Journal of Catalysis 400 (2021) 103–113

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Reductive imino-pinacol coupling reaction of halogenated aromatic imines and iminium ions catalyzed by precious metal catalysts using hydrogen

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ARTICLE INFO

Article history:
Received 2 March 2021
Revised 23 May 2021
Accepted 25 May 2021
Available online 29 May 2021

Keyword:
Heterogeneous catalysis
Imino-pinacol coupling reaction
Precious metal catalyst
Vicinal diamines

ABSTRACT

The first heterogeneously catalyzed process for the reductive coupling of imines and iminium ions is reported using precious metal catalysts in combination with hydrogen gas as the terminal reductant. The optimized method in terms of catalyst composition and reaction conditions allowed to produce aromatic vicinal diamines without the use of stoichiometric amounts of zero or low valent metals, which is currently the preferred method. The most important mechanistic features of the reaction were unraveled by a combined experimental and computational approach. The developed methodology is very efficient for the coupling of aromatic iminium ions with yields up to 88% while imines give only low to moderate yields.

1. Introduction

Vicinal diamines represent a valuable class of organic compounds used in several applications such as medicinal chemistry and catalysis [1]. In addition to their natural occurrence, the vicinal diamine moiety can be found in several active pharmaceutical ingredients (API) such as ethambutol and esimertinib [2].Moreover, several different new potential drug candidates have this vicinal diamine backbone incorporated in their final structure [3].The reductive coupling of imines towards vicinal diamines is well-known and one of the most efficient chemical reactions towards vicinal diamines, discovered independently by Peterson and Smith in 1966 who studied the coupling of N-phenyl benzaldimine [4]. Currently known as the imino-pinacol coupling reaction, it is still a valuable synthetic method for carbon-carbon bond coupling. The imino-pinacol coupling reaction, named after the original pinacol reaction, is thought to proceed via a single-electron transfer (SET) to the C=N bond initiated by a pre-reduced metal, metal complex or photochemical approach resulting in a radical anion. The obtained radical anion can then dimerize via a radical–radical coupling reaction (Fig. 1) [5].

The use of metal-based reductants is the most widely developed approach to this coupling reaction and different options were already explored: zero valent metal-based reagents such as alkali metals (Li, Na) [4,6] and to a lesser extent alkali earth metals (Mg) [7] or metals from the p-block of the periodic Table (Al [8], In [9], Bi [8], Zn [10]). Also, *in situ* generated low valent metal-based reagents such as Ti(II), Ti(III) [11] and other transition metals (Mn [12]) and divalent lanthanide salt-based systems have been used [13].These coupling reactions, with both metalorganic catalysts and stoichiometric high valent metals require a significant excess of high potential reduction agents resulting in a waste intensive process and therefore, alternatives have already been developed. Pawda et al. investigated the photoreduction of aromatic imines and showed that various benzaldehyde derived N-alkylimines led to the corresponding vicinal diamines under photochemical irradiation [14]. However, to increase the yield and decrease the residence time, these photochemical reactions benefit from the addition of a photosensitizer [15], such as zinc carboxylate which again makes this a waste generating process due to the difficulty of regenerating these metal complexes.

Although some ‘catalytic’ processes have been developed in which metal salts regenerate *in situ* a highly active reducing metal that acts as the catalyst [16], no example could be found of a truly catalytic process in which none of the metals used in the process were consumed or could be easily reused. Keeping the 12

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https://doi.org/10.1016/j.jcat.2021.05.023
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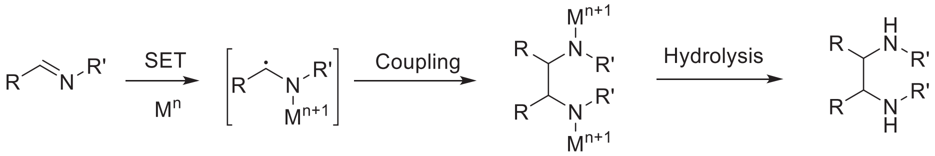


Fig. 1. Mechanism of the imino-pinacol coupling reaction by the use of low valent metals [3].

principles of Green Chemistry in mind [17], a (heterogeneous) catalytic process involving hydrogen as a terminal reductant without the generation of waste would be desirable. Focus of this research lies in the use of different bimetallic catalysts based on precious metals for the reductive coupling of different imines and iminium ions for the formation of vicinal diamines to develop a new, sustainable and minimal waste process towards vicinal diamines.

2. Results and discussion

2.1. Discovery of the reaction

Previous research performed by some of the present authors on the reductive amination of halogenated aldehydes with aliphatic amines [18], and more specifically the reductive amination of o-Cl-benzaldehyde **1** (o-Cl-BZA) with dimethyl amine **2** (DMA) in the presence of hydrogen gas and a heterogeneous palladium catalyst, showed unexpectedly the formation of vicinal diamines **6** as a side-product along with the (at that time) desired halogenated benzyl, N,N-dimethyl amine **5** (Fig. 2) as well as other side products resulting from hydrogenation, dehalogenation and acetalization.

The imino-pinacol side-reaction however, was extensively studied in order to decrease the formation of these vicinal diamines during the reductive amination reaction of o-Cl-benzaldehyde with DMA since the formed vicinal diamines (**6**) give rise to issues on industrial scale. These vicinal diamines are insoluble in the reaction mixture used for the reductive amination reaction, and therefore, precipitate when formed causing clogging and caking of the industrial installation.[18c] Because it is known that intermediary iminium ions **4** are formed [19] during these reductive amination reactions, the formation of these vicinal diamines should proceed through an imino-pinacol coupling mechanism, which is widely described in literature. Although at that time, not a lot of attention was given to this imino-pinacol side-reaction other than trying to minimize it, it holds an interesting potential: namely a catalytic imino-pinacol coupling reaction. As it was seen in our previous research that certain parameters, such as the amount of aminating agent used, had a large effect on the extent of the imino-pinacol coupling side-reaction, it was decided to further explore the imino-pinacol coupling reaction and to optimize it to become the main reaction.

First, preliminary experiments were performed to have a better understanding of this imino-pinacol coupling reaction and to investigate the role of both the bimetallic Pd-Cu catalyst, the catalyst on which this coupling reaction was first observed, and the hydrogen gas. In each experiment, one reagent or catalyst was left out to assess the necessity of the different raw materials. The turnover number (TON), which expresses the amount of mol of

