

Redox-Neutral Imination of Alcohol with Azide: A Sustainable Alternative to the Staudinger/Aza-Wittig Reaction

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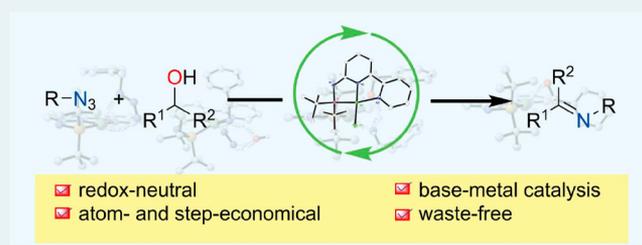
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ABSTRACT: The traditional Staudinger/aza-Wittig reaction represents one of the most powerful tools for imine formation. However, for this multistep procedure, the sacrificial phosphine has to be used, resulting in difficulties in the purification process and waste disposal at the same time. Here, we report a redox-neutral azide–alcohol imination methodology enabled by a base-metal nickel PN³ pincer catalyst. The one-step, waste-free, and high atom-economical features highlight its advantages further. Moreover, mechanistic insight suggests a non-metal–ligand cooperation pathway based on the observation of an intermediate and density functional theory calculations.

KEYWORDS: imination, redox-neutral process, base-metal catalysis, atom and step economy, PN³ pincer



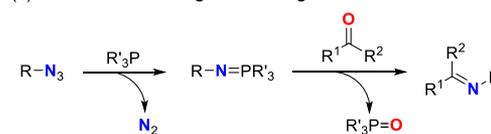
and density functional theory calculations.

Imines are essential intermediates and precursors in the synthesis of various dyes, pigments, polymers, natural products, agrochemicals, and pharmaceuticals.¹ The conventional method for the synthesis of imines is the acid-catalyzed condensation of aldehydes or ketones with amines. Recently, several alternative approaches of imine synthesis have been reported,^{1c} such as oxidation of amines,² oxidative or acceptorless dehydrogenative coupling of alcohols and amines,^{2e,3} hydroamination of alkynes by amines,⁴ hydrogenative coupling of nitriles and amines,⁵ transfer hydrogenative cross-coupling of nitriles and alcohols,⁶ and hydrogenation of nitriles.⁷ Generally, most of the methods for imine synthesis employ either an amine or a nitrile as a nitrogen source, along with using stoichiometric amounts of sacrificial oxidants or reductants.

Organic azides offer another alternative and fascinating nitrogen source for the synthesis of various N-containing compounds because of their versatile reactivity.⁸ Prominent examples are the Schmidt reaction,⁹ Staudinger ligation,¹⁰ C–H bond amination,¹¹ and azide–alkyne cycloaddition.¹² Concurrently, a wide range of organic azides are readily available, primarily due to the development of “click” azide–alkyne cycloaddition. Despite these significant advances in azide chemistry, to date, there are only a few methods on the use of organic azides as the nitrogen source for imine synthesis. In this regard, the classical Staudinger/aza-Wittig reaction, which starts from an azide and a suitable phosphine, via iminophosphorane formation, followed by the reaction with aldehydes or ketones, has provided a powerful tool to prepare imines (Scheme 1a).¹³ However, the phosphine has to be used as a sacrificial reagent during this multistep process. At the same time, the formation of phosphine oxide byproduct leads to difficulties in the separation

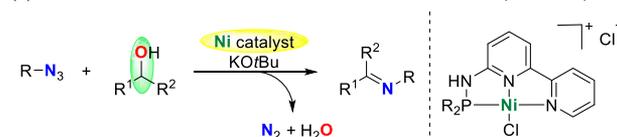
Scheme 1. Methods of Imine Synthesis with Organic Azides

(a) well-known: Staudinger/aza-Wittig reaction



- multistep process
- the use of phosphine as sacrificial reagent
- waste formation and separation issues

(b) unknown: Redox-neutral azide–alcohol imination reaction (this work)



- more accessible, more stable alcohols as the reaction partners
- one-step, redox-neutral, waste-free, and high atom-economical process
- base-metal catalysis

and waste disposal.¹⁴ In addition to the traditional Staudinger/aza-Wittig reactions,¹⁵ there are only two reports on the transformation of azides to imines.¹⁶ Nevertheless, both of them are limited to self-coupling of benzyl azides to the corresponding

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symmetric imines with narrow substrate scopes. Therefore, the development of efficient, waste-free, and environmentally benign synthetic methodologies for the imine synthesis using readily available azides as the nitrogen source remains challenging and attractive.

