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Letter

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.6b03040 • Publication Date (Web): 06 Dec 2016

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Nickel catalyzed deamidative step-down reduction of amides to aromatic hydrocarbons

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Supporting Information Placeholder

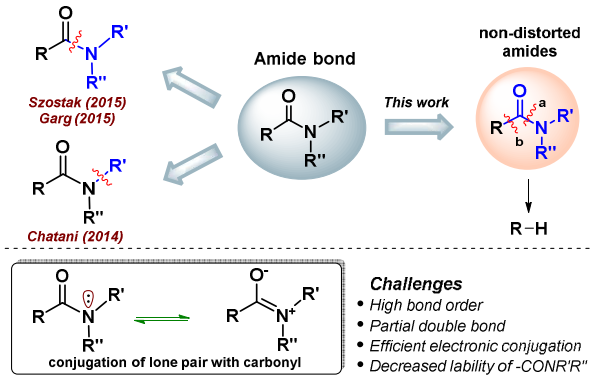
ABSTRACT: Till date, cleavage of the C–N bond in aromatic amides was found to be possible in molecules with a distorted constitutional framework around the nitrogen atom. In this report, a nickel catalyzed reduction of planar amides to the corresponding lower hydrocarbon homologue has been reported. This involves a one pot reductive cleavage of the C–N bond followed by a tandem C–CO bond break in presence of a hydride source. Substrate scope circumscribes deamidation examples which proceed via oxidative addition of nickel in the amide bonds of non-twisted amides. Mechanistic studies involving isolation and characterization of involved intermediates via different spectroscopic techniques reveal a deeper introspection into the plausible catalytic cycle for the methodology.

Keywords: nickel, amides, deamidation, C–N bond, catalysis, reduction

The advent of transition metal catalysis in organic transformations have revamped the synthetic efficacy for chemical reactions. As novel synthetic routes unfold creating wider dimensions for retrosynthetic applicability, chemists continue to pool their efforts leading to discovery of benign protocols time and again. Incorporation of functional groups at strategic locations within a molecule has now become easier owing to the availability of diverse C–H functionalization pathways. Functionalization at both sp^2 and sp^3 carbon centres has been performed with transition metals acting as effective catalyst partners.[1] On the contrary, execution of defunctionalization strategies manifest immense significance especially when they equate with an admirable degree of selectivity. Over the decades, ample reports on C–X defunctionalization (X = functional group) validate the competence of transition metals in overpowering the high bond dissociation energy of the C–X bond.[2] A variety of approaches such as deformylation, decyanation, desulfurization, decarboxylation, dehalogenation, etc. therefore delineated the tale of metal mediated defunctionalization.[3] Extending the similar approach towards amides would mean confrontation with three distinct possibilities of bond disconnection (Scheme 1). First, cleavage of the N(amide)–aryl bond, as was demonstrated by Chatani in presence of nickel catalyst.[4] Second, cleavage of the CO(amide)–N(amine) bond, as was performed by Szostak and Garg.[5] The final possibility was the reductive cleavage of the CO–C bond that has however remained less explored.[6]

A challenging aspect with the chemistry involving amides has been the generation of acyl electrophile from cleavage of the amide linkage. Cleavage of the CO–N bond is rendered problematic owing to conjugation of the lone pair of nitrogen with the carbonyl group. Also, high basicity of the amine group makes it a poor nucleofuge. Unequivocally enough, scission of the CO–N bond had therefore been performed by the use of nickel, a late transition series metal which is electropositive and can undergo oxidative addition to bonds.[2f,7] Oxidative additions into the CO–N bond followed by a tandem reductive cleavage of the CO–C bond have been reported only for sterically distorted/twisted amides.[8] In this report, we present a nickel catalyzed reductive deamidative cleavage of the CO–C bond of planar amides.

