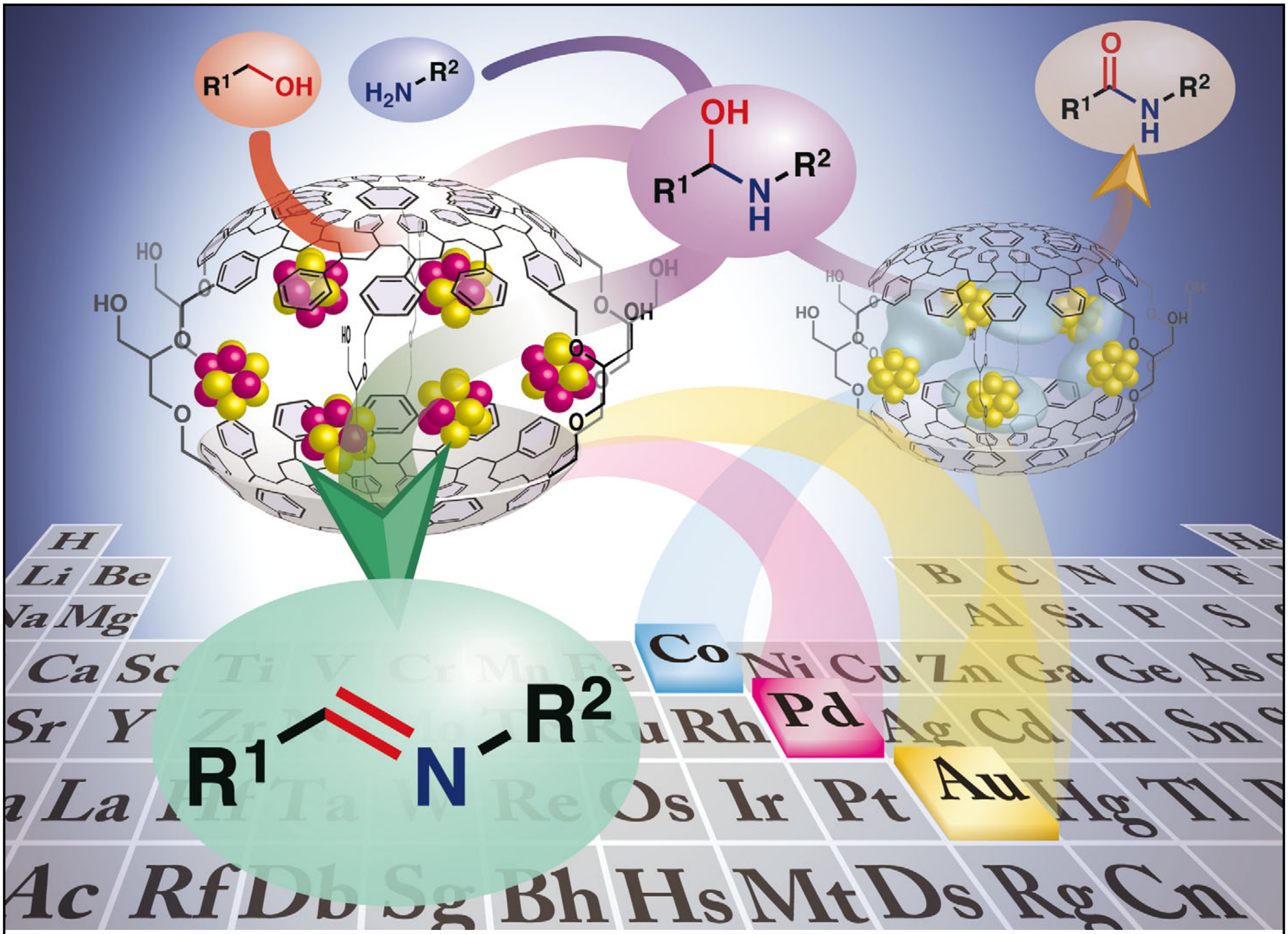

Showcasing research from the laboratory of Shū Kobayashi in the Department of Chemistry at the University of Tokyo, Japan

