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Selective and Sustainable Nitro Reduction and Reductive *N*-Alkylation Using a Recyclable V_2O_5/TiO_2 Catalyst for Amine Synthesis

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ABSTRACT. We present a sustainable and versatile catalytic platform for the synthesis of primary and secondary amines via the selective reduction of nitroarenes, employing a heterogeneous V_2O_5/TiO_2 catalyst. This methodology eliminates the use of stoichiometric metal hydrides, molecular hydrogen, and homogeneous catalytic systems, aligning with green chemistry principles. The catalyst exhibits excellent chemoselectivity across a diverse array of nitroarenes,

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including substrates bearing alkenes, alkynes, halogens, and functionalized heterocycles, demonstrating broad functional group tolerance. Furthermore, we extend this platform to a one-pot reductive alkylation of nitroarenes with alkyl halides (Br, I), affording N-alkylated amines in high yields under mild conditions. The catalytic system is recyclable over multiple cycles with minimal loss of activity or selectivity, showcasing its practical utility. The synthetic value of this approach is highlighted through the preparation of 47 (hetero)arylamines, 12 secondary amines, and seven pharmaceutically relevant molecules, including paracetamol, phenacetin, and bromhexine. Mechanistic insights derived from DFT calculations and controlled experiments provide a molecular-level understanding of the selective nitro group activation on the V_2O_5/TiO_2 surface. This work contributes a green, efficient, and mechanistically informed catalytic solution for amine synthesis from abundant nitroarenes.

KEYWORDS: V_2O_5/TiO_2 catalyst, Nitroarene reduction, Reductive alkylation, Amine synthesis, Heterogeneous catalysis, Sustainable chemistry

Introduction. Owing to the broad applicability of amines for the preparation of pharmaceuticals, agrochemicals, polymers, and dyes, the development of efficient processes for their synthesis is an area of intense research.[1-4] Nitro compounds are widely used to synthesize industrially important precursors such as amines[5-8], azides[9], hydroxyl amine[10,11], and azo compounds[12,13]. The catalytic reduction of nitroarenes represents a most benign and classical method for preparing a diverse range of functionalized amines in chemical industries. In past decades, the industry utilized the Ranney nickel and hydrogen gas to reduce nitroarenes, which are associated with several hazards

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like an explosion. Various noble metal-catalysed processes using Pd, Au, Ag, and Rh, based catalysts were reported to reduce nitro compound to the amine.[14-20] Apart from this, other metal-based catalytic systems were also used, which include Sn, V, Cr, Fe, Co, Ni, and Zn, but these catalytic systems require the stoichiometric amount of acid/base treatment, long reaction time etc. for the reduction of nitro compounds.[1,21-28] The previously reported methods utilized toxic and expensive metal catalysts, cumbersome catalyst synthesis, hazardous reaction conditions, and required stoichiometric amounts of reducing agents. In the case of a homogenous catalytic system, the products are often contaminated with metals. Their removal adds an extra step and raises the

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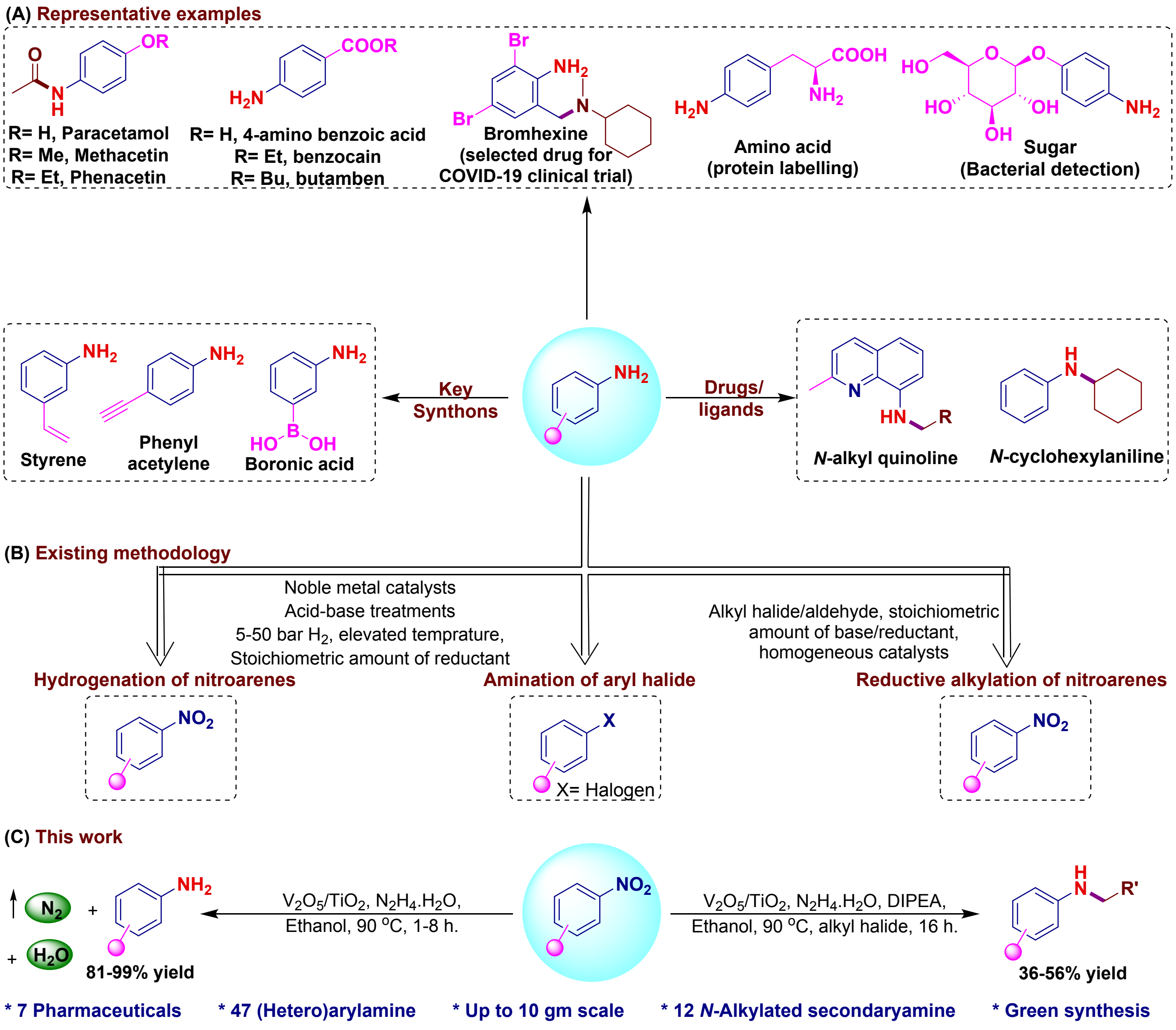

Fig. 1: (A) Representative examples **(B)** Existing methodology for the synthesis **(C)** Waste-free reduction and *N*-alkylation of nitroarenes (This work)

environmental and complicated alarming health hazards, which demands the safe disposal of these metals and by-products.[29,30] The previous methods also suffer from competitive halogenation/dehalogenation, alkene/alkyne reduction, prolonged reaction time, and generation of by-products, which lead to the reduction in atom economy of the process (**Fig. 1, B**). Recently few groups reported catalytic systems for reduction of nitroarenes utilizing hydrazine hydrate in

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stoichiometric amounts.[31,32] To overcome these challenges, here we report recyclable heterogeneous V_2O_5/TiO_2 catalysed efficient methodology for the reduction of nitro compounds to their respective amines in good to excellent yield (**Fig. 1, C**). The developed protocol requires low catalyst loading, green solvents, moderate temperature, and less amount of reducing agent. Recently in 2021, we have reported the utilization of vanadium catalysts for the sustainable synthesis of carboxylic acid from olefins.[33] Further, for this study, we have synthesized various strengths of the V_2O_5/TiO_2 catalyst system by using a modified procedure.[33] Due to the vast application of alkylated amines, the direct alkylation of nitroarenes for the synthesis of secondary and tertiary amines has gained much attention in recent times. In past decades, these amines were mainly synthesized by utilizing Buchwald-Hartwig coupling,[34] Ullmann coupling,[35] aminations of carbonyls and alcohols,[36,37] and alkylation of anilines with alkyl halides.[38] Among them, the direct alkylation reaction utilizes a stoichiometric amount of base. These amines are usually prepared by reduction nitroarenes, which adds an extra step to the alkylation. Recently few methodologies have been reported to synthesize *N*-alkylamines *via* direct reductive alkylation of nitroarenes.[39-41]

