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Heterogeneous Photocatalytic C-C Coupling: Mechanism of Plasmon-mediated Reductive Dimerization of Benzyl Bromides by Supported Gold Nanoparticles

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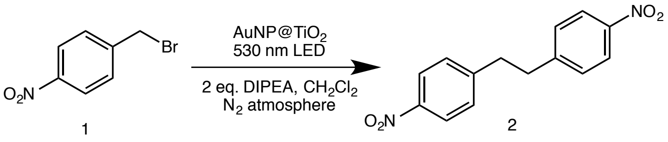
The use of gold nanoparticles supported on TiO_2 (Au@TiO_2) as photocatalysts was extended to include photoinduced reductive C-C coupling. Surface plasmon excitation of supported AuNP in the presence of an amine leads to the C-C coupling for a variety of substituted benzyl bromides at room temperature with good yields in a free-radical mediated reaction. The overall efficiency of the C-C coupling is largely dependent on the nature of the amine used.

Reactions leading to C-C coupling are key to organic synthesis. The majority of these reactions are not mediated by free radicals and for example trans-metalation, has been the subject of many studies and has been extensively reviewed.[1, 2] While radical-radical reactions can readily lead to C-C bond formation, their role in organic synthesis is not as important as catalytic processes frequently involving palladium centers.[1] This is due to the fact that while the kinetics of free radical self-reactions frequently approach diffusion control, radicals under steady state conditions are present only in nanomolar concentrations and thus, radical-molecule reactions tend to dominate radical decay pathways, at least in those systems that are not controlled by the persistent free radical effect (PRE),[3, 4] although examples controlled by PRE are also known.[5]

Organic halides are very important and versatile compounds with many applications as starting materials, solvents, reagents, and intermediates in synthetic organic chemistry. Conventional methods for reducing alkyl, alkenyl and aryl halides bonds consist of metal–halogen exchange, a hydride source or radical reductive dehalogenation.[6] Radical reactions are a powerful class of chemical transformations. However, the formation of radical species to initiate these reactions has often required the use of stoichiometric amounts of toxic reagents.[7] In this sense, the use of visible-light-mediated photoredox catalysis to generate radical species under milder conditions has been extensively studied in the past decade.[8, 9-11] Additionally, catalysis by supported gold nanoparticles in organic transformations has become popular in the last few years.[12] Reactions using photoinduced methods and supported AuNP are promising due to the strong visible absorption of the AuNP surface plasmon band (SPB),[13] plus the robustness, easy separation and potential recyclability associated with heterogeneous nanocomposites. Excitation of the plasmon band in AuNP by visible light leads to NP surface electrons that can be exploited in several ways, including photothermal and photochemical strategies.[11, 14] Recently, the reduction of nitro compounds has been reported with catalysts comprising AuNP on different semiconductor supports like TiO_2, CeO_2 and ZrO_2.[15]

We report here on the ability of AuNP supported on TiO_2 to photocatalyze reductive C-C coupling reactions mediated by free radicals. Several catalysts were used in the past to photoassist C-C coupling of benzyl bromide and its derivatives, through an electron-transfer mechanism using an amine as a sacrificial electron donor.[9, 16] Here we assess supported AuNP as a heterogeneous photocatalyst for reductive dehalogenation reactions using the dimerization of the 4-nitrobenzyl bromide (Scheme 1) as a model reaction. We concentrate on mechanistic aspects and try to understand what conditions will favour C-C coupling. We were pleased to observe that supported AuNP successfully catalyze radical C-C coupling of 4-nitrobenzyl bromide by plasmon mediated catalysis; further, the catalyst is easy to separate and reuse (*vide infra*). It is in fact fascinating that some systems lead to efficient radical recombination reactions, even if the active radicals are at steady state nanomolar concentrations.[9, 17,18]



Scheme 1. Reductive dimerization of 4-nitrobenzyl bromide.

The reductive dimerization of 4-nitrobenzyl bromide is easily obtained by green LED light irradiation of a catalyst suspension in CH_2Cl_2 under nitrogen atmosphere, using diisopropylethylamine (DIPEA) as sacrificial electron donor. The reaction approached completion after irradiation for 5 h, showing the formation of the dimer as the main product and minor yields of of *p*-nitrotoluene, the only by-product. Because of the milder conditions used in this reaction, any traces of the amino product were found.[19] As it was expected, in the presence of oxygen, nitrobenzaldehyde is obtained almost