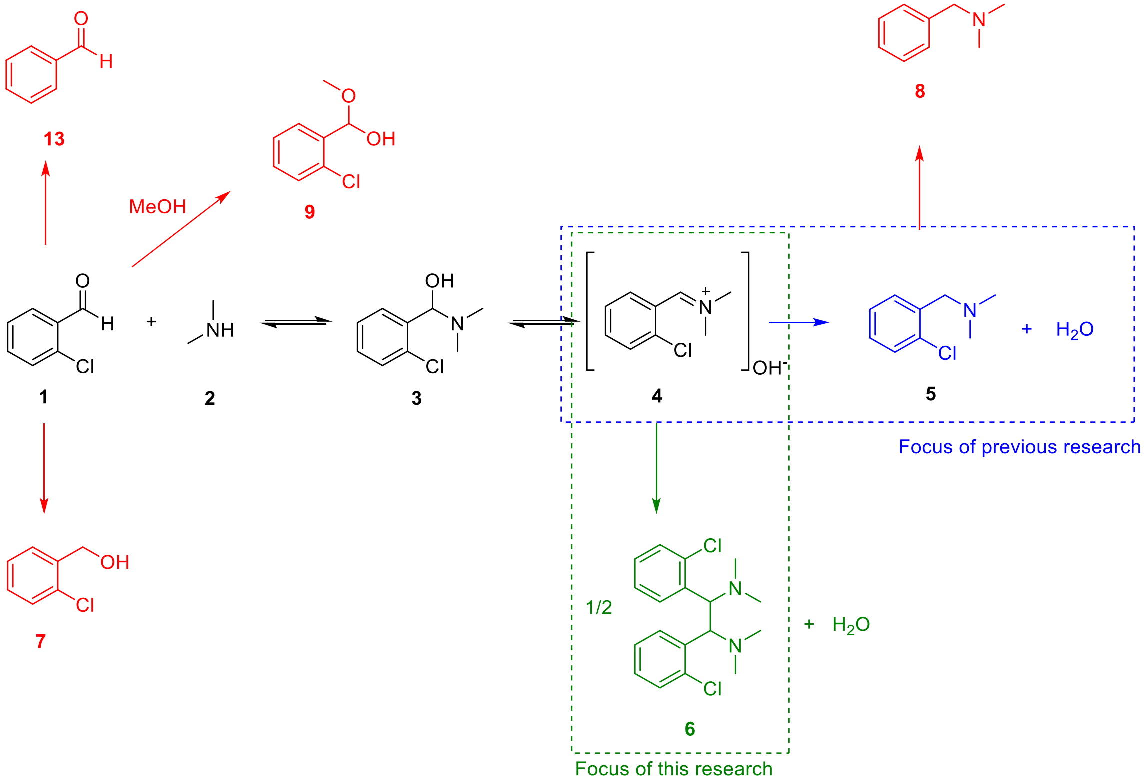


Fig. 2. Reaction network indicating the focus reaction of previous research and current research.

substrate that was converted per mol of active metal, was calculated for the imino-pinacol coupling reaction to see if this is a truly catalytic process. Because no information was available on whether the palladium or the copper is the active metal, both metals were taken into account when calculating the TON. In all cases, unless mentioned otherwise, a two-step, one-pot approach was applied. The 2-Cl-benzaldehyde and dimethyl amine were mixed together with the solvent prior to the addition of hydrogen and catalyst in order to form the intermediate iminium ion. The results are shown in Table 1. When the aldehyde, the aminating agent, the catalyst and the hydrogen are present during the reaction, compound **6** could be obtained in a yield of 5% with a TON of 91. When no catalyst, DMA or hydrogen was present, no formation of this imino-pinacol coupling product was observed. Moreover, the metals are mandatory as no reaction was observed if only the catalyst support was used. These observations indicate that the observed imino-pinacol coupling reaction should be a catalytic process with the need of hydrogen, presumably for the regeneration of the catalyst active state. Moreover, a difference in yield was observed in a one-step versus a two-step approach (Entry 1a versus 1b, Table 1)

Because all the procedures described in literature either use a stoichiometric amount of a reducing metal or an electrochemical or photochemical approach to generate the SET, this is the first observation of a truly catalytic process in which hydrogen can act as the terminal reductant to regenerate the metal in the active oxidation state. Therefore, the research hereafter described, will focus on exploiting this observed side reaction as a catalytic imino-pinacol coupling reaction and attempt to convert it to the main reaction. In all experiments, the imine or iminium ion was prepared *in situ* through reaction of an aldehyde with an aminating agent (such as primary and secondary amines). No intermediate purification of the imine or iminium ion was performed.

2.2. Catalyst screening

In order to find a catalyst for which the imino-pinacol coupling reaction was dominating over the reductive amination, a screening was performed with 36 different metal combinations precipitated on activated carbon. The reductive amination reaction of o-Cl-benzaldehyde with dimethyl amine (Fig. 2) was chosen as a model reaction to perform the screening. The formation of the vicinal diamines **6** together with the hydrogenated product **5** was monitored (Table 1). It could be observed that heterogeneous catalysts containing ruthenium as a first or second metal or platinum as a first metal showed the

highest potential for this carbon–carbon coupling reaction in comparison with catalysts which contain palladium in the highest concentrations. A yield of 23% and a TON of 1307 could be obtained using a catalyst containing 3 wt% palladium and 6 wt% ruthenium on an activated carbon support. (Entry 19, Table 2). Although a palladium-ruthenium catalyst gave the highest TON and yield of the vicinal diamine **6**, there was a clear influence of the ratio of the metals.

A catalyst with a molar ratio of palladium/ruthenium of 1:1 resulted in a yield of the diamine of only 6% (Entry 18, Table 2), while a catalyst with molar ratio of 1:2 resulted in a yield of 23% (Entry 19, Table 2).

Because hydrogen gas is used as the terminal reductant (see Table 1), direct hydrogenation of several reagents and intermediary products can also occur in competition with the single electron transfer reaction. Both the direct hydrogenation of the aromatic aldehyde (starting reagent) and the intermediary iminium cation were observed leading to o-chloro benzyl alcohol **7** and o-chloro benzylamine **5** respectively. Another side reaction was the dehalogenation reaction leading to formation of the benzyl species (especially benzyl amine **8**). Acetalization of the substrate with the solvent methanol led to formation of the methoxy hemi-acetal **9**.

2.3. Optimization of the catalytic system

Encouraged by these results, several other catalysts containing either palladium and ruthenium or ratios here off with similar metal surface areas, were tested in identical reaction conditions. At first instance, it could be observed again that no coupling reactions occurred when using no catalyst or activated carbon (Entry 1 and 2, Table 2) indicating that a metal is needed for this single electron transfer reaction. By varying the palladium/ruthenium ratio, while keeping the total amount of added metal constant, the yield could be increased to 68% using a 0,5 wt% Pd- 4,5 wt% Ru on activated carbon (Entry 8, Table 3). Comparing entry 8 and 9 in Table 3, a synergistic effect could be noticed of the addition of a small amount of palladium to a ruthenium catalyst. By the addition of 0,5 wt% palladium, the yield could be increased with 10% (absolute). A physical mixture of a 0,5 wt% Pd/C and a 4,5 wt% of Ru/C catalysts (Entry 10, Table 3) gave intermediate results compared to the use of the pure catalysts, indicating that a proximity of the two metals is needed in the catalytic center to obtain the synergistic effect. As also shown in Fig. 3, increasing the Ru fraction of the catalyst thus leads to a higher conversion and a higher yield towards **6** while the yield towards **5** decreases. However, the presence of a small amount of palladium still leads to higher conversion and yields towards the coupling product compared to a pure monometallic ruthenium on carbon catalyst.