A highly desirable goal is the direct conversion of alcohols and azides into imines without adding any external redox reagents because it is a redox-neutral, waste-free, and highly atom- and step-economical process (Scheme 1b). Furthermore, the use of alcohols as reaction partners for this azide–alcohol imination protocol are of highly practical advantage due to their availability and stability compared to that of carbonyl compounds, which might allow access to a great variety of imines from these very simple substrates.^{3g,17} Herein, we describe such a redox-neutral azide–alcohol imination reaction catalyzed by an abundant base-metal nickel PN³ pincer complex, leading to various cross-imines.

As part of our ongoing interest in the PN³(P) pincer chemistry,¹⁸ the bipyridine- and phenanthroline-based PN³–Ni pincer complexes Ni1, Ni2, and Ni3 (Figure 1) were synthesized

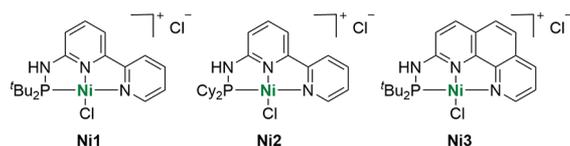


Figure 1. Bipyridine- and phenanthroline-based PN³–Ni pincer complexes Ni1, Ni2, and Ni3.

readily by the treatment of NiCl₂ with the corresponding pincer ligands at 110 °C in toluene in high yields. The solid-state structures of complexes Ni1, Ni2, and Ni3 were determined by single-crystal X-ray diffraction crystallography. The Ni(II) centers in the three complexes featured square-planar coordination spheres with a meridional tridentate bipyridine-based pincer ligand, one chloride ligand, and a non-coordinating chloride anion. Similar geometrical parameters have been observed in these three complexes, as well. While the Cl1–Ni1–N2 angles are linear, the P1–Ni1–N3 angles are deviated from linearity (Figure 2).

We began our catalytic studies for the azide–alcohol imination reaction with benzyl alcohol (**1a**) and phenyl azide (**2a**) as the model substrates to optimize the reaction conditions. Unprecedented chemoselectivity was shown upon heating a solution of **1a** and **2a** in the presence of Ni1 (2 mol %) and KO^tBu (8 mol %) in toluene at 130 °C for 24 h. *N*-Benzylideneaniline (**3a**) was afforded as the major product together with only a trace amount of the amidation product *N*-phenylbenzamide (**4a**), albeit in a lower conversion (55%) (Table 1, entry 1). A control experiment without the catalyst resulted in no reaction under these conditions (Table 1, entry 2). A lower yield of **3a** was observed when complex Ni2 was employed as the catalyst (Table 1, entry 3).

The phenanthroline-based PN³–Ni pincer complex Ni3 also demonstrated a lower catalytic reactivity, despite the high selectivity in this transformation (Table 1, entry 4). Encouraged by such unique catalytic performances, we carried out further optimization to increase the conversion and yield. Changing the solvent to *p*-xylene or benzene led to lower yields of **3a** under otherwise analogous conditions (Table 1, entries 5 and 6). In contrast, the formation of amidation product **4a** was favored over formation of the imination product **3a** at higher conversion