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quantitatively.[20] The reductive dehalogenation reaction was studied under the screening conditions summarized in Table 1, monitoring the conversion by HPLC. Solvent effects on the role of electron donors were evaluated using commercial supported AuNP@TiO_2 as a photochemical catalyst under 532 nm LED irradiation. A survey of solvents revealed the reaction appears to work best in halogenated solvents such as CH_2Cl_2 (or $ClCH_2CH_2Cl$, not shown). In addition, results strongly suggest that the reductive dimerization of 4-nitrobenzyl bromide only takes place in the presence of an electron donor (ED). In this sense, amines are the most suitable sacrificial electron donors for this reaction (Table 1). Three different amines were used and as expected for the weaker electron donor, the secondary amine (diisopropylamine – DIPA) showed the lowest conversion from reactant. Our group has recently demonstrated that the substrate-reduction is shared by the transition metal photocatalysts and the α-aminoalkyl radicals in photoredox catalysis of a reductive cyclization reaction.[21] We can extend this concept for the C-C coupling reaction studied here. It is well known that deprotonation of an amine-derived radical cation leads to an α-aminoalkyl radical,[22] which is a strong reducing agent.[23] For instance, the oxidation potential in ACN (against SCE) for the radical from Et_3N is -1.12 V,[24] enough to reduce the 4-nitrobencylbromide (-0.86 V).[20] However, diisopropylethylamine (DIPEA) exhibited a significant increase in yield for almost the same conversion than triethylamine (TEA), and it was selected for our standard reduction protocol.

Table 1. Yields (%) of 2 obtained by the reductive dimerization of 1 under different conditions using supported AuNP@TiO_2 as photocatalyst and 532 nm LED irradiation.

#	ED	Solvent	Time (h)	% Yield
i	none	CH_2Cl_2	22	ND
ii	*i*-PrOH	*i*-PrOH	24	ND
iii	Glycerol	$MeOH/CH_2Cl_2$*	24	ND
iv	DIPEA	Cyclohexane	5	4
v	DIPEA	CH_3CN	5	16
vi	DIPEA	CH_2Cl_2	5	83
vii	TEA	CH_2Cl_2	5	20
viii	DIPA	CH_2Cl_2	5	20

ND= values under Limit of Detection. *$MeOH/CH_2Cl_2$ = 1:2

Once the best conditions for the reaction were found, the photo-catalytic activity of supported AuNP was tested. Under dark conditions and heating up the solvent boiling point, no traces of product were found (Table 2, entry *ii*). This indicates light is required to drive the reaction. In order to determine whether the plasmon excitation of AuNPs was involved in the photo-catalytic cycle, blank experiments were carried out in the presence and in the absence of TiO_2 used as a catalyst. Both reactions showed noticeable formation of 2 (Table 2, entries *iii* and *iv*). However, when a long pass cut-off filter (500 nm) is used no photochemical reactions take place without the AuNP (Table 2, entry *vii*), while good yields are obtained with AuNP@TiO_2 (Table 2, entry *v*); this suggests that the short wavelength light contamination present in LED sources (see SI, Figure S5) was contributing to the reaction. These results show that the reaction is taking place under plasmon-mediated photocatalysis.

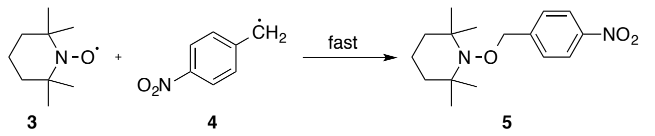
Further, it has been shown that the AuNP size can affect its catalytic activity.[25] In our case, the use of AuNP@TiO_2 catalyst with a mean diameter particle *ca.* 6 nm (synthesized in our laboratory using the TiO_2 recovered from the commercial catalyst. See SI) shows no reaction product under the same irradiation conditions (Table 2, entries *xii* and *xiii*). In addition, it is well known that the injection of electrons from Au to TiO_2 upon visible light irradiation can be easily achieved.[26] In order to determine the role of the TiO_2, we also performed the reaction using small AuNP (average size *ca.* 2.5 nm) supported on an inert material (Fenton treated diamond nanoparticles - AuNP@HO-DNP- see SI). In this case, neither the support nor the AuNP@HO-DNP showed photocatalytic activity under the same irradiation conditions (Table 2, entries *x* and *xi*).