Results and Discussion

Catalyst preparation and characterization

The catalysts V_2O_5/TiO_2 were prepared *via* the sol-gel method utilizing vanadium pentoxide and titanium (IV) butoxide. TiO_2 was selected as the support due to the compatibility of the Ti^{4+} ionic radius and oxidation state with those of vanadium, which facilitates strong metal-support interactions and improved catalyst stability. Unlike non-redox supports such as SiO_2 and Al_2O_3,

TiO_2 can participate in redox processes, which may enhance the catalytic performance. These factors make TiO_2 a more suitable support material for this study. Using the method, we synthesized a varied strength of V_2O_5 supported over TiO_2 (C-05, C-10, C-20) and characterized using different techniques.[33] Moreover, in continuation here we run the X-ray photoelectron spectroscopy (XPS) to provides detailed information about the catalysts. The V 2p core level spectrum was recorded for three different catalysts containing 10%, 20%, and 30% V_2O_5. The intensities of the V 2p spin-orbit core levels for all catalysts were normalized to the 20% V_2O_5 sample to facilitate direct comparison of binding energy (BE) changes and the full-width at half-maximum (FWHM) of the core-level features. The 20% V_2O_5-loaded catalyst exhibited the largest FWHM of 2.7 eV with a peak maximum at a BE of 517.2 eV, while the 30% V_2O_5 catalyst showed the smallest FWHM of 2.0 eV at a lower BE of 516.7 eV. This significant decrease in FWHM and the lower BE for the 30% V_2O_5 catalyst suggests that vanadium is predominantly in the 4+ oxidation state. In contrast, both V^{4+} and V^{5+} oxidation states are evident in the 10% and 20% V_2O_5 catalysts, as indicated by the higher BE and broader spectral features. The intensity-normalized V 2p core-level features further confirm broadening on the higher BE side in the 10%, 20%, and 30% V_2O_5 catalysts, while the lower BE side remains consistent across all compositions. However, the broadening observed at the onset of the V $2p_3/_2$ feature for the 20% V_2O_5 catalyst suggests a relatively high, or at least comparable, amount of V^{4+} to the other catalysts. This highlights the presence of a unique combination of V^{4+} and V^{5+} oxidation states in the 20% V_2O_5 catalyst, which correlates with its superior catalytic performance Fig. 2, **A.** Representative V $2p_{3/2}$ core level result is shown in the inset of Fig. 2A for the best performing 20% V_2O_5/TiO_2 catalyst.

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Very similar result observed, as that of fresh catalyst, directly demonstrates the robustness of the catalyst to withstand the reaction conditions. Although the redox couple of V^{4+}/V^{5+} could undergo changes under reaction conditions, very similar results observed before and after reaction underscores the preservation of mixed valent states at the end of the reaction. Indeed, several cycles of reactions carried out testify this conclusion of preservation of mixed valent states, irrespective of reaction conditions. The Ti 2p core levels were also analyzed by XPS, and the results, shown in Fig. 2, **B**, were obtained after deconvolution. All three catalysts exhibit a Ti^{3+} component at 457.3±0.1 eV, accounting for 3-6% of the total Ti, while Ti^{4+}, observed at 458.5±0.1 eV, is the predominant oxidation state. This indicates that the primary role of TiO_2 is as a support material. Ti 2p spectral features of spent catalyst remains the same as that of fresh catalyst, reiterating the maintenance of mixed valent states, irrespective of reaction conditions. Spent Previously, we have explored the oxidation potential of these synthesized catalysts over various scaffolds.[42-44] Building upon this research, we now shift our focus towards exploring their potential in reduction reactions. Specifically, we are interested in utilizing these catalysts for the reduction of nitroarenes into their corresponding amines.

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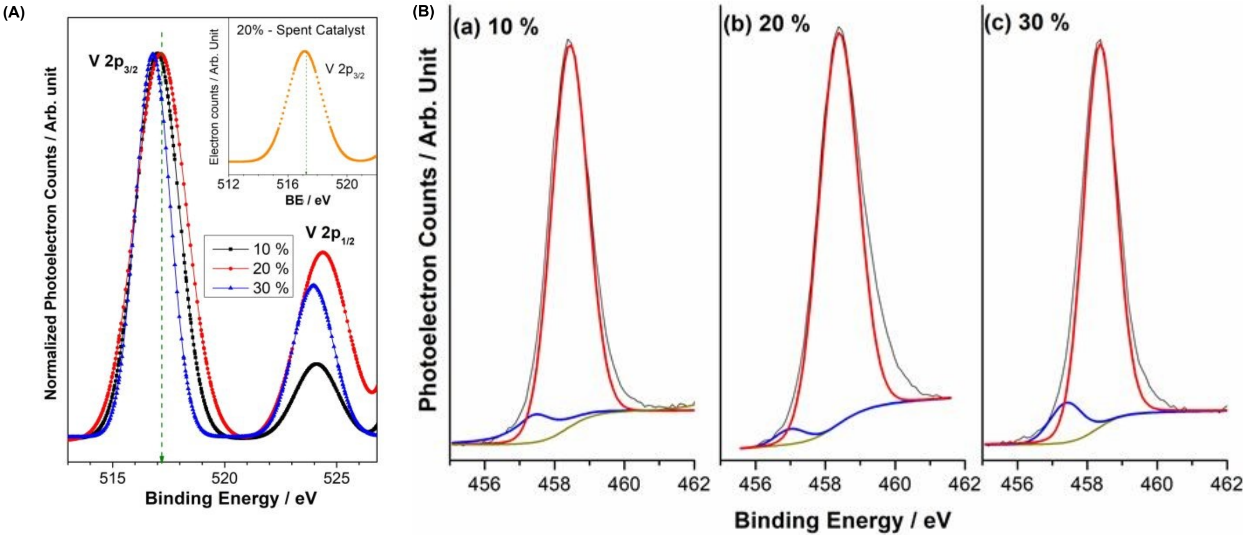

Fig. 2: (A) Vanadium 2p core level spectrum recorded for different loading of V_2O_5 supported on TiO_2 and spent catalyst **(B)** Titanium 2p core level spectra recorded for different loading of V_2O_5 supported on TiO_2

Catalyst screening and optimization of reaction conditions

To begin our investigation, nitrobenzene was selected as a model substrate to optimize reaction conditions. Initially, nitrobenzene (0.5 mmol) was dissolved in ethanol (2 mL) and was added V_2O_5/TiO_2 catalyst (10 wt%) of different strengths (C-05, C-10, and C-20), hydrazine hydrate (25 equiv.), and the resulting reaction mixture was then stirred at 25 ^{o}C up to 12 hours, but a trace of the product was observed with C-20 catalyst (Table S1, entries **1-3**). However, no reaction was observed when the reaction was performed in other solvents (Table S1, entries **4-7**). Next, the reaction temperature was optimized using ethanol as a solvent, and to our delight, an excellent yield of the desired amine was obtained at 90 ^{o}C in 1.0 h (Table S1, entries **8-10**). However, lowering the catalyst strength to 10 % at 90 ^{o}C resulted in a decrease in the product yield (Table

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S1, entry **11**). Reducing agents other than hydrazine hydrate resulted in no reaction under similar conditions (Table S1, entries **12-14**). Further, the amount of reducing agent was optimized, and three equivalent of hydrazine hydrate was found to be sufficient for the complete conversion (Table S1, entries **15-18**). The amount of catalyst loading directly affects yield, and a significant decrease in the yield of the product was observed when the amount of the catalyst was reduced from 10 to 7.0 wt%. (Table S1, entry **19**). No reaction was observed in the absence of either a reducing agent or catalyst (Table S1, entries **20** and **21**). Surprisingly, the reaction does not respond to their parent TiO_2 and V_2O_5 when used separately to catalyse the reaction (Table S1, entries **22** and **23**).