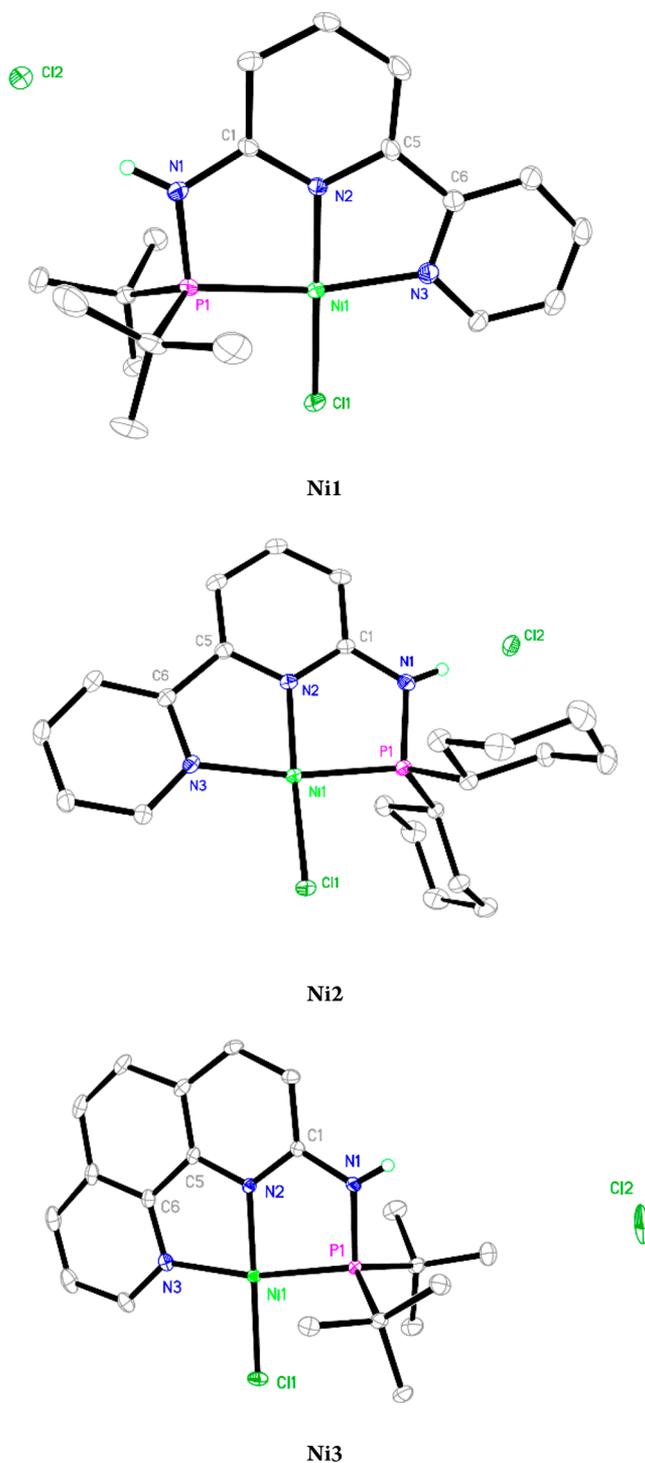


Figure 2. X-ray structures of complexes Ni1, Ni2, and Ni3 at 30% ellipsoid probability. Hydrogen atoms (except for pincer arms) are omitted for clarity. Selected bond lengths (Å). Ni1: Ni1–Cl1 2.1843(1), C1–N1 1.335(3). Ni2: Ni1–Cl1 2.1348(2), C1–N1 1.363(3). Ni3: Ni1–Cl1 2.1470(8), C1–N1 1.358(3). Selected bond angles (deg). Ni1: Cl1–Ni1–N2 179.79(1), P1–Ni1–N3 168.01(1). Ni2: Cl1–Ni1–N2 177.26(1), P1–Ni1–N3 169.76(1). Ni3: Cl1–Ni1–N2 179.43(8), P1–Ni1–N3 167.08(7).

of **2a** (83%) while using more polar solvent, THF (Table 1, entry 7). Notably, increasing the amount of **1a** to 2 equiv under otherwise identical conditions furnished the desired product **3a** in 71% yield at 77% conversion of **2a** (Table 1, entry 8).

Table 1. Optimization of Reaction Conditions^a

entry	catalyst	solvent	T (°C)	t (h)	conv (%)	yield (%) ^b	
						3a	4a
1	Ni1	toluene	130	24	55	53	trace
2 ^c		toluene	130	24	<1	trace	trace
3	Ni2	toluene	130	24	48	44	<5
4	Ni3	toluene	130	24	48	30	trace
5	Ni1	<i>p</i> -xylene	130	24	40	33	<5
6	Ni1	benzene	130	24	45	36	<5
7	Ni1	THF	130	24	83	27	51
8 ^d	Ni1	toluene	130	24	77	71	<5
9 ^e	Ni1	toluene	130	24	>99	93	<5
10 ^e	Ni1	toluene	130	18	>99	92	<5
11 ^e	Ni1	toluene	120	24	87	80	<5

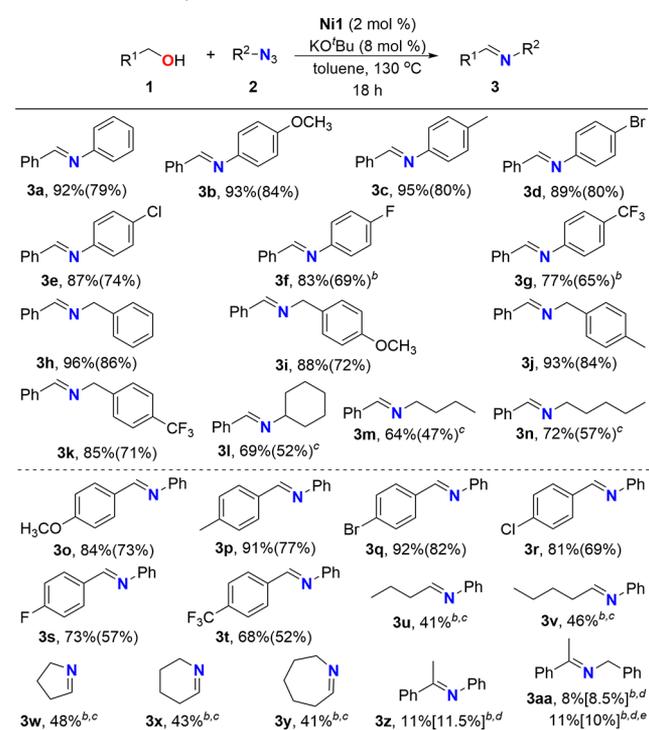
^a[Ni] complex (0.02 mmol), **1a** (1.1 mmol), **2a** (1 mmol), KO^tBu (0.08 mmol), solvent (6 mL). ^bDetermined by ¹H NMR spectroscopy of the crude reaction mixture using CH₂Br₂ as the internal standard or GC-MS. ^cWithout catalyst. ^d**1a** (2 mmol). ^e**1a** (3 mmol).

