent-free conditions (entries 2–8). The TiO_2 support was demonstrated to be catalytically inactive (entry 9) whereas the incorporation of a solvent in the reaction medium had a deleterious effect on the conversion (entries 10–17). The same trend was observed when varying the catalyst loading (18–21) or the reaction temperature (entries 22 and 23). The conversion was notably depleted under microwave irradiation (entry 24); other variables such as light protection or the atmosphere exerted a less significant effect (entries 25–27). We concluded that the optimum catalytic system was that comprised of CuNPs/TiO_2 (1.5 mol%) at 70 ºC in air (entry 8). It is remarkable that this standard reaction was successfully accomplished without the need for a solvent or added oxidant and using, comparatively, a slight excess of the nitrocompound (2.4 equiv.).

An array of representative substrates was tested under the optimized conditions in order to gauge the scope of the method (Table 2). The simplest dihydroindoloisoquinoline **4aa** was obtained in nearly quantitative isolated yield. The effect of the 4-substituent at the *N*-phenyl ring was assessed in the reaction with nitroethane (**3a**). Electron-neutral and -donating substituents led to the expected products in moderate-to-good yields (**4ba**, **4ca** and **4da**). In the case of electron-withdrawing substituents, however, a decrease in the yield was observed parallel to their capacity to delocalize the negative charge (**4ea**, **4fa** and **4ga**). This situation had dramatic consequences in the case of the nitro derivative **4ga**, what is related to the reaction mechanism (see below). In contrast, a high yield was recorded for the fluorinated dihydroindoloisoquinoline **4ha**. The 3,5-disubstituted *N*-aryl isoquinolines **2i** and **2j** were utilized to estimate the influence of the steric hindrance in the reaction outcome; a non-bonding repulsive *peri*-type effect between one of these substituents and the methyl group could explain the relatively low yields displayed in these two cases (**4ia** and **4ja**). The regiochemistry of the cyclization was analyzed through the *N*-(3,4-dimethylphenyl) and *N*-(3,4-dimethoxyphenyl) isoquinolines **2k** and **2l**, respectively. The lower steric encumbrance of the methyl group led to a 1:1 regioisomeric ratio of **4ka** and **4ka'**; gratifyingly, **4la**, with the more sterically demanding methoxy group was formed as a single regioisomer. The procedure was also proven effective for the isoquinoline dimethoxylated in the bicyclic aryl ring (**2m**), albeit prolonged heating was required. Finally, longer-chain nitrocompounds were more reluctant to react with the isoquinoline **2a**, though the alkyl fragments were successfully incorporated into the products (**4ab** and **4ac**) by increasing the temperature at 100 ºC. (Nitromethyl)benzene did not react under these conditions.