Substrate scope for the reduction of nitroarenes

We began our endeavor to study substrate compatibility for the developed protocol with optimized conditions in hand (Table S1, entry **18**). Accordingly, the methyl-substituted nitroarenes were transformed into the corresponding aniline in excellent yields (Scheme 1, **2b, 2c**). The methoxy and methylsulfane substituted nitroarenes provided the desired amine in excellent yields (Scheme 1, **2d, 2e**). The ethoxy and propoxy derivatives were smoothly converted into their respective amine (Scheme 1, **2f, 2g**). Halogenated amines are the key intermediates for the agrochemicals; however, halogen substituent on nitroarenes is susceptible to dehalogenation during reduction under hydrogenation conditions and is the challenging substrate for this transformation.[45] Different halogenated substrates were subjected to the developed reaction conditions, and interestingly a good yield of corresponding amines was obtained without affecting the substitution over the benzene ring (Scheme 1, **2h-2k**). The developed methodology was found to be efficient for reducing *ortho*, *meta*, and *para*-substituted di-nitroarenes, and comparable yields of diamine

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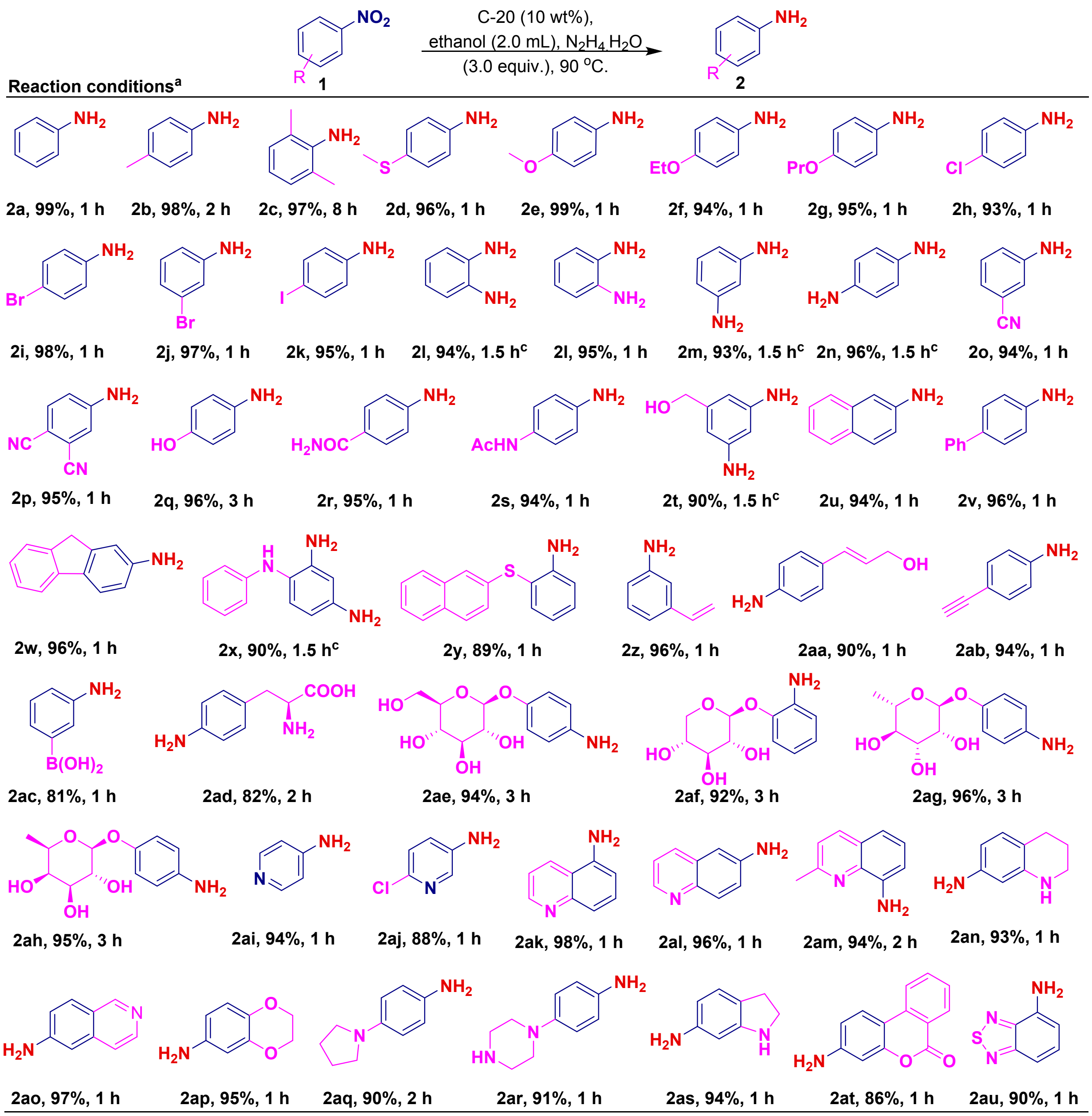
Scheme 1. Substrate scope for the reduction of nitroarenes



[a]Reaction condition: Nitroarenes **1** (1.0 equiv., 100 mg), C-20 (10 wt%), $N_2H_4.H_2O$ (3.0 equiv.), ethanol (2.0 mL), 90 °C for 1-8 h., [b]isolated yield, [c]$N_2H_4.H_2O$ (6.0 equiv.).

products were obtained (Scheme 1, **2l-2n**). Nitrile substituted nitroarenes were well tolerated and furnished the desired amine in excellent yield with excellent selectivity towards the nitro reduction

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(Scheme 1, **2o, 2p**). The *p*-hydroxy nitrobenzene provided a quantitative yield of desired aniline (Scheme 1, **2q**). Benzamide and acetanilide derivatives of nitrobenzene were effectively reduced to their corresponding aniline derivative in good to excellent yields without the formation of any by-product (Scheme 1, **2r, 2s**). Synthesis of 3,5-di-amino benzyl alcohol was achieved by reducing 3,5-di-nitrobenzyl alcohol, which is an important intermediate for the synthesis of 9-anilinothiazolo[5,4-b] quinoline derivatives as potential antitumoral and 4-anilinoquinoline derivative as potential antimalarial agents (Scheme 1, **2t**).[46,47] The nitro derivative of naphthalene, biphenyl, and fluorene were efficiently reduced to the respective amines in excellent yields (Scheme 1, **2u-2w**). The synthesis of 2,4-Diaminodiphenylamine was successfully achieved in 90% yield utilizing respective dinitro derivatives (Scheme 1, **2x**). The naphthalen-2-yl(2-nitrophenyl)sulfane derivative get reduced efficiently in corresponding 2-(naphthalen-2-ylthio)aniline ion 89% yield (Scheme 1, **2y**). Further, the hetero and unsaturated nitro compounds were tested for their feasibility towards reducing under developed protocols. It was observed that the method was efficient in reducing them into corresponding amine. The selective reduction of the challenging substrate, such as 3-nitro styrene, was achieved in excellent yield and selectivity; pleasingly, no double bond reduction was observed under developed reaction conditions (Scheme 1, **2z**).[48,49] The nitro substituted cinnamyl alcohol tolerated well to furnish the corresponding amine in excellent yield (Scheme 1, **2aa**). Similarly, an excellent yield was obtained when reducing nitro substituted phenylacetylene derivatives, where alkyne was unaffected under developed reaction conditions (Scheme 1, **2ab**).[50] The nitroarene containing important functionality such as boronic acid, which is frequently utilized for different chemical transformations, was subjected under the developed protocol, and pleasingly a good yield of the desired amine was obtained (Scheme 1, **2ac**).[51] Interestingly, the amino acid derivative like 4-nitro-*L*-phenylalanine gave the corresponding 4-amino-*L*-phenylalanine in good yield, which is an important compound used in protein labelling (Scheme 1, **2ad**).[52] In the continuation, the sugar derivatives of nitroarenes transformed smoothly into their corresponding amine in good to excellent yields (Scheme 1, **2ae-2ah**). The heterocyclic nitro derivative, such as 4-nitro pyridine and 2-chloro-5-nitro pyridine resulted in good yields of respective amine (Scheme 1, **2ai** and **2aj**). To our delight, the medicinally important compound such as nitro substituted quinoline derivatives provided an excellent yield of aminoquinolines (Scheme 1, **2ak-2am**). The tetrahydro quinoline derivative was also getting transformed into respective amine (Scheme 1, **2an**). Moreover, the isoquinoline derivative yielded the desired amine in excellent yield (Scheme 1, **2ao**). The nitro derivative of benzo dioxane was reacted well in the developed reaction condition and gave the desired amine in a 95% yield (Scheme 1, **2ap**). The optimal yield of the desired 4-(pyrrolidine-1-yl) aniline is obtained from the reduction of the 1-(4-nitrophenyl) pyrrolidine (Scheme 1, **2aq**). The 4-(piperazin-1-yl)aniline was obtained in 91% yield by subjecting respective nitro derivatives (Scheme 1, **2ar**). Interestingly, the indoline and benzochromenone derivatives provided 94 and 86% yield, respectively (Scheme 1, **2as** and **2at**). The nitro derivative of benzothiadiazole was efficiently converted into their respective amine in good yield (Scheme 1, **2au**).