Modifying the reaction conditions allows to further favor C-C coupling reactions over the direct hydrogenation of the intermediate iminium ion **4** to the tertiary amine **5**. The most important parameter (in the tested range of conditions) was found to be the excess of the amine. If a large excess of amine is used, the selectivity towards the diamine **6** can reach 63% (Entry 9, Table 4) while with a small excess (1,2 eq. amine), the selectivity drops to 6% (Entry 7, Table 4) in favor of the direct reductive amination reaction of the aldehyde towards o-Cl-benzyl N,N-dimethyl amine **5**. If almost equimolar amounts of reagents are used (1,01 eq. –Entry

Table 1
Effect of raw materials/catalyst on the imino-pinacol coupling reaction[a]

Entry	Aldehyde 1	DMA	Bimetallic Catalyst	Activated carbon support	H_2	Aldehyde conversion (%)	Yield 6 (%)	TON 6 (/)
1a	x	x	x		x	99	5	91
1b[b]	x	x	x		x	99	2	32
2	x		x		x	32	0	N/A
3	x	x			x	0	0	N/A
4	x	x		x	x	0	0	N/A
5	x	x	x			0	0	N/A

[a] Two step – one pot approach; Reaction conditions: T = 383 K; 5.5 MPa H_2 pressurized at room temperature; 0.3 g MeOH/g o-Cl-BZA; 5 eq. DMA; 1.5 mg catalyst/g o-Cl-BZA; Reaction time: 90 min; Catalyst: 3 wt% Pd-7 wt%Cu/C
[b] One step approach

Table 2
Catalyst screening for the reductive amination of o-Cl-Benzaldehyde with dimethylamine; Yield and TOF of vicinal diamine formation[a]

Entry	First metal (wt%)	Second metal (wt%)	Third metal (wt%)	Aldehyde conversion (%)	Yield 6 (%)	Yield 5 (%)	TON 6 (/)
1	Pd (3)	Fe (2,35)	–	100	< 1	54	–
2	Pd (3)	Fe (4,7)	–	100	< 1	66	–
3	Pd (3)	Ni (2,5)	–	100	< 1	53	–
4	Pd (3)	Ni (4,9)	–	100	< 1	51	–
5	Pd (3)	Ni (6)	–	100	< 1	54	–
6	Pd (3)	Co (2,5)	–	100	< 1	53	–
7	Pd (3)	Co (4,9)	–	100	< 1	60	–
8	Pd (3)	Zn (2,7)	–	100	< 1	57	–
9	Pd (3)	Zn (5,4)	–	100	< 1	65	–
10	Pd (3)	Ag (3)	–	100	< 1	91	–
11	Pd (1)	Ag (2)	–	100	1	82	130
12	Pd (3)	Cu (2)	–	100	1	83	89
13	Pd (3)	Cu (7)	–	100	1	89	43
14	Pd (3)	Pt (1)	Fe (1,6)	100	1	84	81
15	Pd (3)	Pt (1)	Ag (3,1)	100	1	82	97
16	Pd (3)	Pt (1)	Au (5,5)	100	1	79	54
17	Pd (3)	Pt (1)	Ru (2,9)	95	2	80	146
18	Pd (3)	Ru (2,9)	–	88	6	46	534
19	Pd (3)	Ru (5,7)	–	83	23	55	1307
20	Pd (3)	Pb (11,7)	–	60	<1	27	49
21	Pd (3)	Sn (6,7)	–	66	1	14	81
22	Pd (3)	Rh (2,9)	–	82	6	76	492
23	Pd (3)	Rh (5,9)	–	87	5	78	297
24	Pd (3)	Mo (5,4)	–	97	<1	93	–
25	Pd (3)	Au (5,5)	–	97	<1	82	–
26	Ru (3)	Cu (3,8)	–	78	10	46	513
27	Ru (3)	Sn (7)	–	80	20	35	1069
28	Ru (3)	Ag (6,4)	–	81	12	34	637
29	Pt (3)	Cu (2,0)	–	86	10	77	659
30	Pt (3)	Ag (3,3)	–	64	7	42	502
31	Pt (3)	Pb (15,9)	–	42	1	6	949
32	Pt (3)	Sn (9,2)	–	88	3	63	119
33	Pt (3)	Re (14,3)	–	96	6	71	254
34	Pt (3)	Au (8,3)	–	93	6	72	259
35	Pt (3)	Rh (7,9)	–	71	10	10	405
36	Pt (3)	Mo (7,4)	–	66	11	43	454

[a] Reaction conditions: T = 383 K; 5,5 MPa H_2 pressurized at room temperature; 0,3 g MeOH/g o-Cl-BZA; 1,4 eq. DMA; 1,5 mg catalyst/g o-Cl-BZA; Reaction time = 90 min; Catalyst support: activated carbon

Table 3
Imino pinacol coupling reaction catalyzed by several palladium/ruthenium catalysts[a]

Entry	Catalyst	Aldehyde conversion (%)	Yield 6 (%)	Yield 5 (%)
1	–	30	0	0
2	Activated carbon	30	0	0
3	5 wt% Pd/C	70	21	35
4	(4.5 wt% Pd-0.5 wt% Ru)/C	80	22	42
5	(3.75 wt% Pd – 1.25 wt% Ru)/C	83	28	29
6	(2.5 wt% Pd – 2.5 wt% Ru)/C	92	48	18
7	(1.25 wt% Pd – 3.75 wt% Ru)/C	93	58	13
8	(0.5 wt% Pd – 4.5 wt% Ru)/C	95	68	9
9	5 wt% Ru/C	92	58	8
10	0.5 wt% Pd/C + 4.5 wt% Ru/C[b]	90	53	21

[a] Reaction conditions: T = 343 K; 1.2 MPa H_2 pressurized at room temperature; 0.3 g MeOH/g substrate; 5 eq. DMA; 0.7 μmol metal/g substrate; Reaction time: 20 h
[b] Physical mixture of 0.07 μmol Pd/g substrate and 0.63 μmol Ru/g substrate

8, Table 4), the dimer formation is almost negligible and the selectivity to the single reductive aminated product **5** increases significantly.

In order to obtain high yields of the diamine, also the reaction temperature and the hydrogen pressure also play a crucial role. Increasing the temperature leads to a higher conversion (Entry 1 versus 2, Table 4) but too high temperatures lead to the formation of side products **5** and **7** (Entry 3, Table 4). Increasing the hydrogen pressure at first leads to a higher yield (caused by a faster reaction) (Entry 5 versus 6, Table 4) until a pressure of 25 barg after which no effect on the yield is observed anymore (Entry 6, Table 4).

In order to assess the influence of the type of solvent used, several experiments were performed using the optimal conditions (Entry 5, Table 4) and the optimized catalyst (Entry 8, Table 3), only varying the solvent.

The highest yields are obtained with two different dipolar aprotic solvents: N,N-dimethylacetamide resulted in 70% yield (Entry 8, Table 5) and N,N-dimethyl formamide even in a yield of 81% (Entry 7, Table 5). Secondly, it was observed that when decreasing the polarity of the alcoholic solvent (table 4, entry 1, 2 and 3) both the conversion of the aldehyde and the yield towards the vicinal diamines decreases. While a yield of 68% could be obtained when using methanol as the solvent (Entry 1, Table 5), 1-octanol only leads to 34% yield (Entry 3, Table 5). Water, when used as the solvent, will have an influence on the aldehyde – iminium ion equilibrium reaction, shifting the equilibrium more towards the aldehyde

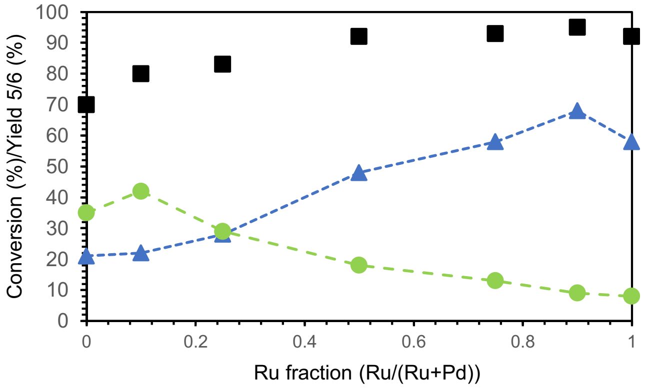


Fig. 3. Effect of Ru fraction on conversion (■) and yield of **5** (●) and **6** (▲).

function. This effect was clearly shown by the lower aldehyde conversion and the large excess of unreacted iminium ions present in the reaction mixture. Moreover, there is a clear trend noticeable between the yield of the reductive coupling reaction and the dipolar intermolecular forces δp of the solvent (Hanssen Solubility Parameter) (see Fig. 4).