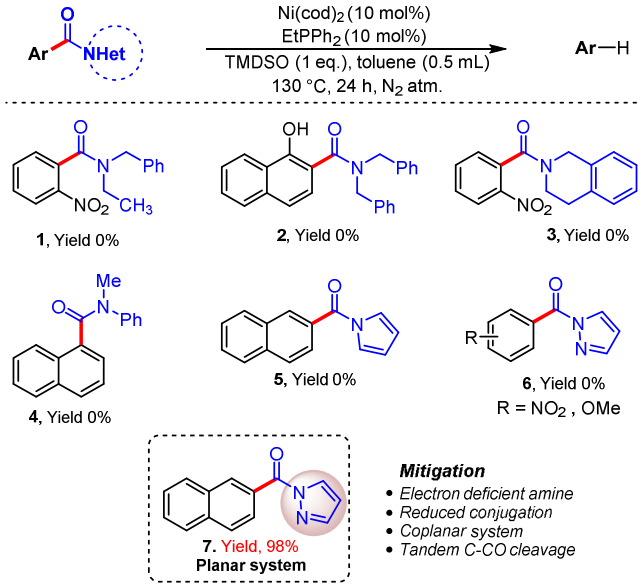
Reduction of amides to the corresponding lower hydrocarbon homologue requires elimination of the amine partner and a concomitant decarbonylation. Use of standard aluminium based reducing agent like $LiAlH_4$ is not helpful as its greater hydride donating ability reduces amides to amines. Similarly, reduction to aldehydes occurs in presence of diisobutyl aluminium hydride or by other methods.[9] We furnish a one-pot direct step-down protocol for conversion of an amide into a hydrocarbon.



Scheme 1. Various modes of amide bond scission.

In order to execute a successful oxidative addition of nickel into the CO–N bond, controlling the electron donation from n_N to π^*_{CO} was a supreme need. This necessitated amides with destabilized ground-state. Commencement was therefore made with twisted amides where barrier to rotation is controlled by geometrical factors.[5f,10] An attempt for execution of deamidative cleavage of the benzamide (Scheme 2, **1**, **3**) failed to produce any desired result. Increase of π-electron density by introduction of naphthyl/naphthol ring on the acyl portion of the amide was not helpful (Scheme 2, **2**). Increase of the CO–N twist angle was thought to improve the

situation since this would reduce planarity and decrease electronic delocalization. However, it remained unchanged even after attaching phenyl ring to N (Scheme 2, **4**).



Scheme 2. Screening of twisted *vs* planar amide conformations for deamidation. GC yields are reported.

We envisaged a system with coplanar CO–N bond plane but with an electronically deficient amine partner. However, coplanar pyrrole amide derivatives gave no useful results (Scheme 2, **5**). Consequently, a pyrazole moiety was ligated to the carbonyl center which would inturn activate the C–N bond. This would ensure a destabilized ground state which was crucial for the defunctionalisation chemistry involving