Synthetic application in medicinal chemistry

A one-pot transformation of 4-nitro phenol further demonstrated the versatility of the developed protocol to a pharmaceutically active molecule, *i.e.,* paracetamol, in good yield at a 10 g scale

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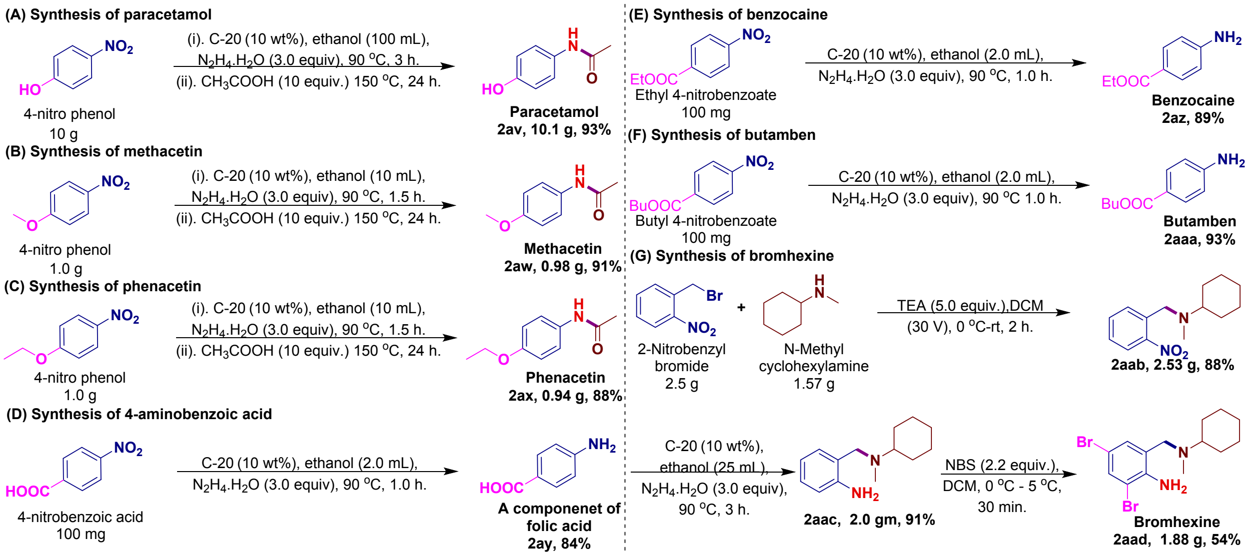
(Scheme 2, **2av**). Paracetamol is a frequently used over-the-counter drug in clinical practice, including for the patient suffering from COVID-19, and has been synthesized by different protocols mostly in multiple steps.[38,53] By utilizing similar reaction conditions, the other parallel pharmaceuticals, such as methacetin and phenacetin, were also synthesized in good yields (Scheme2, **2aw, 2ax**). The synthesis of 4-amino benzoic acid, which is a component of folic acid, was successfully achieved in good yield (Scheme 2, **2ay**). The synthesis of other medicinally important molecules, such as benzocaine and butamben, which are used as anesthetic drugs, was accomplished smoothly (Scheme 2, **2az** and **2aaa**). Bromhexine, another important active pharmaceutical ingredient, is a mucolytic drug used to treat respiratory tract infections associated with excess mucus.[54] The previous synthetic protocol for bromhexine utilized the Raney nickel to reduce the nitro group to the respective amine. Herein, we used a recyclable heterogeneous catalytic system to reduce the nitro functionality into the corresponding amine in 91% yield

Scheme 2. Synthesis of the important pharmaceuticals



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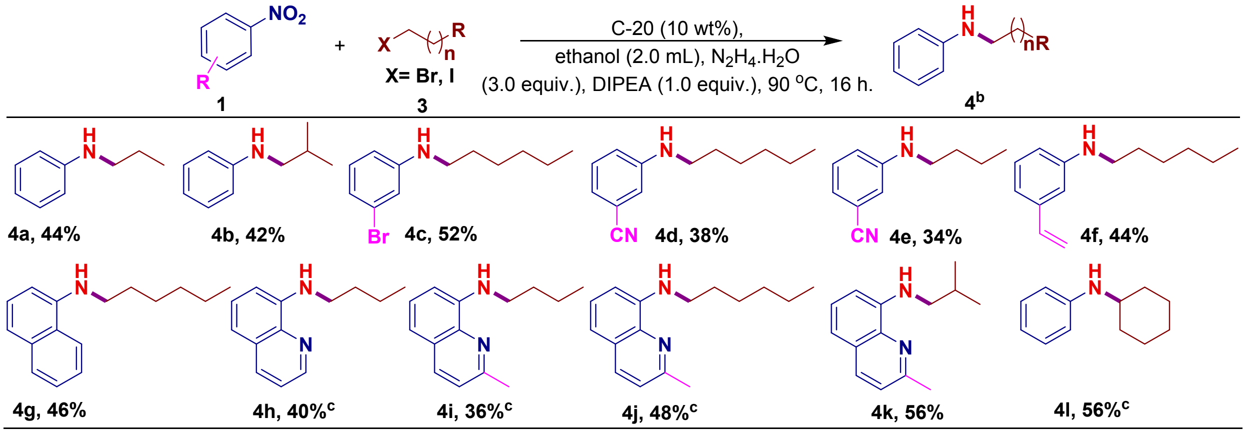
(Scheme 2, **2aab**). The resulting compound was finally reacted with *N*-bromosuccinimide to obtain bromhexine in 54% yield (Scheme 2, **2aad**).

Reductive alkylation of nitroarenes

The reductive alkylation of the nitroarenes into their respective amines was successfully achieved (Scheme 3). Exclusively, the monoalkylated amines were formed, and a low selectivity towards the dialkylated amine was observed under the developed protocol. The nitrobenzene was alkylated with propyl and isobutyl halide in 44% and 42% yield, respectively, under developed reaction conditions (Scheme 3, **4a** and **4b**). The bromo-substituted nitrobenzene derivative was successfully transformed into their corresponding amine in good yield (Scheme 3, **4c**). The nitrile substituted nitroarenes were found to be compatible and provided the desired product in 38% and 34% yields

Scheme 3. Reductive alkylation of nitroarenes



[a]Reaction condition: Nitroarenes **1** (1.0 equiv., 50.0 mg), alkyl halide **3** (3.0 equiv.), C-20 (10 wt%), $N_2H_4.H_2O$ (3.0 equiv.), DIPEA (1.0 equiv.), ethanol (2.0 mL), 90 °C for 16 h., [b]isolated yield, [c]alkyl halide **3** (5.0 equiv.).