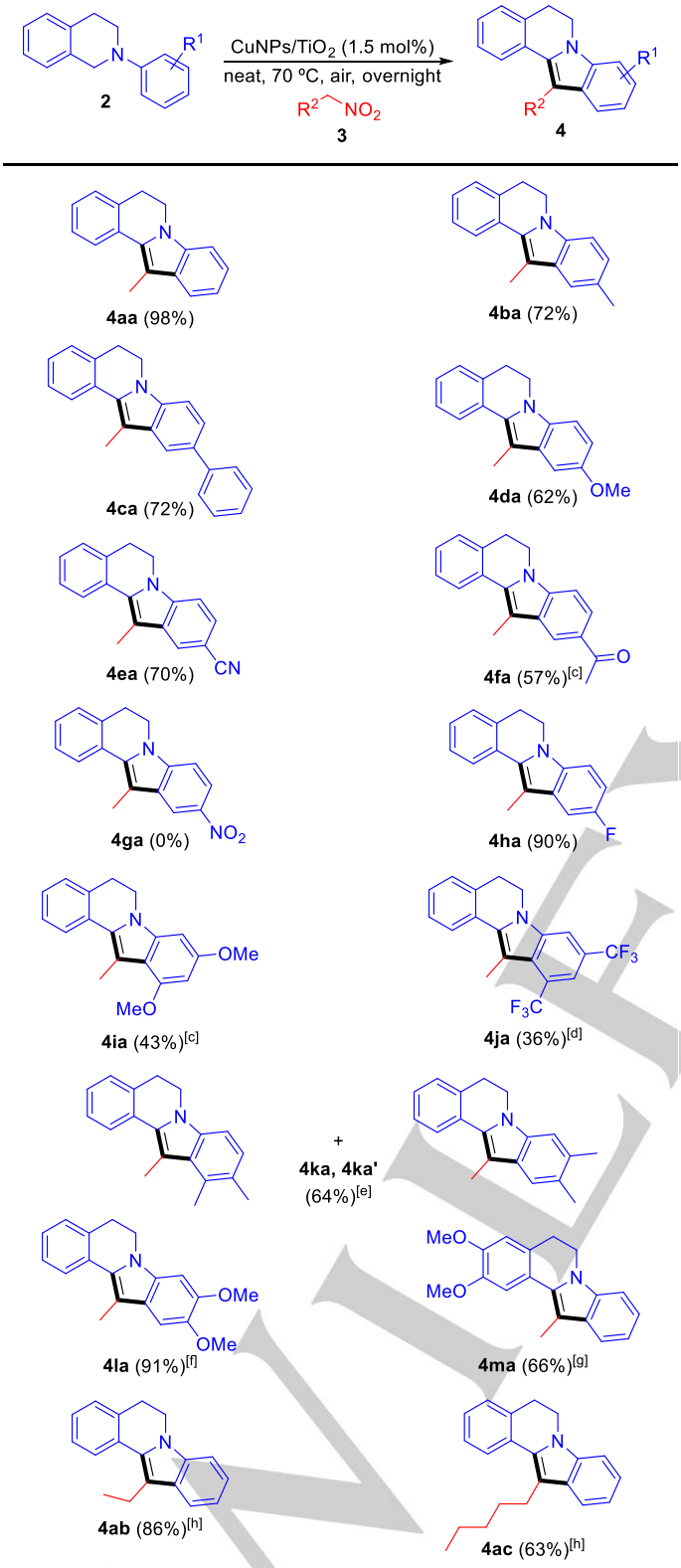
Table 1. Optimization of the catalyst and conditions[a]



Entry	Catalyst [mol%][b]	Solvent	*T* [ºC]	Conv. [%][c]
1	-	neat	70	0
2	CuNPs/ZY	neat	70	52
3	CuNPs/MK-10	neat	70	43
4	CuNPs/C	neat	70	32
5	CuNPs/CeO_2	neat	70	31
6	CoNPs/ZY	neat	70	24
7	MnNPs/TiO_2	neat	70	8
8	**CuNPs/TiO_2**	**neat**	**70**	**>99**
9	TiO_2	neat	70	0
10	CuNPs/TiO_2	H_2O	70	17
11	CuNPs/TiO_2	MeOH	70	10
12	CuNPs/TiO_2	*i*-PrOH	70	39
13	CuNPs/TiO_2	DMF	70	85
14	CuNPs/TiO_2	CH_3CN	70	37
15	CuNPs/TiO_2	DMSO	70	71
16	CuNPs/TiO_2	PhMe	70	6
17	CuNPs/TiO_2	DCE	70	8
18	CuNPs/TiO_2 [0.15]	neat	70	21
19	CuNPs/TiO_2 [0.38]	neat	70	52
20	CuNPs/TiO_2 [0.75]	neat	70	53
21	CuNPs/TiO_2 [2.25]	neat	70	76
22	CuNPs/TiO_2	neat	rt	3
23	CuNPs/TiO_2	neat	100	71
24	CuNPs/TiO_2	neat	70[d]	2
25	CuNPs/TiO_2	neat	70[e]	93
26	CuNPs/TiO_2	neat	70[f]	78
27	CuNPs/TiO_2	neat	70[g]	80

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (2.4 equiv.), catalyst, air, overnight. [b] Catalyst loading: 1.5 mol%, unless otherwise stated; ZY = zeolite Y; MK-10 = montmorillonite K-10; C = activated carbon. [c] Conversion determined by GLC based on **2a**. [d] MW (100 W), 1 h. [e] Reaction protected from light. [f] Under O_2 atmosphere. [g] Under Ar atmosphere.