Moreover, since the reductive coupling reaction leads to the formation of a chiral carbon atom at the benzylic position, the diastereomeric ratio for the different experiments executed at different reaction conditions (see Table 4) and in different solvents (see Table 5) was determined. It was seen that no significant stereoselective preference could be noticed and both diastereoisomers were formed during the reductive coupling reaction leading to an almost racemic mixture.

2.4. Substrate scope

In order to assess the potential of this catalytic imino-pinacol coupling reaction, the reductive coupling of several other imines and iminium cations formed via reaction between different substituted and non-substituted aromatic aldehydes and amines was evaluated. Again, it was observed that there was no significant stereoselective preference for one of the diastereoisomers. Functional groups such as methoxy, chloro, bromo and fluoro substituents were tolerated both at the *ortho*, *para* and *meta* position although for bromo substituents, dehalogenation reactions occurred significantly. However, a clear effect could be noticed involving both the presence of these substituents and the position on the aromatic ring. The presence of two chloro substituents on respectively the *ortho* and the *para* position (Entry 4, Table 6) gives rise to a higher yield compared to only one chloro substituent on the *ortho* position (Entry 2, Table 6) and especially compared to one chloro substituent on the *meta* position (Entry 3, Table 6). Since it is believed that the reductive coupling reaction involves a radical intermediate specie (see also paragraph 2.5), the lifetime of the radical and therefore also its stability is of high importance to assess the effect of the substituent [5b]. The theory of the captodative effect postulates that a combined action of an electron withdrawing and electron releasing agent on a radical center leads to stabilization [20]. In the tested substrates, the aromatic ring with the substituents acts as the electron withdrawing group and the amine function acts as the electron releasing agent to stabilize the benzylic radical. Since fluoro is a stronger electron withdrawing group compared to chloro and therefore, leads to a higher stabilization of the intermediate benzylic radical, higher yields were expected and indeed obtained in case a fluoro substituent was present compared to chloro (entry 5 versus 2, Table 6). In case a bromo substituent was used, dehalogenation reactions were observed (entry 7, Table 6). The effect of the electron releasing agent on the stability of the iminium radical was tested by altering the length of the alkyl chain of the amine. By increasing the length from one carbon (monomethyl amine, Entry 9, Table 6) to two carbons (mono ethyl amine, Entry 10, Table 6), the yield could be increased from 6 to 20% clearly showing the effect of the electron releasing agent. However, one should expect that based on that captodative effect, a chloro substituent on the *meta* position would lead to a lower stability of the formed iminium radical (decreased electron withdrawing capacity) and thus to lower yields compared to the absence of this substituent. However, it was seen that the presence of a halogen substituent on the *meta* position increased the yield from 20% up to 33% (Entry 3, Table 6), indicating the presence of an additional effect of the halogen substituents (see paragraph 2.4). To further elaborate on the effect of the substitution pattern on the captodative effect, Radical Stabilization Energies (RSEs) are calculated by means of DFT calculations (See ESI). With respect to the benzaldehyde (Entry 1, Table 6), a consistent increased stability is observed for the halogenated compounds (Entry 2–4, Table 6). However, the substitution pattern has only a limited effect (<10 kJ.mol^{-1}) on the stability of the formed radicals indicating (Table S9 ESI) that, in line with the experiments, additional effects are to be considered to explain the observations. It was seen that aliphatic iminium ions, formed via the reaction of butyraldehyde and dimethyl amine, show no reductive coupling reaction towards vicinal diamines (Entry 14, Table 6). It is known that benzylic radicals show a higher stability and increased lifetime compared to aliphatic radicals [21]. Moreover, aliphatic iminium ions can transform to the more stable enamine, which is an inactive intermediate for the reductive coupling reaction towards vicinal diamines.

Different primary and secondary amines were also used to prepare several different intermediary imines and iminium ions *in situ* for the coupling reaction. When the formation of an intermediate imine or enamine is not possible and iminium cations need to be formed (thus in case a secondary amine in combination with a benzaldehyde is used), yields are substantially higher compared to the coupling of intermediate imines. Comparing the coupling reaction

Table 4
Varying temperature, hydrogen pressure and equivalents amine in the *in situ* imino-pinacol coupling of compound **4**[a]

Entry	Temperature (°C)	H_2 pressure (barg)	Eq. amine	Aldehyde conversion (%)	Yield 6 (%)	Yield 5 (%)	dr
1	50	12	5	15	9,0	3	55:45
2	70	12	5	95	57	11	51:49
3	100	12	5	93	46	23	57:43
4	70	5	5	73	44	10	55:45
5	70	25	5	94	65	13	54:46
6	70	50	5	94	65	13	58:52
7	100	12	1,2	83	6	63	51:49
8	100	12	1,01	76	< 1	70	N/A
9	100	12	15	96	63	5	50:50

[a] Reaction conditions: 0.3 g MeOH/g o-Cl-BZA; amine = dimethyl amine; Catalyst: (1.25 wt%Pd/3.75 wt% Ru)/C, 0.7 μmol metal/g o-Cl-BZA; Reaction time: 20 h

Table 5
Varying solvent in the *in situ* imino-pinacol coupling reaction of compound **4**[a]

Entry	Solvent	δp	Aldehyde conversion (%)	Yield 6 (%)	Yield 5 (%)	dr
1	Methanol	12,3	95	68	14	60:40
2	Ethanol	8,8	85	37	16	61:40
3	1-Octanol	5	80	34	11	61:39
4	Water	16	60	25	9	60:40
5	THF	5,7	80	25	8	63:37
6	Chloroform	3,1	56	12	8	54:46
7	Benzene	0	95	3	2	67:33
8	N,N-Dimethylformamide	13,7	98	81	5	55:45
9	N,N-Dimethylacetamide	11,5	86	70	5	56:44

[a] Reaction conditions: T = 343 K; 2.5 MPa H_2 pressurized at room temperature; 0.3 g solvent/g substrate; 5 eq. DMA; 0.7 μmol metal/g substrate; Catalyst: (0,5 wt%Pd-4,5 wt%Ru)/C; Reaction time: 20 h.