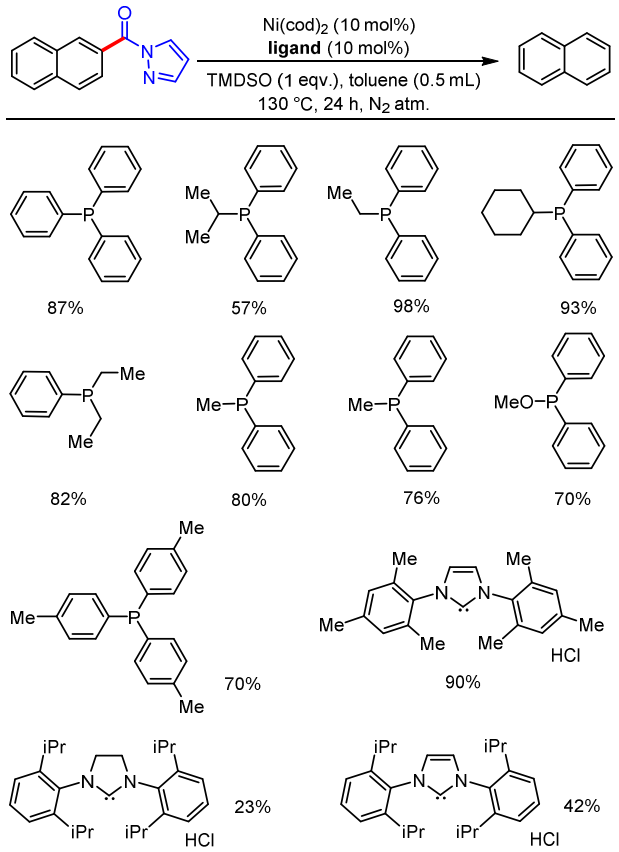


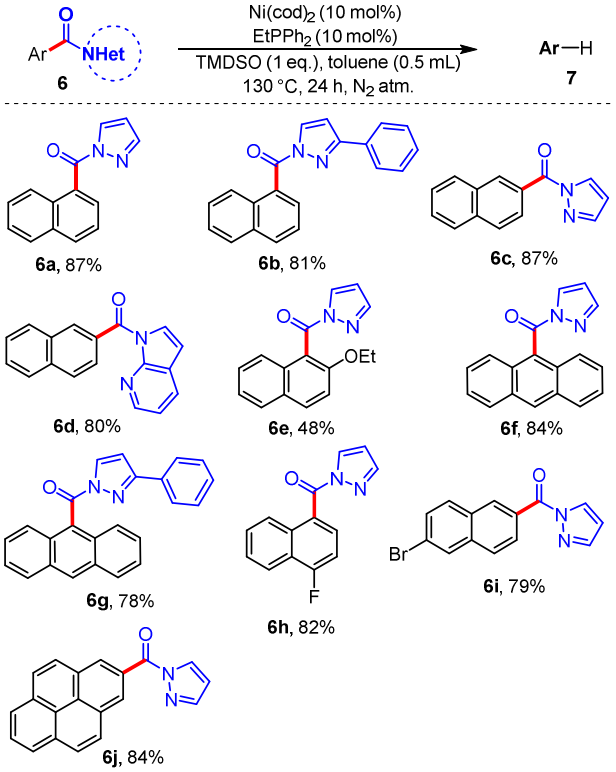
Table 1: Optimization of the ligands by GC yields. See See Supporting Information.

C–N bonds.[8b] Electrophilic character of the attached carbonyl would hence increase. Moreover, a substantial screening of the ligands was also performed (Table 1) in order to obtain better reactivity with the metal catalyst. With $Ni(cod)_2$ as the catalyst, $EtPPh_2$ as the associated ligand and tetramethyldisiloxane as the hydride donor, a successful reductive deamidation of the amide (Scheme 2, **7**) was obtained with formation of the corresponding hydrocarbon. N atom of the pyrazole was presumed to have a positive effect in coordination to catalyst since controlled experiments with a pyrrole amide derivative did not undergo any deamidation (Scheme 2, **5**). No products were formed in absence of the exogenous ligand. Hydride donating role of siloxanes were limited only to reduction of carbonyl group in presence of amides thereby leading to formation of amines from amides.[11] We report an exclusive reduction of the aryl group, *i.e*, controlled cleavage of the C(aryl)–CO(carbonyl) bond, without any competitive acyl reduction in presence of the silylhydride source.[11] A further optimization of the reaction condition under nitrogen atmosphere and at a temperature of 130 °C provided 87% isolated (GC yield, 98%) yield of the desired products. Aromatic π-conjugation was perceived to be important for the protocol as systems lacking unconjugated π-frameworks like amide derivatives of benzoic acid (scheme 2, **1, 3, 6**) did not effectively qualify for the reaction. Similarly, primary amines did not serve to be as effective.