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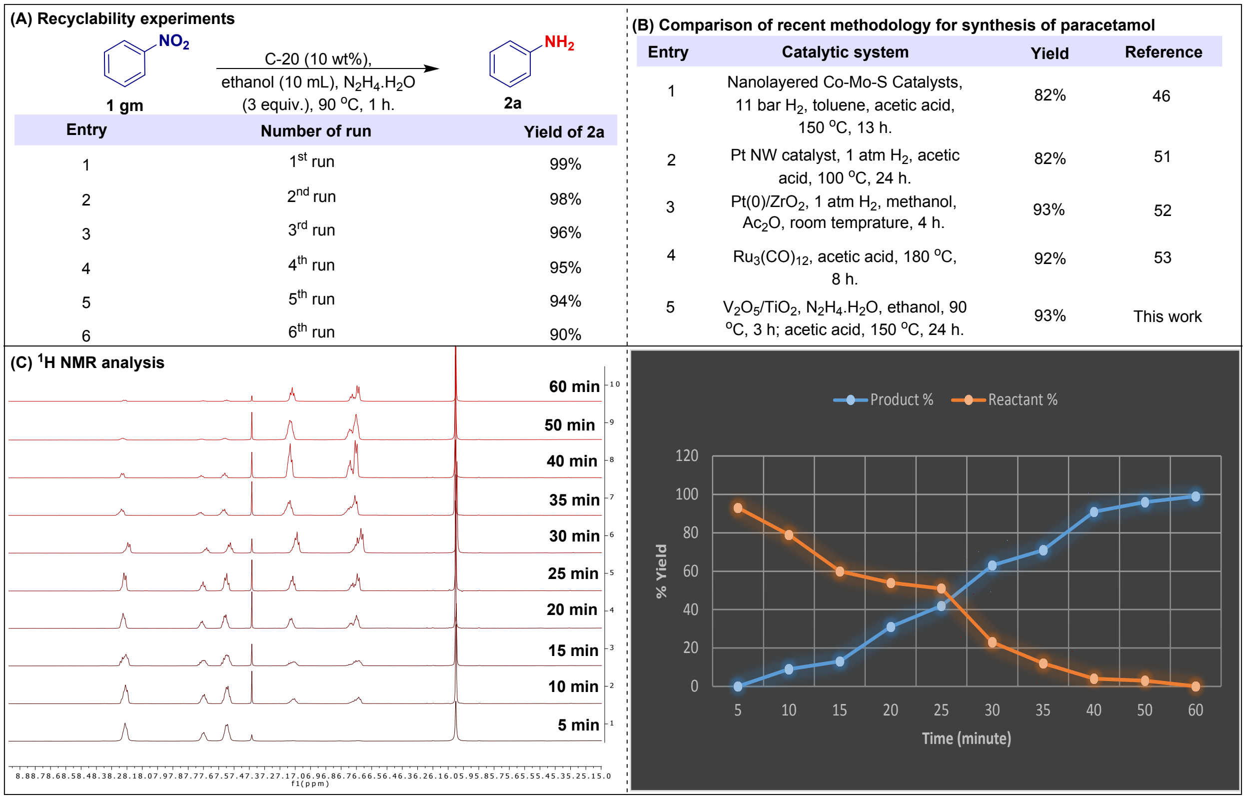
(Scheme 3, **4d** and **4e**). 3-Nitro styrene was alkylated under developed reaction conditions in a 44% yield (Scheme 3, **4f**). The 1-nitronaphthalene gave the corresponding amine in good yield (Scheme 3, **4g**). The 8-nitroquinoline and 8-nitroquinaldine selectively gave monoalkylated products utilizing 5.0 equivalent of alkyl halide (Scheme 3, **4h-4k**). In the case of secondary alkyl halide, the selectivity towards monoalkylated product was relatively high as compared to a primary alkyl halide, and the cyclohexyl iodide provided respective amine in good yield (Scheme 3, **4l**). When the reaction was performed using aromatic halide, *i.e.,* benzyl bromide, it resulted in no desired products, and the formation of hydrazine hydrobromide was observed. This is because of the quick release of bromide ions from benzyl bromide, which gets combined by their counter ion, *i.e.,* hydrogen ion, to form hydrogen bromide.

Catalyst recyclability and comparison studies

Catalyst stability and recyclability are the crucial performance metrics to assess a catalytic protocol's cost-effectiveness and translational potential. The recyclability of the catalyst was performed using nitrobenzene as a substrate under optimized reaction conditions. No considerable decrease in the yield of the desired amine up to six cycles was observed, and the catalyst was found to be efficient to perform the reduction after every reaction cycle without significant loss in the yield. The catalyst was recycled by centrifugation or filtration after each cycle, the residual catalyst was washed with ethanol or acetone and dried in an oven for two h at 100 ^{o}C and reused (Fig. 3, **A**). Further to access the synthetic viability and sustainability of the developed protocol for



Entry	Number of run	Yield of 2a
1	1st run	99%
2	2nd run	98%
3	3rd run	96%
4	4th run	95%
5	5th run	94%
6	6th run	90%

(B) Comparison of recent methodology for synthesis of paracetamol

Entry	Catalytic system	Yield	Reference
1	Nanolayered Co-Mo-S Catalysts, 11 bar H_2, toluene, acetic acid, 150 °C, 13 h.	82%	46
2	Pt NW catalyst, 1 atm H_2, acetic acid, 100 °C, 24 h.	82%	51
3	Pt(0)/ZrO_2, 1 atm H_2, methanol, Ac_2O, room temprature, 4 h.	93%	52
4	$Ru_3(CO)_{12}$, acetic acid, 180 °C, 8 h.	92%	53
5	V_2O_5/TiO_2, $N_2H_4.H_2O$, ethanol, 90 °C, 3 h; acetic acid, 150 °C, 24 h.	93%	This work

Fig. 3: **(A)** Recyclability experiment **(B)** Comparison studies **(C)** ^{1}H NMR of the crude reaction mixture at a different time interval

paracetamol synthesis over reported one-pot synthetic methodology, the comparison with existing methods was studied. The study found that most of the protocol utilizes noble metal (Pt,[55,56] Ru[57]), Co-Mo-S catalyst using 11 bar H_2,[50] and controlled substances like acetic anhydride (Fig. 3, **B**). Here in this case, we performed the reaction under greener conditions (green solvent, heterogeneous catalyst, and non-hazards by-product formation), column-free, and at a multi-gram scale (0.1-10 g). To study the reaction's progress with time, a typical ^{1}H NMR of the crude reaction mixture was recorded at a different time interval and stacked all the obtained spectrum on the same scale. The study resulted in the steady growth of reaction at the beginning concerning product

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formation. It was observed that the reactant concentration was consumed more as a comparison to the product formed, which indicates the formation of some intermediate during the reaction (Fig. 3, **C)**. But there is no significant appearance of a formed intermediate during the reaction in the solution phase, indicating the strong adsorption over the catalyst.

Computational Studies, mechanistic study and plausible catalytic cycle

To investigate the hydrazine dehydrogenation mechanism on the V_2O_5/TiO_2 surface and its subsequent catalytic activity in the reduction of nitrobenzene to aniline, we conducted a comprehensive first principles study utilizing Density Functional Theory (DFT) calculations within the Vienna ab initio simulation package (VASP). The interactions between core and valence electrons were modeled using Projector Augmented Wave (PAW) potentials. The exchange-correlation energy density functional was treated with the Generalized Gradient Approximation (GGA) of Perdew-Burke-Ernzerhof (PBE), and dispersion interactions were accounted for using Grimme's D3 semi-empirical method (PBE-D3). For the expansion of wavefunctions for the valence electrons, a plane-wave basis set was employed with a kinetic energy cutoff of 520 eV, ensuring accurate representation of electronic behavior. To minimize interactions in the non-periodic direction, a vacuum layer of 20 Å was incorporated. The positions of all atoms were optimized by relaxing them under a constant volume constraint, with a force cutoff set at 0.01 eV/Å to reach a stable atomic configuration.