Complete conversion of **2a** to selectively produce imine **3a** in 93% yield took place when 3 equiv of **1a** was applied (Table 1, entry 9). The reaction time could be shortened to 18 h with a comparable yield of **3a**. However, when the reaction temperature was lowered to 120 °C, the conversion of **2a** was decreased (Table 1, entries 10 and 11).

Having identified the optimal reaction conditions, we next explored the scope of our unprecedented redox-neutral azide–alcohol imination protocol, and the results are summarized in Scheme 2. Various aromatic azides bearing either electron-donating or electron-withdrawing groups furnished corresponding imines (**3a–3g**) in good to excellent yields, though the latter required longer reaction times. Notably, halides were tolerated in these cases, which could be very useful for further transformations. This catalytic protocol could also be applied to an array of benzyl azides. For example, the reaction of *p*-OCH₃, *p*-CH₃, and *p*-CF₃ benzyl azides with benzyl alcohol (**1a**) proceeded efficiently to afford imine products (**3i**, **3j**, and **3k**). The aliphatic azides such as cyclohexyl azide, *n*-butyl azide, and *n*-pentyl azide were also found to be suitable substrates to give the desired imine products (**3l**, **3m**, and **3n**) in moderate yields for this Ni1-catalyzed azide–alcohol imination process, albeit with a higher catalyst loading.

Subsequently, we examined the substrate scope of this transformation with respect to various alcohols (Scheme 2). The substrates, benzyl alcohols, containing both electron-donating and electron-withdrawing groups on the benzene rings, reacted with phenyl azide (**2a**) under the catalytic condition to give the desired imine products (**3o–3t**) in good to excellent yields. Halogens were fully compatible with this Ni1-catalyzed azide–alcohol imination process. It is also notable that aliphatic alcohols such as 1-butanol and 1-pentanol smoothly underwent imination reaction with phenyl azide (**2a**) to afford the desired products (**3u** and **3v**) in moderate yields when using higher catalyst loading (6 mol %) and extending the reaction time. In addition, the water formed during the course of the azide–alcohol imination does not hinder the reaction.

One of the most important applications of the multistep Staudinger/aza-Wittig chemistry is the synthesis of *N*-heterocycles via intramolecular reaction.^{13b} To our delight, complex

Scheme 2. Catalytic Azide–Alcohol Imination Reaction^a

^aNi1 complex (0.02 mmol), **1** (3 mmol), **2** (1 mmol), KO^tBu (0.08 mmol), toluene (6 mL), 130 °C, 18 h. Yields determined by ¹H NMR spectroscopy using CH₂Br₂ as the internal standard or GC-MS, with isolated yield in the parentheses and conversion of azide in square brackets. ^b36 h. ^c6 mol % of catalyst, 12 mol % of KO^tBu. ^d10 mol % of catalyst, 15 mol % of KO^tBu. ^eTHF as solvent.

Ni1 was capable of catalyzing the intramolecular azide–alcohol imination reactions in one step. Synthesis of five-, six-, and seven-membered cyclic imines (**3w**, **3x**, and **3y**), which are privileged structural motifs in many pharmaceuticals, was demonstrated. However, secondary alcohols remain difficult substrates for this methodology. Even with a higher catalyst loading (10 mol %) and longer reaction time (36 h), the reaction of 1-phenylethanol with phenyl azide or benzyl azide resulted in the corresponding ketimines (**3z** and **3aa**) in only 11 and 8% yields, respectively. Additionally, changing the solvent to THF under otherwise identical conditions gave only a slightly higher yield of **3aa**. The lower catalytic efficiency might be due to the steric hindrance of the secondary alcohols.