With the optimized condition we surveyed the scope of the substrates. Planar amides with electronically deficient heterocyclic amine partners qualified successfully for the reaction condition (Scheme 3, **6a-j**). Functional group tolerance towards ethers was obtained with pyrazolamide of 2-ethoxynaphthoic acid (Scheme 3, **6e**).[3e,12] Halogens such as fluoro and bromo groups within the naphthyl ring proved to be quite successful (Scheme 3, **6h**, **i**). Efficacy of the reaction protocol was further established with biphenyl systems (Scheme 4, **8a-h**, **k**, **l**). Both electron donating and electron withdrawing groups were functionally tolerant (Scheme 4, **8e-h**, **l**). Amides with bulky substituents at the *ortho*- position underwent deamidation without any steric problem. These include substrates with *ortho*-substituted phenyl ring as well as heterocycles (**8a-d**). Biphenyls containing electron donating substituents like methoxy, benzyloxy and phenoxy groups were found to undergo deamidation with good yields irrespective of the location of the alkoxy groups (**8e-g, l**). Cleavage of the amide bond was performed selectively without any competitive cleavage of the ether linkages.[3e,12] Highly electron withdrawing groups like $-CF_3$ were also tolerated (**8h**). Also, stilbene systems exhibited deamidation with good to excellent yields (**8i**, **j**).

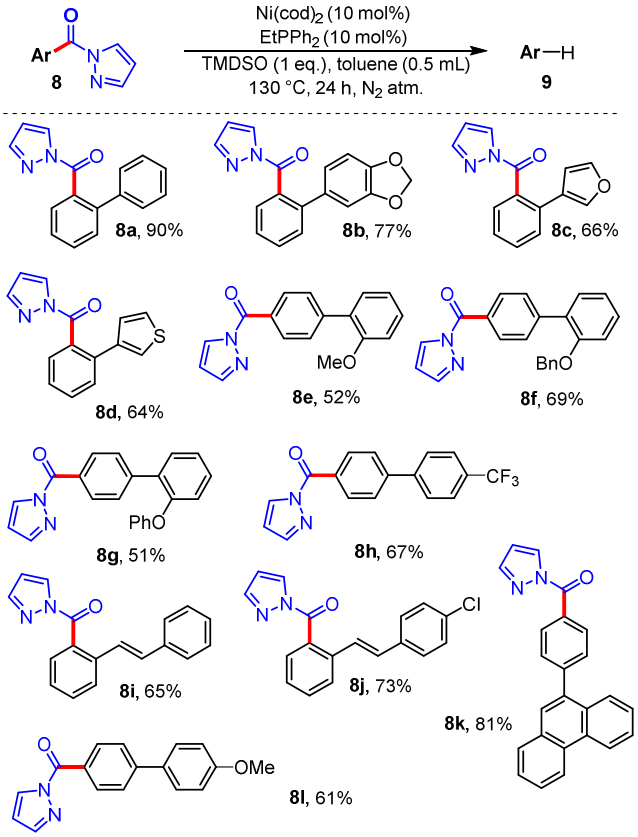
A regioselective oxidative addition of metal to the CO–N bond was crucial for the process to be executed. Nickel with relatively smaller atomic radius and an excess of d-electrons allowed easy donation to the π-acceptor ligands (*viz.* carbonyl group).[7d] Oxidative addition in form of Ni(II) is reversible in nature.[13] Both PPh_3 or $EtPPh_2$ were successful ligands for the reaction. These basic ligands prevented the possibility of decarbonylative coupling between the amine and the acid group.[13] Interaction of Ni-catalyst with substrate was monitored through observing CO bond stretching frequency. Upon addition of stoichiometric $Ni(cod)_2$ and ligand to the amide substrate, the –CO peak shifted from 1699 cm^{-1} to 1935 and 1995 cm^{-1} (Figure 1).[14] This indicated the absence of amide CO–N bond and formation of Ni–CO bond during reac-

tion. The carbon monoxide produced from the reaction may either remain ligated to the intermediate complexes or may be trapped by other zero-valent Ni species.[13]