The crystal structure of anatase TiO_2 was retrieved from the ICSD database and subsequently optimized. The measured optimized cell parameters were determined to be a=b=3.789 Å and c=

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9.593 Å. To investigate the interaction of V_2O_5 with the TiO_2 surface, we focused on the (001) surface of TiO_2, whose optimized cell parameters were determined to be 3.703 Å. To create a suitable model for V_2O_5 adsorption, a 3x3x1 supercell of the optimized (001) TiO_2 surface was constructed and optimized for the adsorption of V_2O_5 units. The resulting structure of this supercell is depicted in Fig. **4**. This approach allowed us to generate the final catalyst model, V_2O_5/TiO_2(001), based on the reconstructed Anatase-V_2O_5 model utilized in previous studies. In the final model, one unit of V_2O_5 is loaded onto the 3x3x1 Anatase surface, interacting with 45 Ti atoms and 90 O atoms. The optimized structure is presented in Fig. 4, **(A)**. Key structural parameters within the V_2O_5/TiO_2(001) model include a V-V distance of 3.281 Å and three distinct V-O distances: bridged O (1.792 Å), terminal O (1.598 Å), and Ti-bound O (1.775 and 1.759 Å).

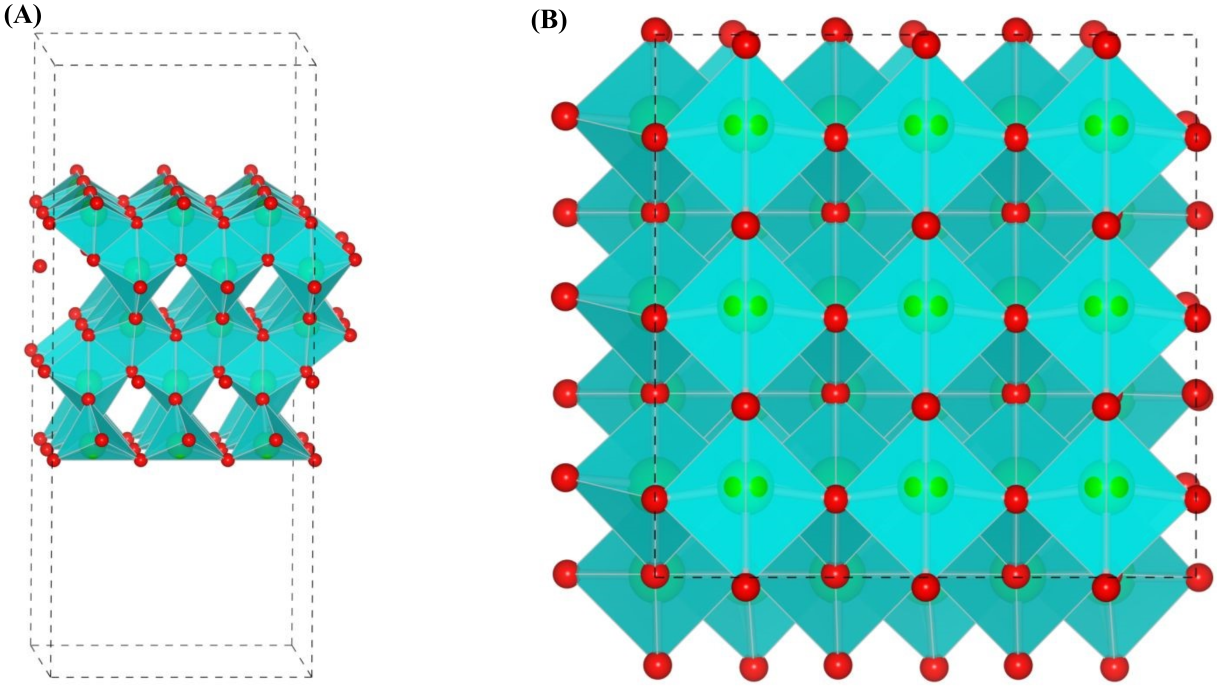

Fig. 4: Optimized structure of TiO_2 (001) surface **(A)** side and **(B)** top views

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The dehydrogenation of hydrazine on an optimized catalyst surface was thoroughly investigated, and the results are depicted in Fig. **5**. In the most energetically favorable configuration of N_2H_4 adsorbed on the catalyst surface, the shortest distance between a nitrogen atom (N) and a vanadium atom (V) was found to be 2.305 Å. The hydrogen atoms of N_2H_4 interacted with the surface through hydrogen bonding, resulting in an adsorption energy of 88.76 kJ/mol. From this adsorbed N_2H_4 structure, we examined the transfer of one of the hydrogen atoms from the hydrazine molecule to various oxygen sites bound to both V and Ti atoms. It was observed that the transfer of hydrogen to an oxygen site bound to vanadium (V) was energetically preferred. However, this particular transfer was endothermic, requiring an input energy of 79.12 kJ/mol. Additionally, the

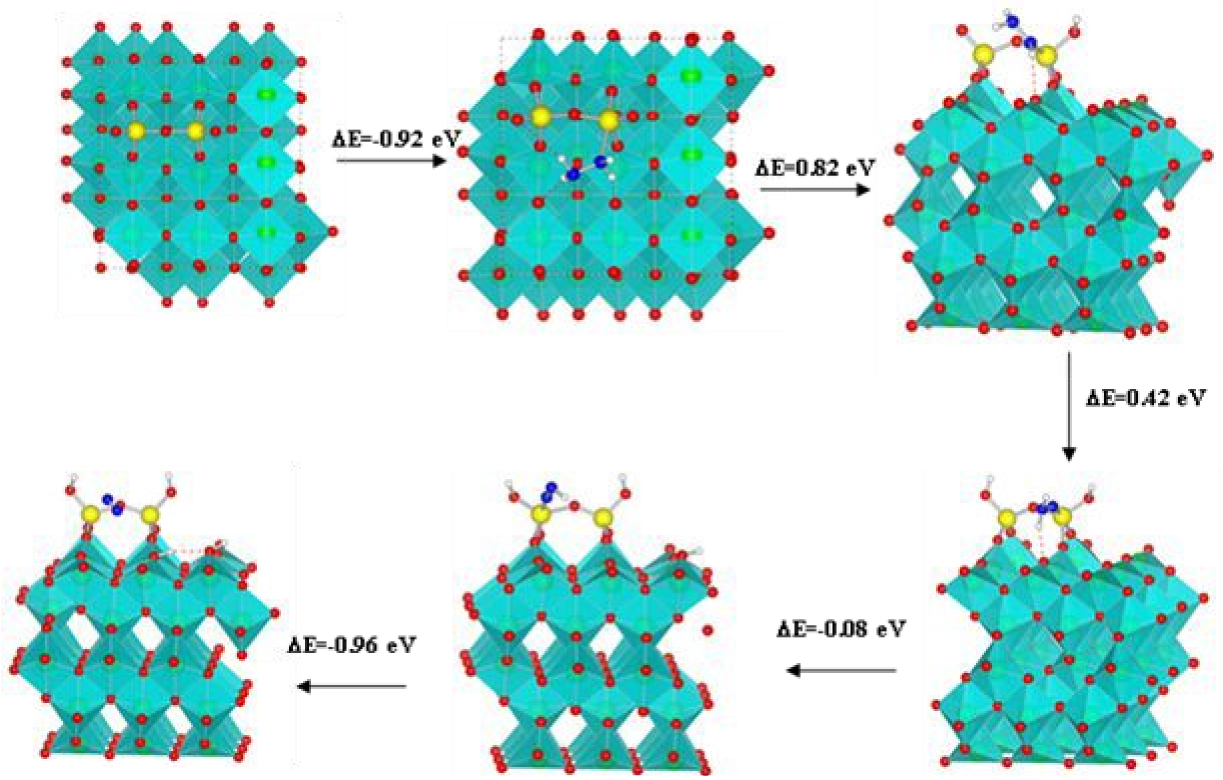

Fig. 5: Schematic representation dehydrogenation of N_2H_4 over V_2O_5/TiO_2

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shortest V-N distance in the optimized structure was shortened compared to the initial 2.305 Å, measuring 1.927 Å. For the subsequent hydrogen transfer, we investigated the transfer of a hydrogen atom bound to a nitrogen (N) atom to different oxygen sites. The transfer of a hydrogen atom from an N atom, bound to a single hydrogen (H), to the second oxygen site bound to vanadium (V) was favored. In this case, the shortest V-N distance was further reduced to 1.707 Å, and this transfer was also found to be endothermic, requiring an input energy of 40.53 kJ/mol. In the following two consecutive hydrogen transfer steps, hydrogen atoms from the NH_2 group were transferred to oxygen sites bound to titanium (Ti) on the surface. These transfers resulted in the physisorption of a N_2 molecule on the catalyst surface, as illustrated in Fig. **5**. Notably, both of these hydrogen transfer steps were exothermic, releasing energy in the amounts of 7.72 kJ/mol and 92.62 kJ/mol, respectively.