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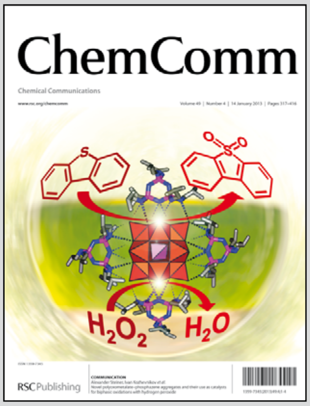

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Selective imine formation from alcohols and amines catalyzed by polymer incarcerated gold/palladium alloy nanoparticles with molecular oxygen as an oxidant†

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Carbon black stabilized, polymer incarcerated gold/palladium alloy nanoparticles (PICB-Au/Pd) act as an efficient, reusable heterogeneous catalyst for imine synthesis from alcohols and amines through a tandem oxidative process using molecular oxygen as the terminal oxidant.

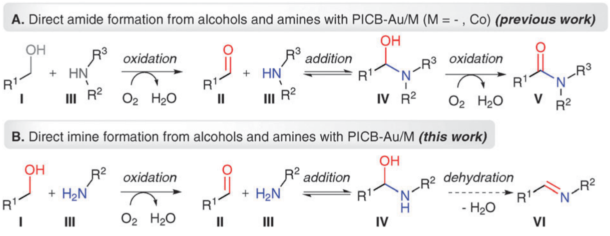
Imine is a very important functional group and imines are useful intermediates in organic chemistry and organic synthesis. They act as electrophilic reagents in many different transformations (*e.g.*, additions, condensations, cycloadditions, multicomponent reactions).[1] Their traditional preparation involves the reactions of ketones or aldehydes with amines.[2] Imines have also been synthesized by dimerization of primary amines under oxidative conditions,[3] oxidation of secondary amines,[4] transition metal-promoted hydrogen transfer from secondary amines,[5] and the direct reaction of nitroarenes and primary alcohols in the presence of heterobimetallic catalysts.[6] The cross-coupling between amines and alcohols is a very useful and suitable alternative preparation method, because many starting materials are readily available. Milstein's major breakthrough on the dehydrogenative coupling of alcohols and amines leading to amides[7] or imines[8] selectively has proved very attractive to other research groups.[8,9] The direct coupling of amines with alcohols has also been conducted under oxidative conditions by a tandem oxidative process (TOP)[10] using a stoichiometric amount of oxidant,[11] or using catalytic systems such as catalytic metallic systems with molecular oxygen as the terminal oxidant[12] including gold nanoparticles (Au-NPs) as catalysts.[13] However, relatively high reaction temperatures were required for most of the reported aerobic oxidative conditions and the recyclability of catalysts was scarcely discussed in these reports.

We have extensively developed the immobilization of metal catalysts using polymeric supports in a microencapsulation process.[14] We have also developed green catalysts for oxidation reactions through the immobilization of Au-NPs and bimetallic gold nanoparticles (Au/M-NPs) with styrene-based copolymers with or without carbon black (CB) as a second support; we call this the polymer incarcerated (PI(CB)) method. These heterogeneous catalysts have shown high activity for the aerobic oxidation of alcohols,[15] hydroquinones[16] and amines[4b] under mild conditions. In addition, we have demonstrated the viability of using these PI(CB) metal nanoparticles as catalysts for TOP such as the direct oxidative esterification of alcohols[17] and sequential allylic oxidation–Michael addition reactions.[18]

Recently, we reported a selective TOP using a nitrogen base as a nucleophile to produce amides from alcohols and amines using PICB-Au/Co or PICB-Au catalysts under aerobic oxidative conditions.[19] This process involves three steps: first, alcohol **I** is oxidized to aldehyde **II**; this aldehyde then reacts with amine **III** to give the carbinolamine (hemiaminal) **IV**, which is directly oxidized to amides **V** (Fig. 1A). Based on this previous study, we envisioned that the selectivity of this TOP might be tuned in favor of imine products **VI** by changing the final step to a dehydration process from the oxidative process (Fig. 1B).