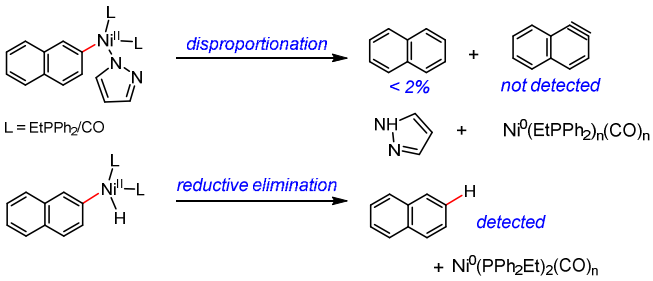
Scheme 3. Deamidative reductive cleavage of various conjugated amides. Isolated yields are reported.

In this case, CO was found incorporated into $Ni(CO)_n(EtPPh_2)_2$ complex that was isolated from the reaction mixture in absence of hydride source and was characterized by X-ray crystallography (Figure 2, **a**). This isolated Ni(0) complex yielded 60% of naphthalene product on repeating reaction with TMDSO. Formation of final product could be traced to two possibilities: (a) disproportionation of



Scheme 4. Deamidative reductive cleavage of various biphenyl and stilbene based amide derivatives. Isolated yields are reported.

the intermediate (Naph)Ni(II)(amine)$(EtPPh_2)_2$ into $C_{10}H_8$ and $C_{10}H_6$ in 1:1 molar ratio along with release of free amine and $Ni(EtPPh_2)_n(CO)_n$ or (b) reductive elimination of hydride coordinated Ni(II) intermediate to generate $Ni(CO)_n(EtPPh_2)_2$ in presence of *in situ* CO.[13] In the absence of hydride source, $Ni(CO)_n(EtPPh_2)_2$ alongwith negligible amount of $C_{10}H_8$ was formed but $C_{10}H_6$ was not detected. No 1:1 ratio was obtained for them. Reaction with TMDSO yielded naphthalene product and $Ni(CO)_n(EtPPh_2)_2$. Thus, final production of naphthalene could be attributed to a reductive elimination from (Naph)Ni(II)(H)$(EtPPh_2)_2$ and not by disproportionation reaction (Scheme 5).



Scheme 5. Competitive step for final product formation.

Aerial atmosphere may lead to oxidation proceeding through a carboxylate intermediate (isolated, Figure 2, **b**) and was unfavourable. In order to further substantiate the hydride transfer step, isotope labelling experiments were conducted with deuterated hydride source. A 69% of deuterium-

incorporation was observed in final deamidated product (Figure 3). This could be ascribed to the possibility of a rapid H/D exchange occurring between Ph_2SiD_2 and the C–H bonds present in toluene (See Supporting Information, Figure S5).[4] Kinetic studies showed first order dependency on the amide substrates (Figure 4). Moreover, a zero-order dependence of the reaction rate on the amount of TMDSO was observed which was indicative of the fact that Ni(I)-silyl species were not involved in the reaction (Figure 5).[3e,k]

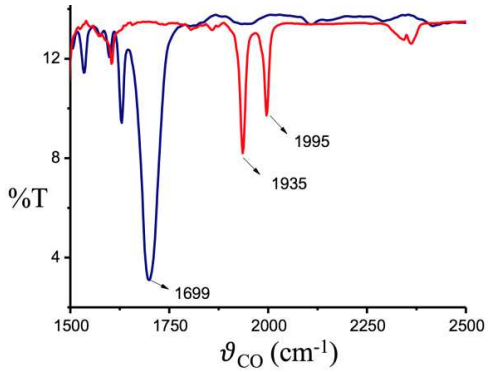


Figure 1. IR data of (a) amide, 6c (blue), (b) reaction mixture involving 6c showing formation of $Ni(CO)_2(EtPPh_2)_2$ (red).