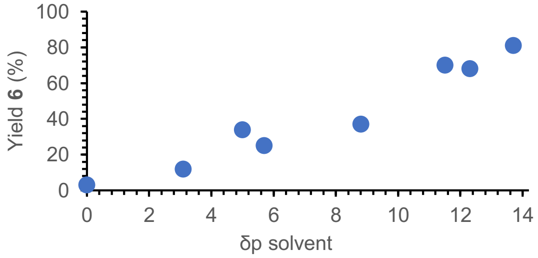


Fig. 4. Yield of **6** (%) as a function of the dipole moment of the used solvent.

of the *in situ* formed imine/iminium cation using of methylamine (Entry 9, Table 6), ethylamine (Entry 10, Table 6) and dimethyl amine (Entry 2, Table 6) in combination with o-Cl-benzaldehyde, it was observed that the use of dimethyl amine leads to a yield of 57% while the use of ethylamine which has a similar electron releasing capacity to stabilize the intermediary radical that is formed (cfr captodative effect), only gives rise to 20% of the desired vicinal diamine product. An elaborate explanation of this observation is discussed in paragraph 2.4. The reaction with a sterically hindered amine such as tertiary butylamine or diphenylamine gives rise to a limited amount of hydrogenation products and either stops at the intermediate iminium ion or shows limited aldehyde conversion.

2.5. Mechanistic consideration for the reaction pathway at the level of imine/iminium ion

Based on the observed phenomena in the heterogeneously catalyzed imino-pinacol coupling with hydrogen as the terminal reductant, the following reaction pathway was proposed based on several different additional experiments and DFT calculations (Fig. 5). Because it was seen that the yield at full conversion mostly depends on the type of intermediate product that can be formed: imine or iminium cation, a distinction was made between the intermediary formation of imines (R^2 = H) and the intermediate formation of iminium ions ($R^2 \neq$ H).

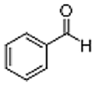
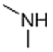
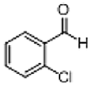
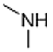
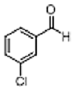
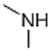
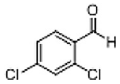
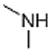
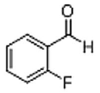
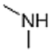
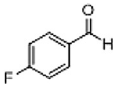
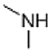
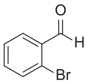
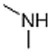
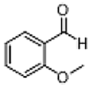
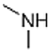
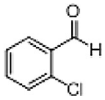
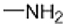
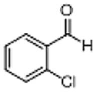
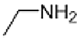
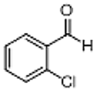
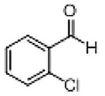
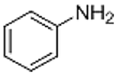
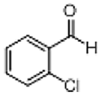
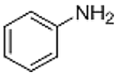
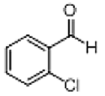
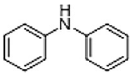
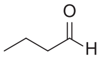
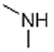
The key difference in the reductive coupling of imines **3** and iminium cations **4** lies in the different pathways from which reductive amination reaction, leading to the main side-product **5**, can occur. It is well described in literature that both for the imine **3** and the iminium cation **4**, the formation of the vicinal diamines **6** through carbon-carbon coupling reactions, proceeds via a Single Electron Transfer (SET) leading to a radical intermediate followed by radical coupling of the two species [5b]. The reductive amination reaction towards the amine, however, relies on a different pathway when iminium ions **4** are formed in comparison with the more stable imines **3**.[19,22] Birtill et al. have shown that, when the formation of an imine or enamine is not possible, the reductive amination reaction proceeds mainly via N-adsorption of the hemi-aminal **2** to the catalyst surface and the subsequent hydrogenolysis of the C-OH bond to the amine product and to a much lesser extend via the direct hydrogenation of the iminium cation **4** [19]. As a consequence, when intermediate imine formation is possible, there is direct competition between the reductive amination reaction and the coupling reaction. This was also shown by the similar yields obtained when applying an isolated imine versus an *in situ* prepared imine (entry 12a and 12b, Table 6). If however no stable imine can be formed, the reductive amination reaction proceeds via the hemi-aminal **2** while the coupling reaction proceeds via the more unstable iminium ion. Moreover, because of the reactivity of the iminium ion, different intermediates can be formed such as N,N-acetals [23] **10** and N,O-acetals **11** by addition reactions with a secondary amine and a methoxy group (in case methanol is used as a solvent), respectively.

Furthermore, since some dehalogenation reaction occurs in case a halogenated aromatic aldehyde is used, also the addition of the chloride to the iminium ion can form intermediate **12**. Formation of these acetals lead to a shift in the iminium ion – hemi aminal equilibrium in preference of the iminium ion. Moreover, the liberated chloride ions into the reaction mixture can also be used as counterion for the iminium ion **4** (called **4-Cl**) instead of a hydroxy anion (**4-OH**). This postulated theory can also explain the increase in yields when higher equivalents of amination agent are used. Increasing the amount of amination agent, such as dimethyl amine, will shift the hemi-aminal – imine/iminium ion equilibrium in favor of the imine/iminium ion, eventually leading to a higher amount of coupled product at the expense of the reductive amination reaction.

To validate this reaction path, several different control experiments were performed using the bimetallic (0.5 wt% Pd – 4.5 wt % Ru)/C catalyst. The intermediate N,N-acetal **10** (R^1 = R^2 = CH_3) was prepared according to the procedure of Sakai et al. [24] and used as a starting material for the formation of vicinal diamines. Water free tertiary butanol was used instead of methanol to avoid the formation of N,O acetals (**2** and **11**) which can undergo hydrogenolysis towards the end product **5**. If o-Cl-benzaldehyde and dimethylamine were used as reactants and tertiary butanol as solvent, a yield of 37% of the vicinal diamines could be obtained. If now the N,N acetal **10** was used as a reactant in the same conditions, a yield of 88% could be obtained (see Table S1). In both cases, the yield loss was attributed to the formation of **5**. The difference in side-product **5** formation indicated that the reductive amination of the iminium ion is less pronounced compared to the hydrogenolysis of the hemi-aminal **2** as formation of intermediary product **2** is not possible when N,N-acetal **10** was applied as starting product in a water free environment.

If higher equivalents of the amination reagents are used (such as dimethyl amine), the equilibrium will shift towards compound

Table 6
Imino-pinacol coupling reaction of different formed imines and iminium ions[a]

Entry	Aldehyde	Amine	Aldehyde conversion (%)	Yield vicinal diamine (%)	dr	Most important side-reaction (yield %)
1			86	20	54:46	Reductive amination reaction: 52
2			95	57[c]	51:49	n/a
3			56	33	40:60	Reductive amination reaction: 20
4			95	88[d]	50:50	n/a
5			81	66	53:47	n/a
6			48	5	n.d.	Halogen substitution reaction: 23
7			>99	<1	n.d.	Dehalogenation reaction: 97
8			98	31	56:44	Reductive amination reaction: 60
9			>99	6	n.d.	Reductive amination reaction: 91
10			>99	20	54:46	Reductive amination reaction: 62
11			>99	3	n.d.	Intermediary imine/hemi-aminal: 75
12a			>99	24	60:40	Reductive amination reaction: 15
12b[e]			>99	22	55:45	Reductive amination reaction: 54
13			4,2	0.0	N/A	n/a
14			45	0.0	N/A	Reductive amination reaction: 47

[a] Reaction conditions: T = 343 K; 1.2 MPa H_2 pressurized at room temperature; 0.3 g MeOH/g o-Cl-BZA; 5 eq. DMA; 0.7 μmol metal/g substrate; Catalyst: (0,5 wt%Pd-4,5 wt%Ru)/C; Reaction time = 20 h.
[b] Yields are determined using GC analysis without isolation of the vicinal diamine product.
[c] Isolated yield: 51%.
[d] Isolated yield: 85%.
[e] Intermediate imine was isolated prior to the reductive coupling reaction.