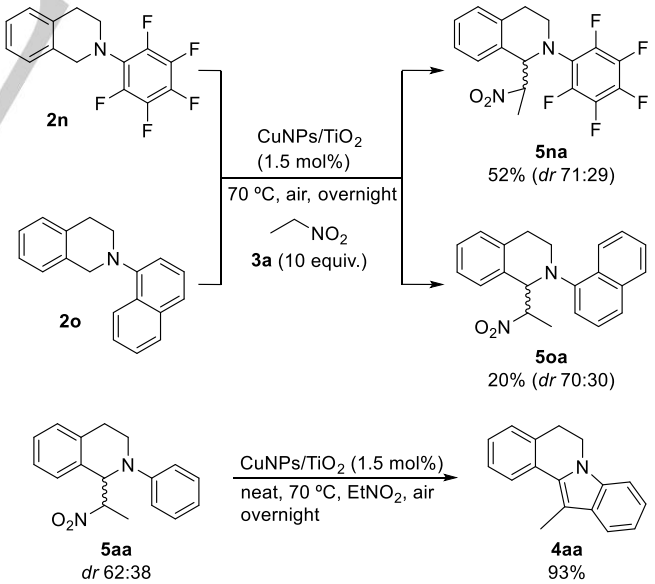
Table 2. Substrate scope.[a][b]



[a] Reaction conditions: **2** (0.5 mmol), **3** (2.4 equiv.), neat, air, 70 °C, overnight. [b] Isolated yield. [c] NMR yield. [d] 30 h. [e] As a *ca.* 1:1 regioisomeric mixture. [f] 10 equiv. of $EtNO_2$. [g] 36 h. [h] Reaction at 100 °C.

Unfortunately, contrary to previous work,[12] the catalyst could not be effectively recycled; the conversion dropped to 50% in the second run. We observed by XPS the adsorption of nitrogen species on the surface of the catalyst after reuse, which might cause its passivation (Figure S2c). XPS spectra also brought into view a substantial decrease of Cu^{I} after the first run (Figure S2b), in agreement with the yield shrinkage, and only Cu^{II} was detected once the catalyst was inactive (Figure S2d). Therefore, the inefficient regeneration of Cu^{I}[12a] together with the surface passivation could account for this catalytic behavior.[14] This limitation is not so important if we take into account that the price of copper and the amount of catalyst used are relatively low. In addition, $CuNPs/TiO_2$ distinctly evinced a distinguished catalytic performance when put alongside with a wide variety of commercial copper catalysts (Table S1).

Given the peculiarity of the title reaction, we felt committed to gain an insight into the reaction mechanism. The facts that the reaction is inhibited or substantially curtailed by the addition of radical traps or catalyst poisons but not by AIBN suggest a radical heterogeneous process (Table S2). Furthermore, by reacting the *N*-pentasubstituted (**2n**) and bulky *N*-substituted (**2o**) tetrahydroisoquinolines with nitroethane (**3a**), the CDC products **5na** and **5oa** could be trapped because of their impossibility or difficulty to cyclize, respectively (Scheme 2). Treatment of preformed **5aa**[5a] under the standard conditions (1.4 equiv. of $EtNO_2$ were added to facilitate the magnetic stirring) furnished the cyclized product **4aa** in excellent yield. These results confirmed that β-nitroamines are the intermediate species and precursors of the dihydroindoloisoquinolines and the unprecedented role of CuNPs in promoting a Friedel-Crafts type reaction where the NO_2 acts as a leaving group.



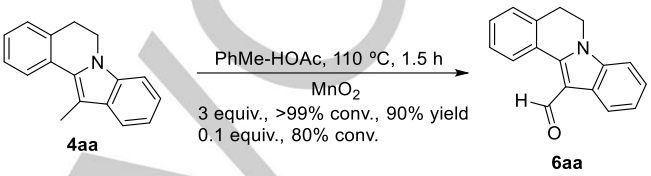
Scheme 2. Experiments to unveil the reaction pathway.