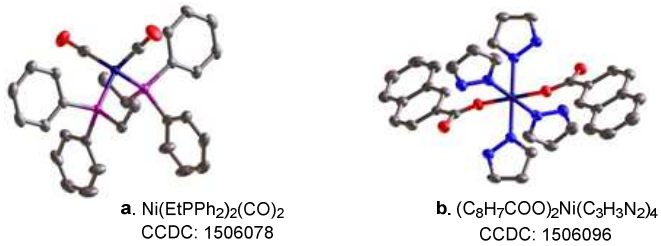


Figure 2. X-ray structures for intermediates.

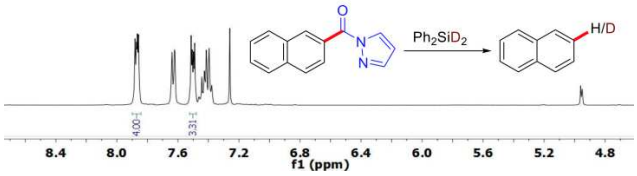


Figure 3. Deuterium incorporation experiment for naphthalene by NMR characterization.

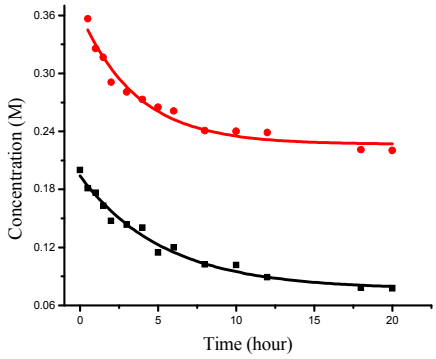


Figure 4. First order reaction kinetics plot for amide substrate. Black line: 0.1 mmol, Red line: 0.2 mmol substrate.

Based on the experimental observations, a plausible mechanism can be proposed (Scheme 6). At the beginning of the cycle, $Ni(cod)_2$ undergoes ligand exchange with $EtPPh_2$ to form **I**. Following this, Ni(0) undergoes oxidative addition across CO–N bond leading to C–N bond activation **II** (con

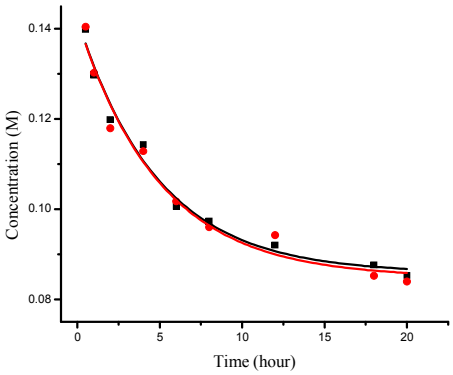
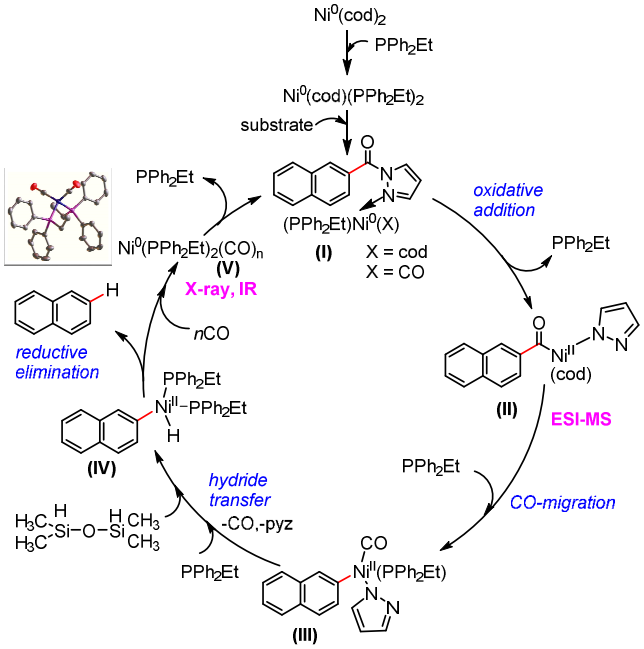