Tanaka,[16] and more recently Álvarez-Griera,[27] suggested that the product 2 may be formed by the radical−radical dimerization of 1, or alternatively by a second reduction of 1 into the benzyl carbanion, which may react with benzyl bromide via a nucleophilic S_N2 mechanism to give 2. In order to better understand the mechanism of the reaction, the same experiment was performed in the presence of (2,2,6,6-tetramethyl-piperidin-1-yl)-oxyl (TEMPO) (Table 2, entries *viii* and *ix*). This very well known radical-trapping agent [28, 29] clearly reduces the yield of the reaction. In fact, the trapping adduct (Scheme 2) was detected by ^1H NMR (see SI) proving the reaction takes place under radical coupling rather than by a nucleophilic substitution. These adducts are well known as they have been widely used as polymerization initiators.[29, 30]

Table 2. Yields (%) of 2 obtained by the reductive dimerization of 1 under different conditions using 2 eq. of DIPEA as electron donor in CH_2Cl_2.

#	Time (h)	Catalyst	Filter	% Yield
i	5	AuNP@TiO_2	--	83
ii	22[a]	AuNP@TiO_2	Dark	ND
iii	5	--	--	25
iv	5[b]	TiO_2	--	21
v	5	AuNP@TiO_2	500 nm	69
vi	5	--	500 nm	ND
vii	5[b]	TiO_2	500 nm	ND
viii	5[c]	AuNP@TiO_2	--	NQ
ix	5[c]	--	--	ND
x	5	AuNP@HO-DNP	--	10
xi	5	HO-DNP	--	26
xii	5[d]	AuNP@TiO_2	--	33
xiii	5[d]	AuNP@TiO_2	500 nm	ND

NQ = values under the limit of quantitation. [a] Heating at 39 °C. [b] TiO_2 obtained by the etching of AuNP on the commercial Au@TiO_2 used (See SI). [c] Addition of 2 equivalents of TEMPO. [d] Homemade.



Scheme 2. Reaction between TEMPO (3) and the *p*-nitrobenzyl radical (4) gives the trapping adduct (5).

The C-C centered radical coupling is the less favored of the conventional methods used for reducing alkyl, alkenyl and aryl halides bonds.[6, 10, 31] However, it is well known that free radicals can interact with the AuNP surfaces,[32, 33] and in the present system, the radical-radical dimerization could be favoured by the presence of AuNP. A plausible mechanism (Scheme 3) involves the injection of the photoexcited electrons at the AuNP into the TiO_2 conduction band (CB),[34] and the injected electrons can be transferred to the alkyl

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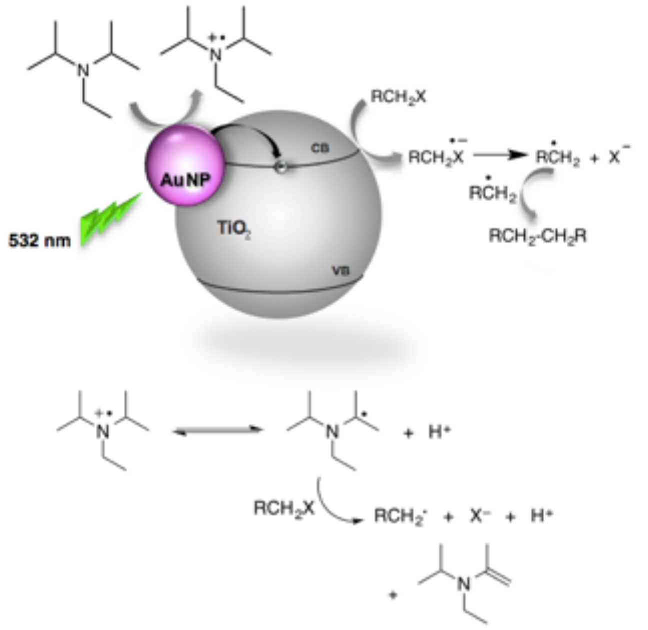
halide. This is followed by halide anion release and formation of a carbon-centered radical.[35] In this mechanism, the AuNP is returned to its original oxidation state by the sacrificial electron donor. As mentioned above, the α-aminoalkyl radical formed by deprotonation of the sacrificial electron donor can also act as a strong reducing agent[21, 23] and generate benzyl radicals in the same process (Scheme 3 bottom). Interestingly in the case of nanodiamonds as support (see Table 2), the material is unable to accept the electron from gold and as a result AuNP do not improve the catalytic performance upon plasmon excitation.



Scheme 3. *Top*: Proposed mechanism for the plasmon-mediated reductive dimerization of 4-nitro-benzylbromide by supported AuNP. R = p-nitrophenyl. *Bottom*: Reduction of RCH$_2$X by α-aminoalkyl radicals.