4 and **10** and thus lead to lower yields of the reductive amination reaction (lower amount of compound **2**) and higher yields of the vicinal diamines. To eliminate the effect of the basicity due to higher amounts of amination reagents, a trial was conducted with equimolar amounts of the secondary amine as starting product and the addition of a non-nucleophilic base, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU). No increase in yield was observed when DBU was added indicating that the effect of the higher amounts of secondary amine should come from an equilibrium shift and not from a base effect (see Table S2).

Besides the formation of an N,N acetal **10** and a N,O acetal **11**, the formation of N,X acetals from iminium ions (such as compound **12**) are described [25] and these acetals could also have a beneficial effect on the yield. As described above, there is a clear effect seen from the presence of chloro substituents on the aromatic ring, but this effect could not originate from the

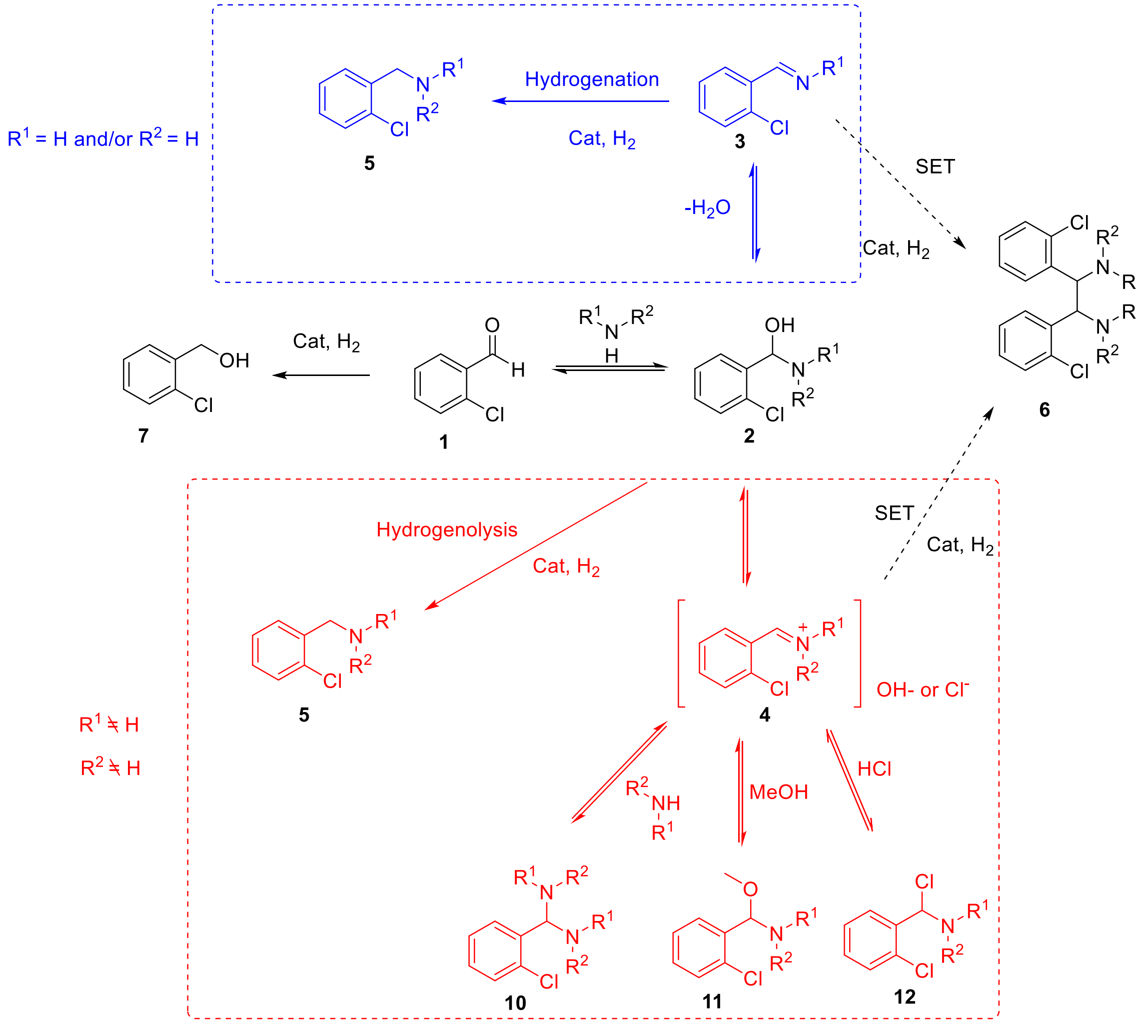


Fig. 5. Proposed reaction pathway.

captodative effect alone (based on the computational results) and thus on the stability of the intermediary iminium radical. If halogenated substrates are used, a small amount of dehalogenation is also observed (with chloro substituted aromatic compounds around 10%). The liberation of this HCl could generate N,Cl acetals **12** and thus influence the equilibrium of the hemi-aminal **2** and the iminium ion **4**. However, the liberated chloride ions can also act as counterions for the iminium ion **4** causing a stabilization effect. To investigate this phenomenon, an experiment was conducted in which benzaldehyde and dimethylamine were used as reagents and hydrochloric acid was added in similar amounts as would be produced from dehalogenation reactions in case o-Cl-benzaldehyde was used as a reagent. It was seen that the yield of vicinal diamine increases significantly to 45% compared to 20% when no hydrochloric acid was added and compared to 57% when o-Cl-benzaldehyde is used as a reagent in combination with dimethylamine (entry 1, 3 and 4, Table S3). It can thus be seen that indeed, addition of hydrochloric acid has an effect and this can be explained by either the formation of N,X acetals **12** or the stabilization of the iminium ion 4. To further validate the proposed reaction scheme and obtain mechanistic insight, DFT calculations were performed. Standard reaction Gibbs free energies of both the formation of the imine **3** and the formation of the iminium ion **4** including all formed intermediates were calculated and compared (Fig. 6 and ESI-Table S7).

When an iminium ion can be formed (and thus a secondary amine is used as the aminating agent), it is clear that the most stable compound is the iminium ion **4** with a chloride as counter ion (**4-Cl**) while the least stable compound is the iminium ion with the hydroxy group as counterion (**4-OH**). Based on the stability of the **4-Cl** species it can be concluded that the liberation of chloride from the starting compound, or the addition of hydrochloric acid has a strong stabilizing effect on the iminium compound. The observed increase in yield can thus be explained by the fact this species is stabilized and can hence react toward the vicinal diamine more easily. Potentially this is also the reason why an increase in yield for 3-chlorobenzaldehyde is observed with respect to benzaldehyde. In this case chloride ions can be liberated from the starting material and stabilize the formation of the iminium ion, however specific interactions with the catalyst can potentially also play a role here. Additionally, one can see that if no chloride is present the equilibrium (~ΔG) is in favour of the by-products **10** and/or **11** (w.r.t. **2** and **4 OH**). Hence, as hypothesized, formation of these compounds will shift the equilibrium toward the iminium ion intermediate and enable an increase in yield. When the iminium ion and imine energy diagrams are now compared (compound **1**, **2/13** and **3,** Fig. 6), no significant stabilization effect is observed for imine **3**, leading to a decreased amount of imine in the reaction mixture and thus a decrease yield towards the vicinal diamines. This could explain, together with the different