Figure 5. Kinetics plot for with respect to silylhydride. Black-line: 0.1 mmol, Red line: 0.2 mmol.

firmed by ESI-MS; See Supporting Information). After that β-migration of CO leads to formation of **III**. Following this, hydride transfer occurs from TMDSO to the nickel centre leading to formation of the hydride intermediate **IV**. Release of the free amine at this stage was confirmed when reaction of **6b** yielded 3-phenylpyrazole in 60% yield. This is followed by reductive elimination and $Ni(CO)_n(EtPPh_2)_2$ formation by reacting with the *in situ* generated CO which then continues the catalytic cycle.



Scheme 6. Mechanistic cycle for deamidative reductive cleavage.

In summary, we report the first deamidative tandem reductive cleavage of the C(aryl)–CO linkage following the scission of CO–N(amine) bond in amides. Exercise of effective control over the reaction condition allowed a selective reduction in presence of the hydride donor. A further development of the above reaction protocol would assist in the introduction of other nucleophiles to the acyl ring following the elimination of the amide linkage.

ASSOCIATED CONTENT

Supporting Information

Experimental and Characterization data. The Supporting Information is available free of charge on the ACS publications website.
Procedure and analytical data. (PDF, CIF file)

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Author Contributions

‡Both have contributed equally.

ACKNOWLEDGMENT

This activity is supported by CSIR, India (funding to DM, CSIR, 02(0242)/15/EMR-II). Financial support received from DST-India (fellowship to K.S. YSS/2015/000736) is gratefully acknowledged.

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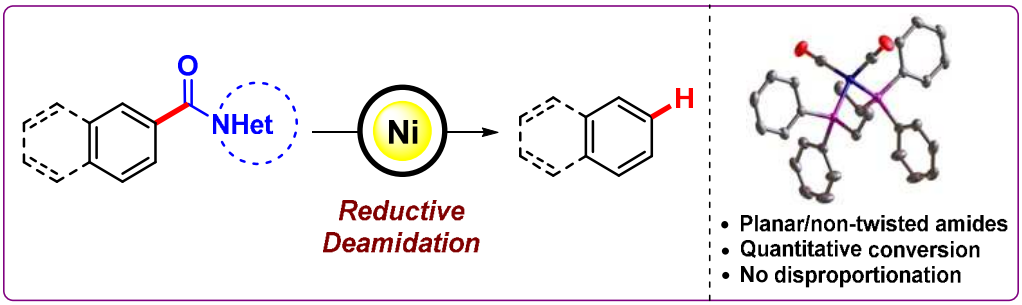

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Nickel catalyzed deamidative step-down reduction of amides to aromatic hydrocarbons

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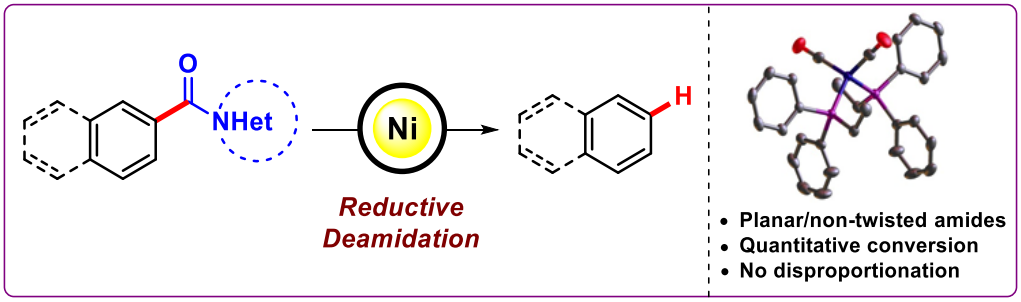
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