The following observations by XPS are also noteworthy in relation with the reaction pathway (Figure S1): (a) the impregnation of $CuNPs/TiO_2$ with **2a** or **4aa** did affect neither the

intensity nor the binding energy of superficial copper at the Cu 2*p* level, whereas a considerable shift to lower binding energy was manifested when impregnating with nitroethane (**3a**), more pronounced in the case of Cu^{II} [from 932.3 to 931.9 eV for Cu^{I} and from 934.5 to 933.5 eV for Cu^{II}, Figures S1a,e); the unexpected concomitant increase in the intensity of the Cu^{II} band, only observed in the case of **3a**, points to Cu^{I} acting as a reductant for the nitrocompound (Figure S1e). (b) Even more marked was the higher binding energy shift experienced by one band at the N *1s* level in the latter case (i.e., CuNPs/TiO_2-**3a**, 406.9 eV) when compared with that of only TiO_2 impregnated with **3a** (402.5 eV). These data denote a strong interaction of the CuNPs with the nitro group of **3a**, presumably, with the implication of CuONPs.

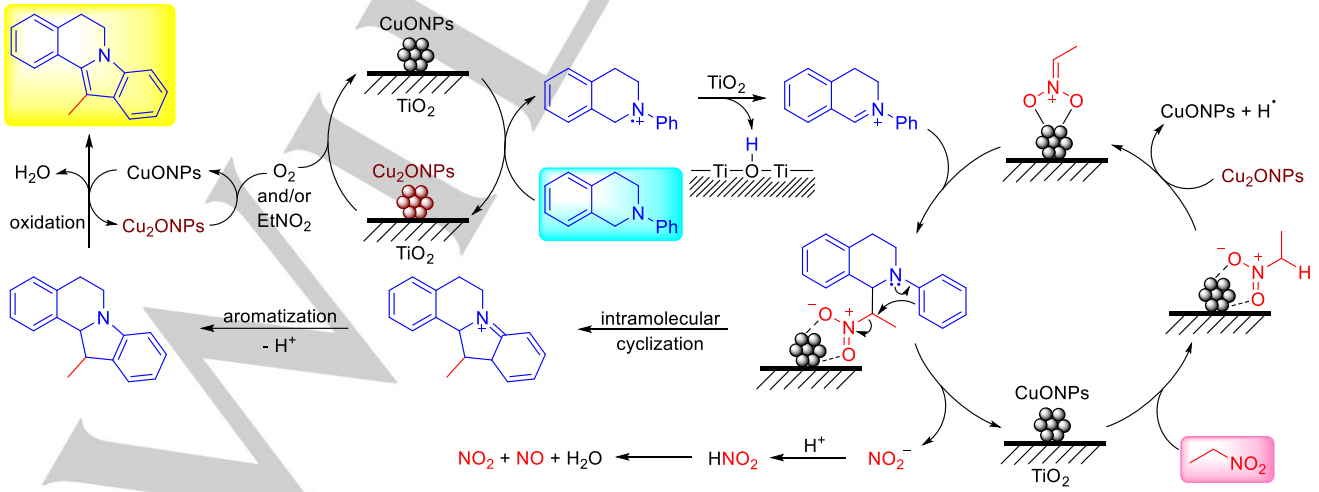
A reaction mechanism has been proposed on the basis of the aforementioned experiments (Scheme 3), including: (a) CuONPs-promoted activation of the nitroalkane to form the nitronate anion through a SET from Cu_2ONPs followed by H abstraction; (b) oxidation of the tetrahydroisoquinoline to the radical cation by CuONPs and the concurrent reduction of the latter to Cu_2ONPs;[12a] (c) re-oxidation of Cu_2ONPs to CuONPs by the action of oxygen and/or the nitroalkane; (d) hydrogen abstraction by the TiO_2 lattice oxygen to generate the counterpart cation and a surface hydroxyl group,[15] (e) addition of the nitronate anion to this cation (iminium ion), (f) intramolecular cyclization with displacement of the nitro group, which can evolve into nitrous acid and further into NO_2, NO and H_2O, (g) re-aromatization of the tetrahydro-5*H*-indolo[2,1-*a*]isoquinolin-7-ium ion and (h) eventual oxidation to yield the 5,6-dihydroindolo[2,1-*a*]isoquinoline. The circumstance that the intramolecular cyclization occurred with nitroethane but not with nitromethane,[16] under the standard conditions, could be rationalized in terms of the more stabilized positive charge developed in the transition state for the secondary C-NO_2 in the case of nitroethane, thus favoring the process. The deep red color of the reaction medium seems to underpin the in-situ generation of NO_2.[17] This reaction mechanism also justifies the failure in the case of the *para*-nitro-substituted tetrahydroisoquinoline **4ga**; the lone electron pair on N participates in a resonant form where the negative charge is strongly stabilized by the nitro group and unavailable to trigger the intramolecular substitution reaction.