To gain insight into this catalytic reaction mechanism, complex Ni1 was reacted with ^tBuOK in THF at room temperature to provide the dearomatized complex Ni4, and its structure was confirmed by X-ray diffraction (Figure 3). A shortened C1–N1 bond length (1.320 Å) of Ni4 was observed, consistent with formation of a C=N double bond. Meanwhile, the upfield shifts in both ¹H NMR and ¹³C NMR spectra of Ni4 compared to those of aromatic complex Ni1 agree with the anticipated dearomatization of the pyridine ring (Figure 3; for full characterization, see the Supporting Information). In addition, the dearomatized complex Ni4 was found to still be stable upon heating at 130 °C in toluene-*d*₈ for 24 h as determined by ³¹P NMR (see Supporting Information for more details). It has been demonstrated that the dearomatized pyridine-based pincer complexes readily react with alcohols and undergo aromatization via metal–ligand cooperation (MLC).^{3g,19} Surprisingly, treatment of the complex Ni4 with

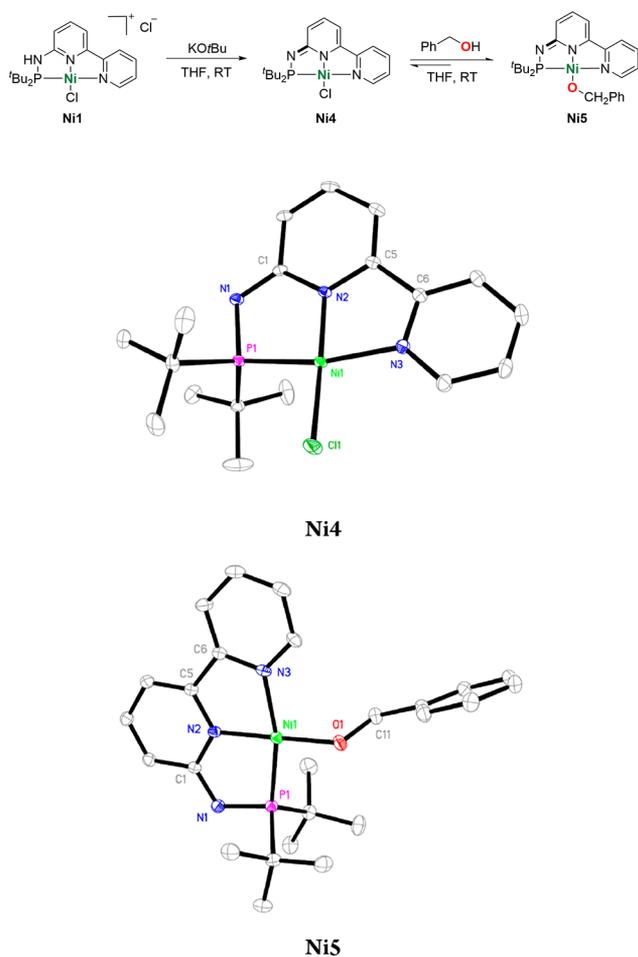


Figure 3. Synthesis of the complexes **Ni4** and **Ni5** and their X-ray structures at 30% ellipsoid probability. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å). **Ni4**: Ni1–Cl1 2.1568(12), C1–N1 1.320(4). **Ni5**: Ni1–O1 1.8464(18), C1–N1 1.327(3). Selected bond angles (deg). **Ni4**: Cl1–Ni1–N2 174.30(8), P1–Ni1–N3 164.67(10). **Ni5**: O1–Ni1–N2 177.90(9), P1–Ni1–N3 165.22(6).

benzyl alcohol resulted in the formation of a new dearomatized complex **Ni5**, whereas the expected rearomatization of the pyridine ring of the PNN ligand did not occur. The shorter bond length of C1–N1 (1.327 Å) in the X-ray structure of **Ni5** together with its high-field signals of both ^1H NMR and ^{13}C NMR spectra clearly demonstrated the dearomatic nature of the pyridine moiety (Figure 3; for full characterization, see the Supporting Information). When the reaction of **1a** and **2a** was carried out with complex **Ni5** as a catalyst under the optimal reaction conditions (Table 1, entry 10) but without a base, the imine product **3a** could be obtained in 87% yield. These observations, together with the results from density functional theory (DFT) studies allowed us to suggest the non-MLC catalytic cycle shown in Figure 4 (see Supporting Information).