We began our studies by preparing various combinations of PICB-Au/M catalysts following our previously reported procedure[19] and evaluated their ability to catalyze direct imine formation from alcohols and amines (Table 1).

4-Methylbenzyl alcohol **1a** and benzylamine **2a** were used as model substrates, and we chose the optimized reaction conditions described for the direct amidation under the TOP (*i.e.*, PICB-Au/Co as catalyst, 1 equivalent of NaOH, at rt) with a small modification of the solvent system: tetrahydrofuran (THF) alone was used without water to optimize the dehydration step (Table 1).


A. Direct amide formation from alcohols and amines with PICB-Au/M (M = - , Co) ***(previous work)***

B. Direct imine formation from alcohols and amines with PICB-Au/M ***(this work)***

Fig. 1 Tandem oxidative process (TOP) between alcohols and amines.

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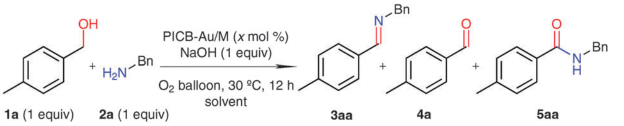
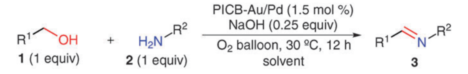
Table 1 Oxidative imine formation reaction: initial optimization

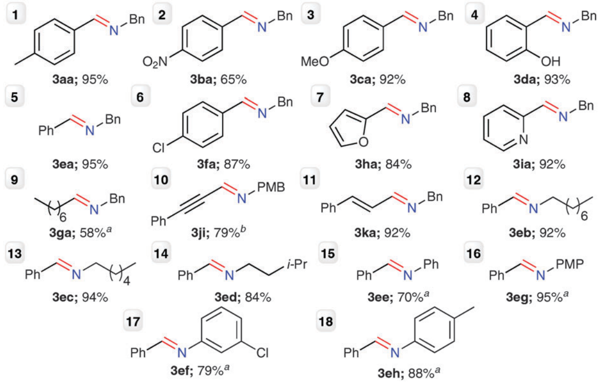


Entry	M	x	Solvent	Conv.[a] [%]	**3aa**[a] [%]	**4a**[a] [%]	**5aa**[a] [%]
1	Co	1	THF	54	Trace	12	40
2	—	1	THF	100	15	38	42
3	Pt	1	THF	51	4	37	8
4	Pd	1	THF	100	6	83	6
5	Pd	1	$PhCH_3$	100	6	59	29
6	Pd	1	MeOH	37	32	3	2
7	Pd	1	THF–MeOH (9 : 1)	50	26	10	5
8	Pd	1	THF–*i*-PrOH (9 : 1)	52	38	8	2
9	Pd	1	THF–HFIP (9 : 1)	30	29	0	0
10	Pd	1	THF–TFE (9 : 1)	85	83	Trace	0
11	**Pd**	**1.5**	**THF–TFE (9 : 1)**	**100**	**>95**	**Trace**	**0**
12[b]	Pd	1.5	THF–TFE (9 : 1)	0	0	0	0
13[c]	Pd	1.5	THF–TFE (9 : 1)	100	>95	Trace	0
14[c,d]	Pd	1.5	THF–TFE (9 : 1)	100	>95	Trace	0
15[c,e]	—	0	THF–TFE (9 : 1)	0	0	0	0
16	Co	1.5	THF–TFE (9 : 1)	100	53	Trace	45
17	Pt	1.5	THF–TFE (9 : 1)	100	83	6	9
18	—	1.5	THF–TFE (9 : 1)	100	82	8	12

[a] Determined by ¹H-NMR with respect to tetrachloroethane as internal standard. [b] No base used. [c] 0.25 equivalents of NaOH used. [d] Reaction was performed under an atmosphere of air for 24 h. [e] No catalyst was used. Conv. = conversion. Bn = benzyl. TFE = 2,2,2-trifluoroethanol.