The catalytic reduction of nitrobenzene to aniline over a hydrogenated catalyst has been investigated in detail, and the step-by-step intermediate reactions are depicted in Fig. **6**. The adsorption energy of the nitrobenzene molecule on the hydrogenated catalyst is calculated to be -94.55 kJ/mol. In the optimized structure, the shortest distance between the V-nitro oxygen and the catalyst surface is measured to be 2.162 Å, while the other V-O(-NO_2) distance is 2.613 Å. The first step involves the transfer of a hydrogen atom from the V-bound oxygen to both nitro oxygen atoms. The minimum energy structure corresponds to the transfer of hydrogen to the oxygen farther from the V site, as shown in Fig. **6**. This intermediate reaction has an energy change of -4.82 kJ/mol. For the subsequent hydrogen transfer, we considered the transfer of hydrogen from

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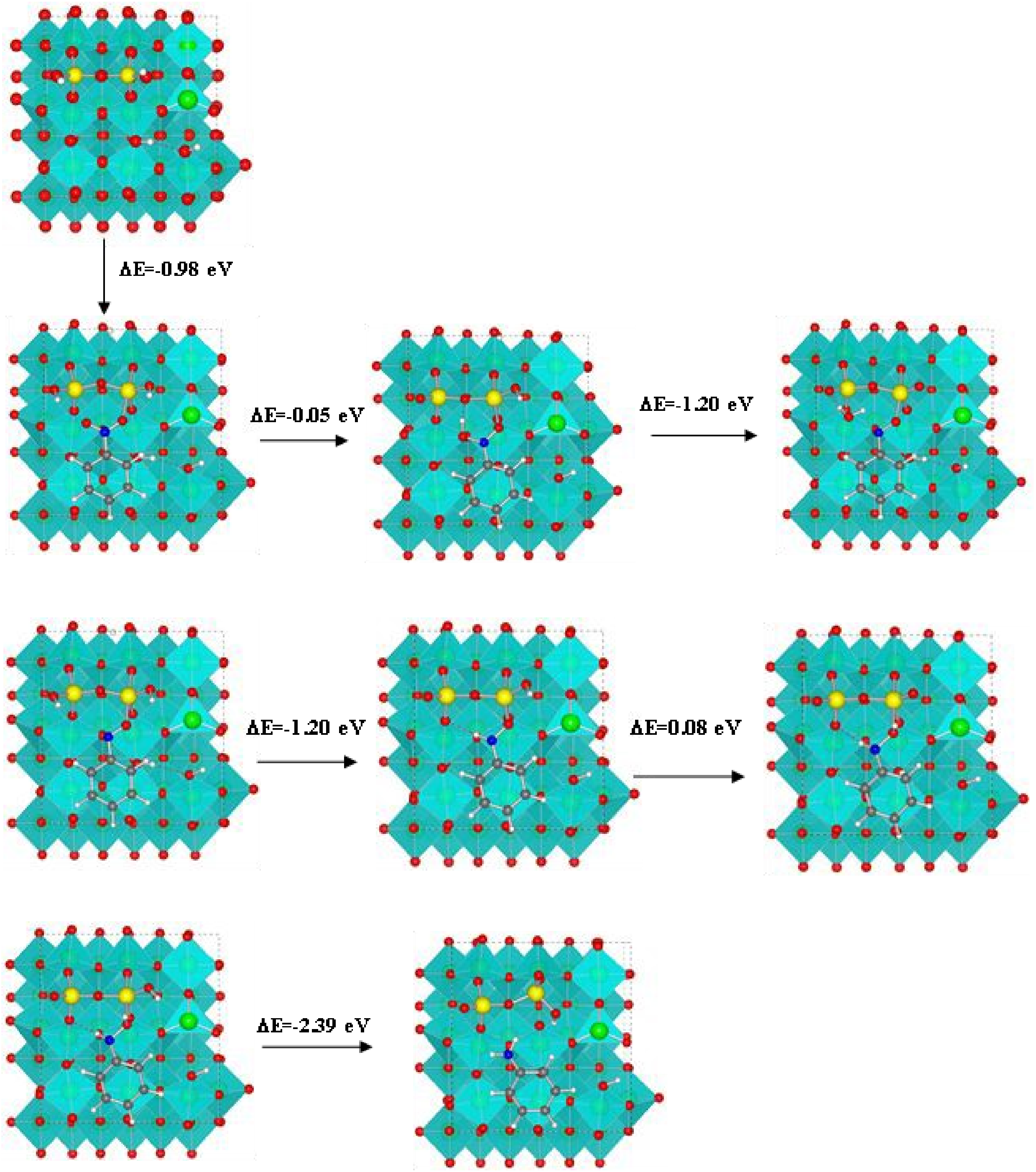

Fig. 6. Schematic representation of catalytic reduction of nitrobenzene to aniline over hydrogenated V_2O_5/TiO_2

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the oxygen bound to the V site to both the -O and -OH of Ph-NOOH. The preferred path involves transferring the hydrogen to the -OH, leading to the separation of a water molecule, with Ph-NO remaining bound to the catalyst surface. In this configuration, the V-O(Ph-NO) distance is measured to be 1.979 Å. At this point, we focused on the hydrogenation of the two terminal oxygen atoms bound to the V sites to explore further intermediate reactions in the nitrobenzene reduction. Starting from the Ph-NO bound hydrogenated catalyst surface, we considered the transfer of one hydrogen atom from the V-bound oxygen to both the N and O sites of Ph-NO. This results in the formation of Ph-NHO, with an energy change of -115.78 kJ/mol and a V-O(Ph-NHO) distance of 1.941 Å in the optimized structure. The subsequent hydrogen transfer from the Ph-NHOH species is slightly endothermic with a reaction energy of 7.72 kJ/mol. To proceed, one of the V-bound oxygen atoms is hydrogenated, and the transferred OH group binds to the V site. This results in the formation of aniline adsorbed over the catalyst, as shown in Fig. **6**. This final reaction is highly exothermic, with a reaction energy of -230.60 kJ/mol. For a comprehensive overview of the reaction energy profiles, Figures **7A** and **7B** display the profiles for both the dehydrogenation of hydrazine and the reduction of nitrobenzene to aniline, respectively.