The reaction of **Ni4** to **Ni5** was found to be reversible, and an excess of alcohols was required to drive the equilibrium toward formation of the dearomatized complex at approximately 83% yield. This may explain why a 3-fold excess of alcohol is required to maintain good conversions for this azide–alcohol imination protocol. Starting from **Ni5**, the first step of the reaction is β -hydrogen elimination to give benzaldehyde and the hydride complex **Ni6**. Since **TS5,6**, the dehydrogenation of the alcoholate, seems to be the step with the highest energy barrier,

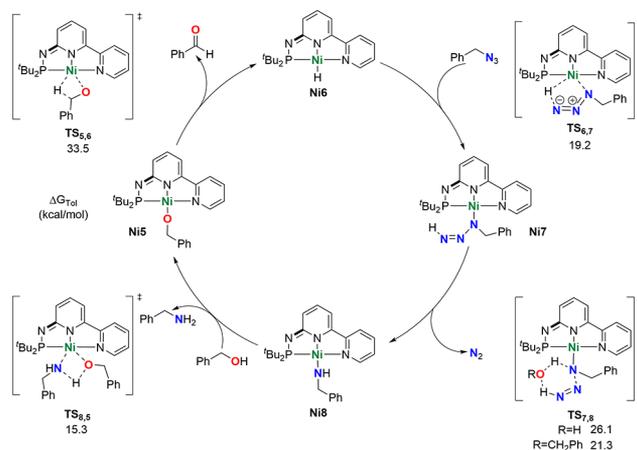


Figure 4. Proposed catalytic cycle for the main reaction steps.

populating its starting point **Ni5** as highly as possible, by employing the 3-fold excess of alcohol, should facilitate the reaction. The next step, **TS6,7**, is the insertion of the azide into the Ni–H bond to form **Ni7**, which can expel nitrogen via the water-mediated **TS7,8** to form the amide complex **Ni8**.²⁰ The final step is a ligand exchange,²¹ liberating benzylamine and coordinating benzylalkoxide (see the Supporting Information for details). The formed amine reacts with the aldehyde to give the imine and water. One interesting difference in this mechanism is the absence of the rearomatization processes. In other words, after the initial activation, the catalyst remains in its “dearomatized” state throughout the reaction, presumably due to the square-planar geometry combined with the bulky phosphine ligand, effectively shielding the nitrogen linker.

In summary, we have developed a redox-neutral azide–alcohol imination protocol catalyzed by an abundant base-metal nickel PN³ pincer complex. Intermolecular and intramolecular variants of this reaction were demonstrated, and a wide range of imines were prepared. Compared with the traditional Staudinger/aza-Wittig reaction, this one-step process generates no waste, which circumvents the need for a sacrificial reagent. Employing more available and stable alcohols as reaction partners instead of carbonyl compounds constitutes another attractive feature of our protocol. Therefore, this nickel-catalyzed azide–alcohol imination process would provide a straightforward and sustainable alternative to the traditional Staudinger/aza-Wittig reaction. A plausible non-MLC catalytic mechanism is proposed, supported by the observation of some plausible intermediates and DFT studies. Further investigations on the applications of this methodology are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.1c00379>.

Experimental procedures, characterization data, spectra of new compounds (PDF)

X-ray structural information for **Ni1** (CIF)

X-ray structural information for **Ni2** (CIF)

X-ray structural information for **Ni3** (CIF)

X-ray structural information for **Ni4** (CIF)

X-ray structural information for **Ni5** (CIF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

This work is dedicated to Professor Tien-Yau Luh on the occasion of his 75th birthday.

REFERENCES

(1) (a) Hadjipavlou-Litina, D. J.; Geronikaki, A. A. Thiazolyl and benzothiazolyl Schiff bases as novel possible lipoxygenase inhibitors

and antiinflammatory agents. Synthesis and biological evaluation. *Drug Des. Discovery* **1998**, *15*, 199–206. (b) Adams, J. P. Imines, enamines and oximes. *J. Chem. Soc. Perkin Trans. I* **2000**, 125–139. (c) Gawronski, J.; Wascinska, N.; Gajewy, J. Recent Progress in Lewis Base Activation and Control of Stereoselectivity in the Additions of Trimethylsilyl Nucleophiles. *Chem. Rev.* **2008**, *108*, 5227–5252. (d) Rappoport, Z.; Liebman, J. F. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; Wiley, 2009; pp 609–651. (e) Patil, R. D.; Adimurthy, S. Catalytic Methods for Imine Synthesis. *Asian J. Org. Chem.* **2013**, *2*, 726–744.