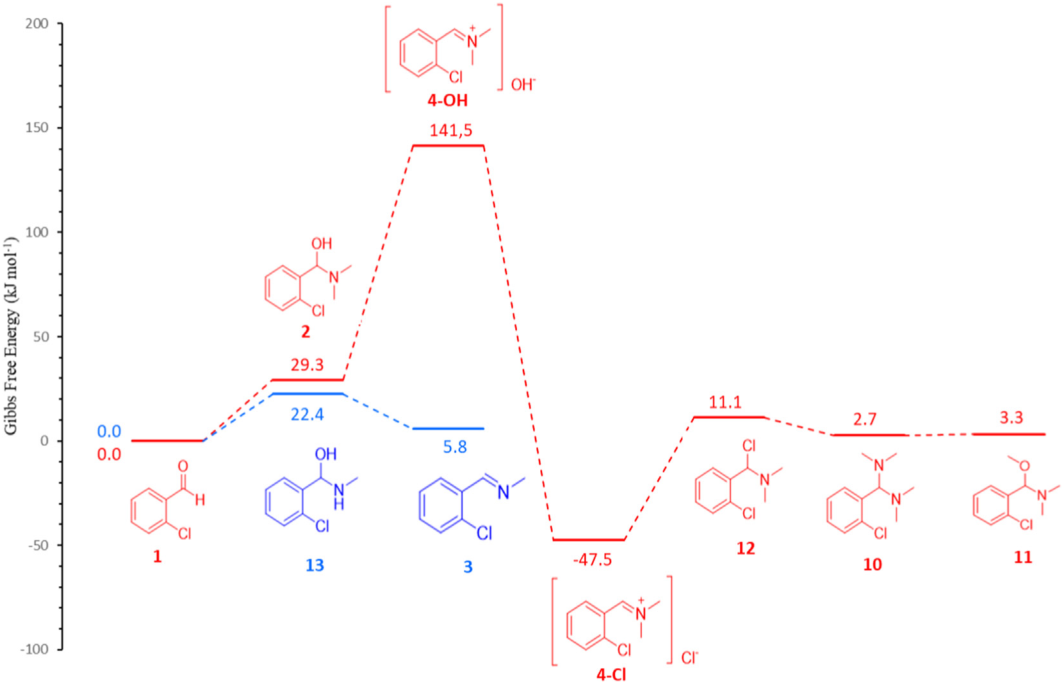


Fig. 6. Energy diagram of imine and iminium ion equilibrium in MeOH as solvent, corresponding energies can be found in Table S7 and S9 ESI.

reaction pathway towards **5** and **13** for respectively a tertiary and secondary amine (reductive amination versus hydrogenolysis), why the yield for vicinal diamine **6** is lower when the amination agent is a primary amine instead of a secondary amine.

As a clear solvent effect was seen on the yield of the coupling reaction, the stability of the different intermediates in different solvents was calculated using an implicit solvent model (computational details are explained in the ESI). A relatively large influence of the solvent was noticed here for the iminium compound **4** shown in Fig. 6 (for a detailed overview of all results the reader is referred to the ESI 7). This iminium compound can be stabilized by either a hydroxide or potentially by a liberated chloride ion or added hydrochloric acid. However, apart from this anionic stabilization, the used solvent clearly influences the stability of this intermediate. For clarification the free energy difference of **4 OH** and **4Cl** is plotted versus the δp Hansen Solubility Parameter (the energy from the dipolar intermolecular force between the solvent molecules) of the used solvent (through implicit solvation) in Fig. 7. The stability of this intermediate for both species corresponds well with the increased yields observed experimentally (Fig. 4). Only a small difference exists between methanol (δp = 12.3) and DMF (δp = 13.7) both in stabilization energy and δp, methanol can however actively influence the equilibria of **4** and **11**.

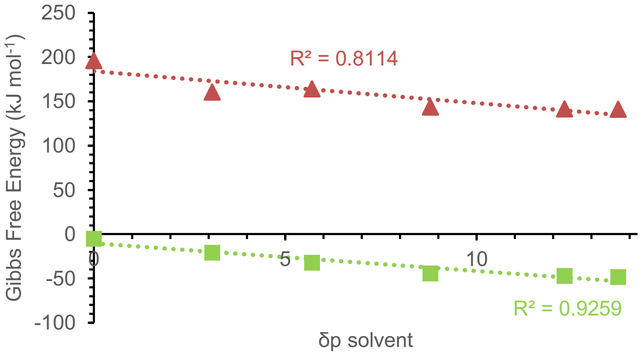


Fig. 7. Gibbs Free Energy of **4-OH** (▲) and **4-Cl** (■) as a function of the dipolar intermolecular forces of the used solvent.

As intermediate **4-OH** and **4-Cl** are the only intermediates of which the stability is correlated with the yield of the final product **6** (and thus also correlated with the dipolar intermolecular force between the used solvent molecules), it is hypothesized that these are indeed the crucial intermediates for the imino-pinacol coupling reaction, which is also the case in the postulated reaction pathway.

2.6. Mechanistic considerations for the coupling reaction of iminium ions in the presence of hydrogen

Analogous to non-catalytic imino-pinacol coupling reactions using equimolar amount of metal, the formation of a benzylic radical through a Single Electron Transfer followed by the coupling of two radical species towards a vicinal diamine could be a valid reaction path. Electron transfer reactions from an electron donor such as alkali metals or various organometals towards an iminium ion, acting as an electron acceptor, is well known [26]. Since a bimetallic Ru/Pd catalyst showed the highest yield (see Table 3), it is important to know what the main active metal is, responsible for the coupling reaction and how the synergistic effect that was observed between the metals, could be explained. First of all, it was seen that a pure Ru/C catalyst leads to a significant higher yield compared to a Pd/C catalyst (Entry 9 versus 3, Table 3), indicating that, although both metals can catalyze the reductive coupling reaction, a ruthenium metal is the most active one. Secondly, it was seen that Pd/C has a higher tendency for dehalogenation reactions compared to Ru/C and its tendency increases if ruthenium is present (see Table S6). Moreover, it was clearly shown that chloride ions stabilize the intermediate iminium ion leading to higher yields of the coupled product (see paragraph 2.4). Therefore, it is postulated that the synergistic effect of the Ru/Pd catalyst comes from the activity of the ruthenium metal as such and the increased dehalogenation reaction of a Ru/Pd catalyst in comparison with a monometallic Ru/C catalyst leading to extra stabilization of the intermediate iminium ion. To validate this theory, an experiment was performed using a monometallic Ru/C catalyst and the addition of HCl mimicking the amount of HCl released during the dehalogenation reaction in case a (0.5 wt% Pd – 4.5 wt% Ru)/C catalyst was used. While the use of a monometallic Ru/C catalyst leads to a yield of vicinal diamine of 58% (entry 9, Table 3) and a bimetallic (0.5 wt% Pd – 4.5 wt% Ru)/C leads to a yield of 68% (entry 8, Table 3), a Ru/C catalyst in the presence of HCl results in a yield of 70% (entry 2, Table S3). The mechanistic considerations for the reductive coupling reaction of iminium ions, presented in this paragraph, therefore will only focus on the ruthenium metal. Inspired by the work of Mukhopadhyay et al., who have investigated the catalytic cycle for the coupling of aryl halide in the presence of a heterogeneous palladium catalyst and hydrogen, a catalytic cycle for the coupling of iminium ions is postulated using a monometallic Ru/C catalyst (Fig. 8) [27].