Table 2 Oxidative imine formation reaction: substrate scope



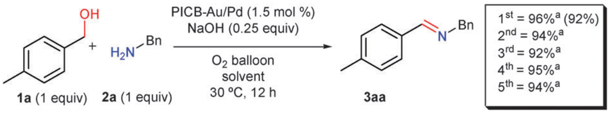


[a] The reaction was performed in THF–TFE (4 : 1) at 60 °C.
[b] The reaction was performed in THF–TFE (4 : 1) at 40 °C.
PMP = paramethoxyphenyl, PMB = paramethoxybenzyl, Bn = benzyl.

As expected, with PICB-Au/Co as catalyst, only a trace amount of imine **3aa** was observed and the amide product **5aa** was obtained in 40% yield (Table 1, entry 1). Next, we examined various combinations of Au and M (–, Pd, Pt) and found that PICB-Au/Pd and PICB-Au/Pt did not provide the desired imine **3aa** but provided the aldehyde **4a** in high selectivity with small amounts of amide **5aa** (Table 1, entries 3 and 4). Among these catalysts, PICB-Au/Pd showed the best single oxidation step selectivity (Table 1, entry 4) and was selected as the best catalyst for this transformation. The imine **3aa** was formed in low yield (6%), and we assumed that the dehydration step was the difficult step in this process because of the basic conditions. To address this issue, we initially examined the role of solvents, because suitable solvents should help to increase the speed of the dehydration step (Table 1, entries 5–11). Gratifyingly, by changing the solvent to MeOH, the reaction proceeded with high imine selectivity, although with low reactivity (Table 1, entry 6). To increase the reactivity while retaining the selectivity, we investigated mixed solvent systems of THF and protic solvents (Table 2, entries 7–11). Finally, THF–trifluoroethanol (TFE) (9 : 1) was identified as the best combination: >95% of imine **3aa** with only a trace of aldehyde **4a** was obtained (Table 1, entry 11). In this process, TFE may act as a Brønsted acid and/or a hydrogen-bond donor to promote the dehydration step.[20] Decreasing the amount of base to 0.25 equivalents had no effect on this reaction, but without a base, no reaction occurred (Table 1, entries 12 and 13). We then attributed the lack of reactivity to the high pH-dependence (basic) during the oxidation step in the presence of an amine, albeit in the absence of an amine the alcohols oxidation to ketones and aldehydes proceeded even under neutral conditions.[15c] Without a catalyst and with only sodium hydroxide (NaOH), no reaction occurred under our mild conditions, although potassium hydroxide can mediate imine formation under harsh conditions, as recently reported (Table 1, entry 15).[21] Finally, we examined the TOP using air (under balloon pressure) as the terminal oxidant, and found that the reaction also proceeded smoothly under the optimized reaction conditions (Table 1, entry 14). Examination of the resulting filtrate from the reaction mixture by inductively coupled plasma (ICP) analysis revealed that no leaching of Au and Pd occurred under the conditions used. To confirm the effect of bimetallic Au/Pd-NPs, we conducted some control experiments in the THF–TFE system (Table 1, entries 16–18). When we attempted to use only PICB-Au/Co as the catalyst, the selectivity decreased and almost the same amounts of amide **5aa** and imine **3aa** were obtained (Table 1, entry 16). With PICB-Au as the catalyst, only 82% of imine **3aa** was obtained with a mixture of amide **5aa** and aldehyde **4a** (Table 1, entry 18). PICB-Au/Pt showed good selectivity in favor of imine **3aa**, but the yield was lower than that obtained using the PICB-Au/Pd catalyst (Table 1, entry 17).