The scope of the reaction was studied with different substituted benzyl bromide compounds all under the same conditions. As can be seen in table 3, electron-withdrawing substituents either *para* or *ortho* position, are prompted to react faster than electron-donor substituents. Electron-donor or non-substituted benzyl bromide derivatives frequently need longer irradiation times to aim complete conversion (See table S1). In addition, using irradiation at lower intensity leads to both less conversion and a reduced Ar-Ar/Ar-H ratio (Table 3, entry *vi*), reflecting the light-intensity dependence on the benzyl radical formation. In accordance with the PRE, the radical-molecule cross-reaction becomes more important when the local radical concentration diminishes.[36]

The supported AuNP used within this work were recovered and reused in the dimerization of 4-nitrobenzyl bromide to test the potential recyclability of the catalyst. Figure 1 presents the percent yield of the reaction after 5 h of LED irradiation over three turnover cycles. The catalyst is clearly reusable for this purpose, although some variability is observed; this is not uncommon with nanostructured catalysts.[37]

The decrease on the yield of the reaction can be related to the growth of the particles (from 2.5 nm to 4.1 nm, see SI) and is reasonable after the catalyst has been reused three times.

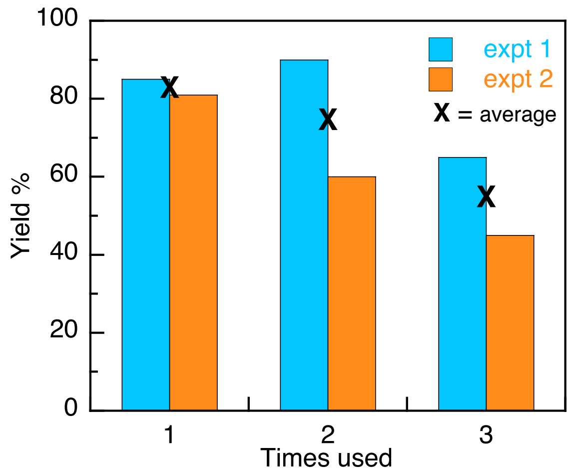
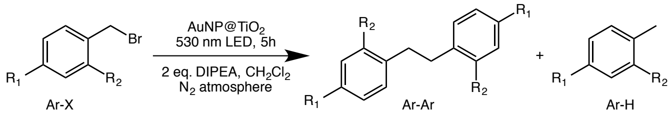


Figure 1. Percent reusability for the catalyst studied for the dimerization of 4-nitrobenzyl bromide under optimized reaction conditions for two independent experiments. The **X** in graph shows average values.

Table 3. Reduction of different substituted benzyl bromides using four 530 nm LEDs working at 3A.



#	R$_1$	R$_2$	% Conv Ar-X	% Yield of Ar-Ar	% Yield of Ar-H	Ar-Ar/Ar-H ratio
i	OCH$_3$	H	83	67	20	3.3
ii	H	H	29	97	ND	>>
iii	CH$_3$	H	28	80	ND	>>
iv	Ph	H	100	74	ND	>>
v	NO$_2$	H	100	81	12	6.9
vi	NO$_2$	H	72[a]	51	15	3.4
vii	H	NO$_2$	100	73	14	5.3

Quantification by H^1 NMR using caffeine as an external standard. [a] Working current: 1.6 A or about half the dose as in entry *v*. ND: values under Limit of Detection.

Conclusions

The use of supported AuNP catalysts was successfully extended to a C-C coupling reaction. To the best of our knowledge, this is the first example where supported AuNP catalyst is used in this type of reactions. AuNP supported on TiO$_2$ demonstrated good catalytic activity on the reductive dimerization of benzyl bromides. We also confirmed the C-C coupling occurs via radical coupling rather than by nucleophilic substitution (S$_N$2). It is in fact surprising to see radicals in very low concentrations (usually nanomolar) undergo self-reaction, rather than radical-molecule reactions. For this to occur several criteria must be met:

- The radicals need to have low reactivity, which generally means high resonance stabilization, as is the case for benzylic radicals. Reversible association with AuNP (as shown for benzyl radical)[32] may contribute to attenuated reactivity.
- Low solvent reactivity, and this is likely the reason that the reaction seems to require halogenated solvents.

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- Low concentrations and modest reactivity for any other free radical traps, and likely the reason why DIPEA gives better yield than the more reactive TEA.
- Absence of efficient radical traps. Note that addition of TEMPO effectively inhibits the reaction.
- Absence of oxygen, as most carbon centered radicals (but not all)[4] react rapidly with oxygen.[38]

It is interesting that these unusual criteria are all met in the current system making radical-radical reactions the preferred process. Finally, the catalyst showed an acceptable stability and reusability.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details, instrumentation used and NMR spectrum are shown in the supplementary information. See DOI: 10.1039/c000000x/

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