The versatility and utility of the dihydroindoloisoquinolines **4** was ultimately evidenced in a fundamental chemical transformation for introducing additional functionalization: the oxidation of the 12-methyl group. We devised a high-yielding direct oxidation of **4aa** into the corresponding carbaldehyde **6aa** utilizing MnO_2 as the oxidant (Scheme 4),[18] very important given the biological activity of compounds **1a** and **1b**, bearing a 12-formyl group.



Scheme 4. Oxidation of **4aa** to **6aa**.

As a conclusion, a singular version of the CDC of tetrahydroisoquinolines and nitroalkanes has been discovered, which produces dihydroindoloisoquinolines instead of the extensively reported β-nitroamines. Three carbon-hydrogen bonds are converted into two carbon-carbon bonds in one step with the following salient features: simple catalytic system, aerobic and solvent-free conditions, relatively low excess of the nitroalkane, absence of ligands and oxidant chemicals, good functional group tolerance and better performance than a broad range of commercial copper catalysts. Moreover, this represents a straightforward access into the family of biologically active 5,6-dihydroindolo[2,1-*a*]isoquinolines, more advantageous than other approaches implying the use of iridium catalysis and/or incompatible conditions with sensitive functional groups. The results of this study bolster the often demonstrated distinctive catalytic activity of the nanostructured catalysts and suggest some new avenues for research in related reactions.



Scheme 3. Proposed reaction mechanism for the typical reaction of tetrahydroisoquinoline **2a** with nitroethane (**3a**).

Acknowledgements

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Keywords: C-C coupling • copper nanoparticles • heterogeneous catalysis • nitrocompounds • nitrogen heterocycles

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[14] The leaching assessed for the reaction of **2a** and **3a** (6 wt%) was found to be rather catalytically inactive. The conversion noted in a first run after 5 h was 30%. The catalyst was then removed by hot filtration after this 5 h period and the filtrate heated for a further 10 h, giving a conversion of 40% after this total 15 h period.

[15] For a review on atomic defects in titanium dioxide, see: T. Minato, *Chem. Rec.* **2014**, *14*, 923–934. Alternatively, molecular hydrogen might be formed.

[16] The reaction of tetrahydroisoquinoline **2a** with nitromethane led to the typical CDC product, i.e., 1-(nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline.

[17] The presence of nitrites or nitrates in the reaction crude can be ruled out because of their negligible detected levels by ionic chromatography (20 and 55 ng, respectively, in a 0.3 mmol scale reaction).

[18] Other oxidants were found to be less effective: Mn_3O_4, I_2, CuBr·SMe_2/DABCO/O_2, DDQ, CuCl/TEMPO. A thorough optimization of the amount of MnO_2 has not been conducted but an acceptable 80% conversion into **6aa** has been obtained with 10 mol% MnO_2 after 1.5 h.

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Entry for the Table of Contents

Layout 2:

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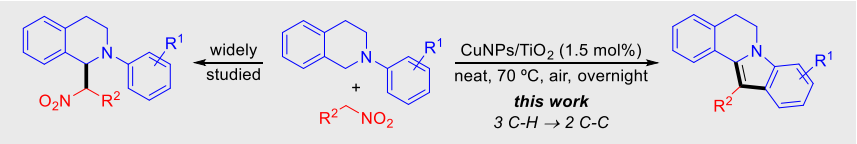

*Iris Martín-García, Francisco Alonso**

Page No. – Page No.

Synthesis of dihydroindoloisoquinolines through the copper-catalyzed cross-dehydrogenative coupling of tetrahydroisoquinolines and nitroalkanes

CuNPs make the difference!: a unique reaction of tetrahydroisoquinolines and nitroalkanes under the catalysis of supported copper nanoparticles is described in which dihydroindoloisoquinolines are produced instead of the corresponding and extensively reported β-nitroamines. Notable features: simple and cheap catalytic system, aerobic and solvent-free conditions, only slight excess of the nitroalkane, absence of additives (ligands, oxidants, etc.) and better catalytic activity than commercial catalysts.