With the optimized reaction conditions established, the scope of imine formation was examined by varying the substitution patterns on both coupling partners (Table 2). Imines could be obtained as analytically pure forms (>95%) after simple filtration to remove the catalyst, followed by simple extraction after an aqueous workup and drying *in vacuo* to remove inorganic and volatile organic impurities. Various alcohols were tested in the reaction using benzyl amine **2a** as a coupling partner (Table 2). The results confirmed that a broad range of substitution patterns on the benzylic alcohol were tolerated, and the products were obtained in good to excellent yields (Table 2, entries 1–6). We also confirmed that the reactions of alcohols bearing heterocycles proceeded well to afford the desired imines in good yields (Table 2, entries 7 and 8). Unsaturated alcohols such as cinnamyl alcohol **2k** or propargyl alcohol **3j** could also be converted into the desired imines in good yields without loss of the C≡C triple or C═C double bonds (Table 2, entries 10 and 11). It is noted that aliphatic alcohols also reacted at higher temperature (40 °C) in

Table 3 Recovery and reuse of the catalyst



[a] Determined by ^{1}H-NMR with respect to tetrachloroethane as internal standard; numbers in parentheses are isolated yields. Bn = benzyl.

THF–TFE (4 : 1) to afford the desired imine **3ga** as a pure form despite the instability of the aliphatic imine (Table 2, entry 9). With regard to the amine part, most of the desired *N*-alkyl imines were prepared successfully in excellent yields (Table 2, entries 12–14). When aniline derivatives were used as amine coupling partners, the oxidation step became slower under standard conditions. To improve the reactivity, we conducted the reaction at 60 °C in THF–TFE (4 : 1), and *N*-aryl imines were obtained in excellent yields (Table 2, entries 15–18).

As previously reported,[17c] the combination of Au and Pd generates bimetallic alloy NPs. The formation of the alloy structure from the two metals gives NPs with different properties from those of the individual metal NPs: Au-NPs and Pd-NPs. We can expect that the Pd in the alloy NPs expresses more electropositive properties and Au expresses more electronegative properties because of their electronegativities. PICB-Au/Pd obtained in this way has a strong Lewis acid character on the Pd part, resulting in an acceleration of the dehydration step with the higher acidic character of TFE in the solvent, which explains why high selectivity in favor of imine products is obtained with the PICB-Au/Pd catalyst. Furthermore, as we have shown previously, the Au/Pd alloy NPs are more active in aerobic oxidation of alcohols than single-metal Au-NP catalysts, and this might operate in favor of imine formation.[15c]

Finally, we performed recovery and reuse studies with the PICB-Au/Pd catalyst for the direct imine formation with 4-methylbenzyl alcohol **1a** and benzylamine **2a** and found that the catalyst could be reused at least five times without noticeable loss of catalytic activity (Table 3). Pretreatment of the PICB-Au/Pd was required to reactivate the catalyst, similar to the case of amidation reactions.[19] This pretreatment consisted of washing with pure water and THF, followed by heating at 170 °C for 4 h without affecting the catalyst morphology.

In summary, we have achieved the selective formation of imines from alcohols and amines using TOPs under mild conditions. The PICB-Au/Pd heterogeneous catalyst showed high activity and selectivity for this transformation and this catalyst can easily be recycled several times without loss of activity. The method has been generalized and a wide variety of substrates has been tested (benzylic, allylic, propargyl and aliphatic alcohols; primary amines; aniline); these have shown excellent activity in this coupling and the imine products can be obtained as an analytically pure product after simple filtration to remove the catalyst and an aqueous workup to remove the inorganic compounds. We are now studying further applications of this catalytic system and conducting mechanistic studies.

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