(2) (a) Ell, A. H.; Samec, J. S. M.; Brasse, C.; Baekvall, J.-E. Dehydrogenation of aromatic amines to imines via ruthenium-catalyzed hydrogen transfer. *Chem. Commun.* **2002**, 1144–1145. (b) LARGERON, M.; CHIARONI, A.; FLEURY, M.-B. Environmentally friendly chemoselective oxidation of primary aliphatic amines by using a biomimetic electrocatalytic system. *Chem. - Eur. J.* **2008**, *14*, 996–1003. (c) Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. Highly efficient oxidation of amines to imines by singlet oxygen and its application in Ugi-type reactions. *Org. Lett.* **2009**, *11*, 4568–4571. (d) Su, F.; Mathew, S. C.; Moehlmann, L.; Antonietti, M.; Wang, X.; Blechert, S. Aerobic oxidative coupling of amines by carbon nitride photocatalysis with visible light. *Angew. Chem., Int. Ed.* **2011**, *50*, 657–660. (e) Chen, B.; Wang, L.; Gao, S. Recent Advances in Aerobic Oxidation of Alcohols and Amines to Imines. *ACS Catal.* **2015**, *5*, 5851–5876. (f) Ray, R.; Chandra, S.; Yadav, V.; Mondal, P.; Maiti, D.; Lahiri, G. K. Ligand controlled switchable selectivity in ruthenium catalyzed aerobic oxidation of primary amines. *Chem. Commun.* **2017**, *53*, 4006–4009.

(3) (a) Blackburn, L.; Taylor, R. J. K. In Situ Oxidation-Imine Formation-Reduction Routes from Alcohols to Amines. *Org. Lett.* **2001**, *3*, 1637–1639. (b) Gnanaprakasam, B.; Zhang, J.; Milstein, D. Direct synthesis of imines from alcohols and amines with liberation of H₂. *Angew. Chem., Int. Ed.* **2010**, *49*, 1468–1471. (c) Maggi, A.; Madsen, R. Dehydrogenative Synthesis of Imines from Alcohols and Amines Catalyzed by a Ruthenium N-Heterocyclic Carbene Complex. *Organometallics* **2012**, *31*, 451–455. (d) Zhang, G.; Hanson, S. K. Cobalt-Catalyzed Acceptorless Alcohol Dehydrogenation: Synthesis of Imines from Alcohols and Amines. *Org. Lett.* **2013**, *15*, 650–653. (e) Saha, B.; Wahidur Rahaman, S. M.; Daw, P.; Sengupta, G.; Bera, J. K. Metal-Ligand Cooperation on a Diruthenium Platform: Selective Imine Formation through Acceptorless Dehydrogenative Coupling of Alcohols with Amines. *Chem. - Eur. J.* **2014**, *20*, 6542–6551. (f) Tamura, M.; Tomishige, K. Redox Properties of CeO₂ at Low Temperature: The Direct Synthesis of Imines from Alcohol and Amine. *Angew. Chem., Int. Ed.* **2015**, *54*, 864–867. (g) Mukherjee, A.; Nerush, A.; Leitun, G.; Shimon, L. J. W.; Ben David, Y.; Espinosa Jalapa, N. A.; Milstein, D. Manganese-Catalyzed Environmentally Benign Dehydrogenative Coupling of Alcohols and Amines to Form Aldimines and H₂: A Catalytic and Mechanistic Study. *J. Am. Chem. Soc.* **2016**, *138*, 4298–4301. (h) Esteruelas, M. A.; Lezaun, V.; Martinez, A.; Olivan, M.; Onate, E. Osmium hydride acetylacetonate complexes and their application in acceptorless dehydrogenative coupling of alcohols and amines and for the dehydrogenation of cyclic amines. *Organometallics* **2017**, *36*, 2996–3004.

(4) (a) Johnson, J. S.; Bergman, R. G. Imidotitanium Complexes as Hydroamination Catalysts: Substantially Enhanced Reactivity from an Unexpected Cyclopentadienide/Amide Ligand Exchange. *J. Am. Chem. Soc.* **2001**, *123*, 2923–2924. (b) Li, Y.; Shi, Y.; Odom, A. L. Titanium Hydrazido and Imido Complexes: Synthesis, Structure, Reactivity, and Relevance to Alkyne Hydroamination. *J. Am. Chem. Soc.* **2004**, *126*, 1794–1803. (c) Ryken, S. A.; Schafer, L. L. N,O-Chelating Four-Membered Metallacyclic Titanium(IV) Complexes for Atom-Economic Catalytic Reactions. *Acc. Chem. Res.* **2015**, *48*, 2576–2586. (d) Mir, R.; Dudding, T. A Au(I)-Precatalyst with a Cyclopropenium Counterion: An Unusual Ion Pair. *J. Org. Chem.* **2016**, *81*, 2675–2679.