To further support the mechanistic insights of the developed protocol, a series of control experiments were conducted. Initial optimization studies were carried out using V_2O_5 and TiO_2 separately, which resulted in no reaction, indicating their lack of direct involvement in the reaction. Subsequent experiments employing different synthesized catalysts (C-05, C-10, and C-20) revealed an increase in the product yield. This observation highlights the pivotal role of vanadium loading on titanium oxide in enhancing the product yield. An increase in vanadium loading

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augments the catalyst's acidity, facilitating its interaction with hydrazine hydrate. In a radical scavenger experiment using butylated hydroxytoluene, it was found that the product yield

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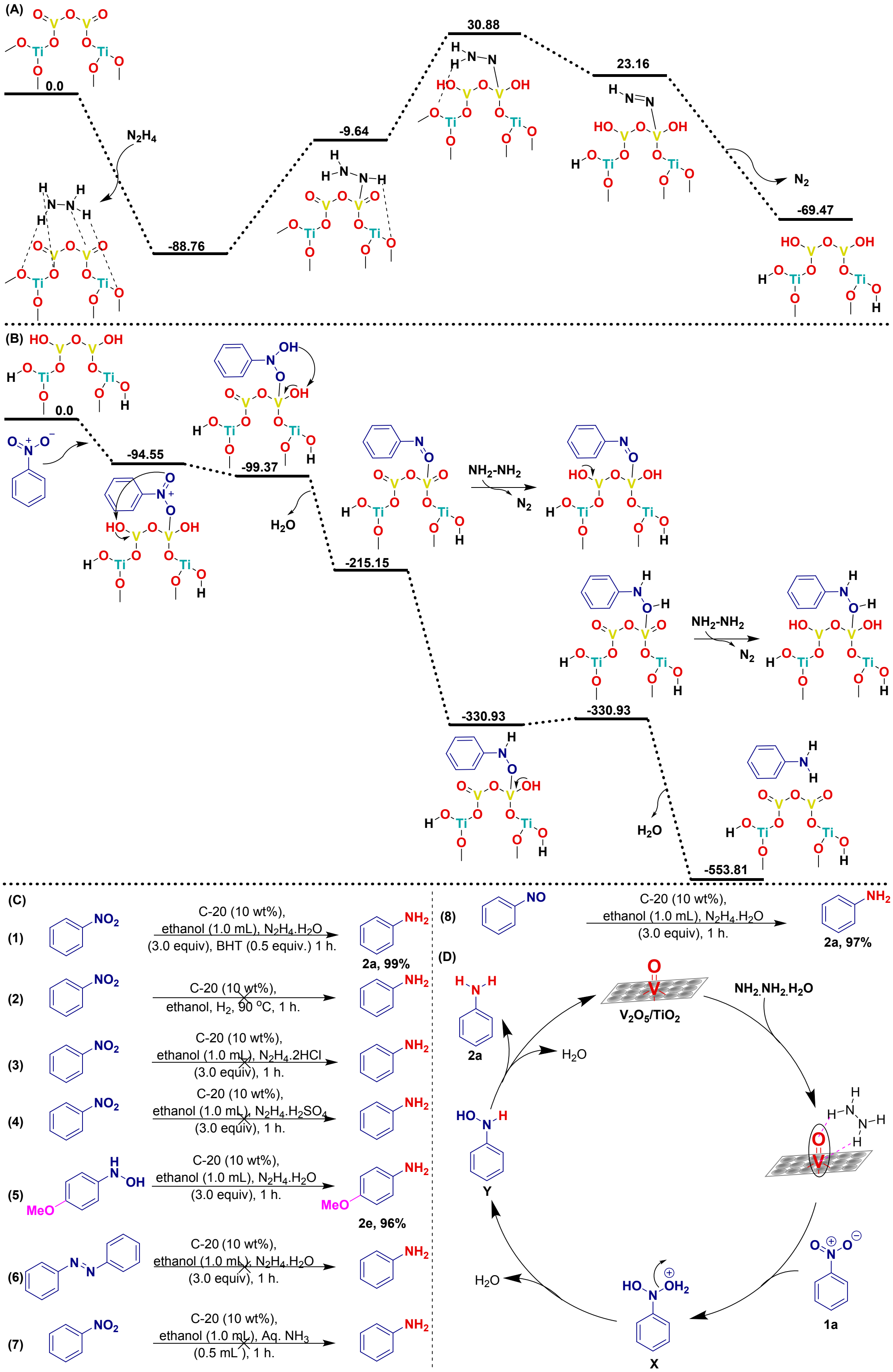

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Fig. 7: **(A)** Reaction energy profile of dehydrogenation of N_2H_4 over the V_2O_5/TiO_2 (001) surface (reaction energies are labelled in kJ/mol) **(B)** Reaction energy profile of nitrobenzene reduction to aniline over hydrogenated V_2O_5/TiO_2(001) (reaction energies are labelled in kJ/mol) **(C)** Control experiments **(D)** Plausible mechanism

remained unaffected, confirming that the reaction does not proceed through a radical mechanism (Fig. **7C, 1**). Furthermore, the introduction of molecular hydrogen had no impact on product formation, ruling out the involvement of molecular hydrogen in the reaction (Fig. **7C, 2**). The effect of different hydrazine salts on the reaction was also investigated by using hydrazine dihydrochloride and hydrazine sulphate instead of hydrazine hydrate, leading to a complete cessation of the reaction (Fig. **7C, 3, 4**). This indicated that the hydrochloride and sulphate salts interfered with the interaction between hydrazine and the catalyst, preventing any reaction. Typically, the reduction of nitroarenes involves the formation of two intermediates: hydroxylamine and azobenzene. However, in this case, mass spectrometry analysis of the reaction mixture did not detect the azobenzene intermediate. To identify the active intermediate generated during the reaction, a reaction with hydroxylamine was performed, yielding an excellent yield of the desired aniline. This result confirmed the generation of the hydroxylamine intermediate during the reaction (Fig. **7C, 5**). In contrast, a reaction with azobenzene did not yield the respective aniline, indicating that the reaction does not follow the azobenzene formation pathway (Fig. **7C, 6**). The reduction of nitrobenzene did not produce the corresponding aniline when conducted in an aqueous ammonia solution (Fig. **7C, 7**), providing evidence that ammonia is not involved in the reaction. Lastly, nitroso benzene yielded the respective aniline in excellent yield under the

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developed reaction conditions, confirming the role of the nitroso benzene intermediate in the reaction (Fig. **7C, 8**).

Based on the outcomes and findings from our mechanistic experiments, we have formulated a plausible reaction mechanism for the catalytic reduction of nitroarenes using V_2O_5/TiO_2 as the catalyst. The reaction initiates with the interaction between hydrazine hydrate and nitroarenes in the presence of the catalyst. This interaction leads to the formation of an intermediate species known as the hydroxyl(phenyl)amino)oxonium ion, denoted as **X**. Subsequently, intermediate **X** undergoes a transformation, eliminating a water molecule in the process, and giving rise to another intermediate, hydroxylamine, labeled as **Y**. This conversion is crucial in the reaction pathway. Finally, complex Y undergoes further reduction to yield the corresponding amine product, denoted as **2a**. Simultaneously, this step releases the catalytic species necessary for the commencement of the next catalytic cycle (as illustrated in Fig. **7D**).

Conclusion

In summary, we have successfully devised an efficient protocol utilizing heterogeneous V_2O_5/TiO_2 catalyst for the reduction of various (hetero)aromatic and unsaturated nitro compounds to their corresponding amines. This methodology demonstrates remarkable versatility, accommodating a wide range of functional groups and substrates. To illustrate its practicality, we applied this protocol to synthesize seven pivotal pharmaceuticals (paracetamol, methacetin, phenacetin, 4-amino benzoic acid, benzocaine, butamben, and bromhexine), as well as 47 (hetero)arylamine and 12 *N*-alkylated secondary amines. Our system offers an eco-friendly and efficient approach for

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generating aniline derivatives, yielding excellent results. Importantly, the only by-products produced are environmentally benign N_2 and H_2O. Furthermore, we have successfully achieved the one-pot reductive alkylation of nitroarenes using alkyl halides. The catalyst is recyclable, and the protocol can be scaled up for multi-gram synthesis, underscoring its translational potential. Additionally, the protocol demonstrates remarkable chemo selectivity, making it a valuable tool for synthetic applications. To attain a more profound insight into the V_2O_5/TiO_2 catalyst, we implemented a multifaceted strategy that encompassed a synergistic blend of Density Functional Theory (DFT) calculations and precisely controlled experimental investigations.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at

https://

The ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Declaration of Interest

CSIR-IHBT Palampur has filed a patent on the process reported herein.
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Applicant: COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH
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Author Contributions

R.U. contributed to preparing the catalyst, optimization, substrate scope for all tables, mechanistic study, data analysis, and manuscript writing. S.K. assisted in the synthesis of the substrate scope. K.S. contributed in computational studies. K.R.S.C. contributed in computational studies and editing of the manuscript. C.S.G. contributed in XPS analysis and editing of the manuscript.

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S.K.M. conceived and supervised the experiments, data analysis, editing of the manuscript, and overall guidance.

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The ^{1}H and ^{13}C NMR spectra for all products (PDF)