The catalytic cycle begins with the coordination of an iminium ion with the ruthenium surface. Single Electron Transfer from the ruthenium surface towards the iminium ion results in the formation of a neutral benzylic radical. It is assumed that this radical remains coordinated to the metastable Ru^+ and can react with a second benzylic radical coordinated to an adjacent metastable Ru^+ center with the formation of a vicinal diamines. After the reaction of two substrate molecules, the two adjacent Ru^+ centers will disproportionate towards a Ru^0 and a Ru^{2+} center due to the inherent instability of this system. The Ru^{2+} center can be reduced back towards the reactive Ru^0 center in a reaction with one mole of dihydrogen. The protons that are formed can react with the chloride ion released with the formation of the benzylic radical with the formation of hydrochloric acid. To support this theory, an experiment with the benchmark reaction was performed in which a stochiometric amount of ruthenium/palladium was used in the absence of hydrogen. It was seen that the yield towards the reductive coupling product reached 90% while only 43% yield was obtained when catalytic amounts of Ru/Pd metal was used in the presence of hydrogen and in similar conditions (see Table S5). No reductive amination reaction was observed. A high yield towards the coupling product was indeed expected while no reductive amination reaction should occur since our theory postulates that no dihydrogen is involved in the radical formation and only allows the regeneration of our catalyst. The reductive amination reaction however does require a hydride shift and thus the involvement of hydrogen gas. Moreover, to prove the involvement of radicals in the reductive coupling mechanism, an experiment was performed with the addition of a radical stabilizer (hydroquinone). It was seen that the reductive coupling reaction was suppressed and the yield towards the vicinal diamine was five times lower in favor of the reductive amination reaction compared to the benchmark reaction without the addition of a radical stabilizer (see Table S4). Moreover, the radical mechanism could also explain the lack of stereoselectivity and the formation of racemic mixture seen in the different experiments. The formed benzylic radicals are, due to the absence of an adjacent chiral center, planar, adopting a trigonal planar shape and so both faces of the radical are identical, leading to the formation of a racemic mixture [28].

3. Conclusion

The first heterogeneous catalyzed process was developed for the reductive coupling of imines and iminium ions towards vicinal diamines using precious metal catalysts in combination with hydrogen gas as the terminal reductant. By eliminating the necessity of equimolar amounts of metal in the traditional well-known procedures for an imino-pinacol coupling reaction, this opens the opportunity to create a waste-free and more sustainable production route for vicinal diamines, important components in for example pharmaceutical applications. It was observed that by using a bimetallic palladium – ruthenium on activated carbon as a catalyst

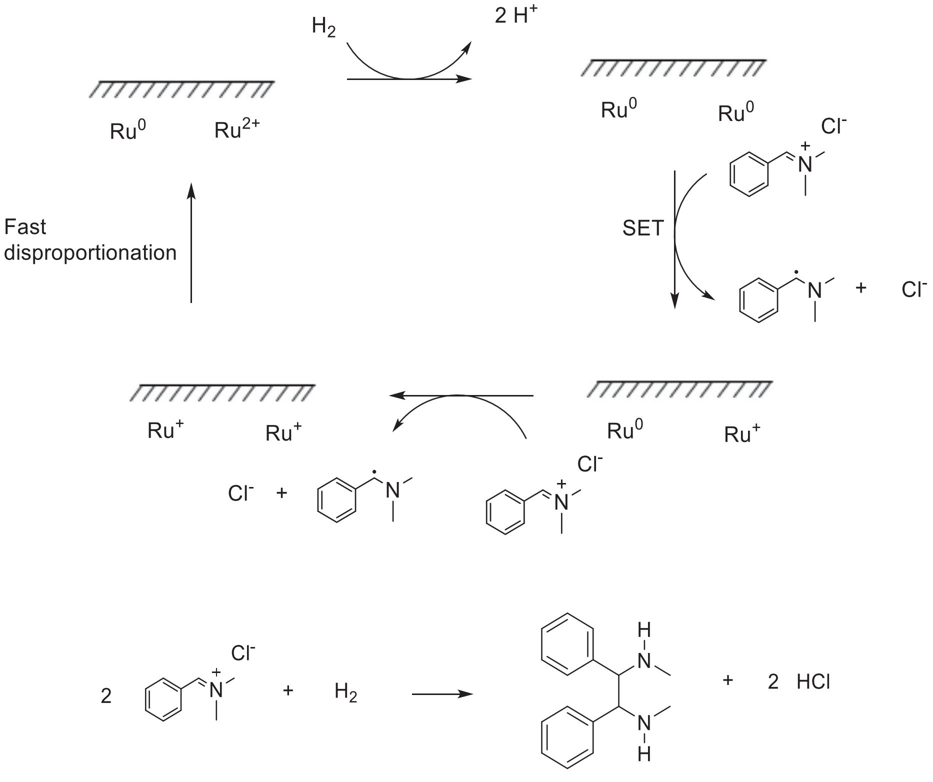


Fig. 8. Reaction mechanism proposal for the reductive coupling of two iminium ions.

and hydrogen gas as the terminal reductant, aromatic iminium ions such as N-(2,4-dichlorobenzylidine)-N-methylmethanamium could be coupled towards vicinal diamines with a maximum yield of 88%. Moreover, this procedure could be used for the coupling of different imines and iminium ions although experimental results show that the yields of the coupling of iminium ions are significant higher compared to the coupling of more stable imines. In order to increase the knowledge of this newly developed process and thus create space for further improvements, an attempt was made to explain the different observed phenomena. Based on a complementary experimental and theoretical approach a mechanistic proposal was postulated and validated. This could explain the observed yield differences between the coupling of imines versus iminium ions and the effect of the presence of chlorides. It was explained that, if iminium ions are formed, reduction towards the monofunctional amine proceeds via hydrogenolysis instead of the hydrogenation of the iminium ion (as is the case if imines are formed) Moreover, it was seen that the addition of chloride (both by the addition of hydrogen chloride in the reaction mixture or the dechlorination reaction if a chlorinated substrate was used), has a stabilization effect on the intermediate iminium ion.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank Eastman Chemical Company for support of this work. We also especially would like to thank Hannah Opdenbosch (thesis student), Bianca Goethals (thesis student), Hannes Rombaut (Eastman-Ghent), Jonas Maes (Eastman-Ghent), Patricia Janssens (Eastman-Ghent) and Ria De Potter (Eastman-Ghent) for all the experimental and analytical help. K.N.R.D. would also like to thank Dr. Peter Roose (Eastman – Ghent), Dr. Kristof Moonen (Eastman – Ghent) and Dr. Willem Van Liemt (Eastman – Ghent) for the opportunity to conduct this research. The computational resources and services used were provided by Ghent University (Stevin Supercomputer Infrastructure), the VSC (Flemish Supercomputer Center), funded by Ghent University, the Research Foundation - Flanders (FWO) and the Flemish Government. E.V.D.B and V.V.S. acknowledge funding from the fund for scientific research flanders.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2021.05.023.

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