(5) Srimani, D.; Feller, M.; Ben-David, Y.; Milstein, D. Catalytic coupling of nitriles with amines to selectively form imines under mild hydrogen pressure. *Chem. Commun.* **2012**, *48*, 11853–11855.

(6) (a) Lee, S.-H.; Nikonov, G. I. Transfer Hydrogenation of Ketones, Nitriles, and Esters Catalyzed by a Half-Sandwich Complex of

Ruthenium. *ChemCatChem* **2015**, *7*, 107–113. (b) Kim, D.; Kang, B.; Hong, S. H. Ruthenium-catalyzed selective imine synthesis from nitriles and secondary alcohols under hydrogen acceptor- and base-free conditions. *Org. Chem. Front.* **2016**, *3*, 475–479.

(7) (a) Zerecero-Silva, P.; Jimenez-Solar, I.; Crestani, M. G.; Arevalo, A.; Barrios-Francisco, R.; Garcia, J. J. Catalytic hydrogenation of aromatic nitriles and dinitriles with nickel compounds. *Appl. Catal., A* **2009**, *363*, 230–234. (b) Chakraborty, S.; Berke, H. Homogeneous Hydrogenation of Nitriles Catalyzed by Molybdenum and Tungsten Amides. *ACS Catal.* **2014**, *4*, 2191–2194. (c) Choi, J.-H.; Precht, M. H. G. Tuneable Hydrogenation of Nitriles into Imines or Amines with a Ruthenium Pincer Complex under Mild Conditions. *ChemCatChem* **2015**, *7*, 1023–1028. (d) Chakraborty, S.; Milstein, D. Selective Hydrogenation of Nitriles to Secondary Imines Catalyzed by an Iron Pincer Complex. *ACS Catal.* **2017**, *7*, 3968–3972.

(8) (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. Organic azides. An exploding diversity of a unique class of compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240. (b) Bräse, S.; Banert, K. *Organic Azides: Syntheses and Applications*; John Wiley & Sons, 2010. (c) Chiba, S. Application of organic azides for the synthesis of nitrogen-containing molecules. *Synlett* **2012**, *2012*, 21–44.

(9) Wroblewski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aube, J. The Schmidt reaction. *Org. React.* **2012**, *78*, 1–320.

(10) Nieto-Garcia, O.; Jaffee, M. B.; Muehlberg, M.; Hackenberger, C. P. R. *The Staudinger Ligation*; Wiley, 2017; pp 97–115.

(11) (a) Hennessy, E. T.; Betley, T. A. Complex N-Heterocycle Synthesis via Iron-Catalyzed, Direct C-H Bond Amination. *Science* **2013**, *340*, 591–595. (b) Shin, K.; Kim, H.; Chang, S. Transition-Metal-Catalyzed C-N Bond Forming Reactions Using Organic Azides as the Nitrogen Source: A Journey for the Mild and Versatile C-H Amination. *Acc. Chem. Res.* **2015**, *48*, 1040–1052.

(12) Singh, M. S.; Chowdhury, S.; Koley, S. Advances of azide-alkyne cycloaddition-click chemistry over the recent decade. *Tetrahedron* **2016**, *72*, 5257–5283.

(13) (a) Eguchi, S. Recent progress in the synthesis of heterocyclic natural products by the Staudinger/intramolecular aza-Wittig reaction. *ARKIVOC* **2005**, *2005*, 98–119. (b) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. The aza-Wittig reaction. An efficient tool for the construction of carbon-nitrogen double bonds. *Tetrahedron* **2007**, *63*, 523–575. (c) Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. Synthetic applications of intramolecular aza-Wittig reaction for the preparation of heterocyclic compounds. *Curr. Org. Chem.* **2009**, *13*, 810–828. (d) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Aza-Wittig Reaction in Natural Product Syntheses*; John Wiley & Sons Ltd., 2017; pp 439–467.

(14) (a) Charette, A. B.; Boezio, A. A.; Janes, M. K. Synthesis of a Triphenylphosphine Reagent on Non-Cross-Linked Polystyrene Support: Application to the Staudinger/Aza-Wittig Reaction. *Org. Lett.* **2000**, *2*, 3777–3779. (b) Mahdavi, H.; Amani, J. Staudinger/aza-Wittig reactions utilizing a novel linear polymer-supported triphenylphosphine as a modified liquid-phase reagent. *Tetrahedron Lett.* **2009**, *50*, 5923–5926.

(15) Biswas, N.; Das, K.; Sardar, B.; Srimani, D. Acceptorless dehydrogenative construction of C = N and C = C bonds through catalytic aza-Wittig and Wittig reactions in the presence of an air-stable ruthenium pincer complex. *Dalton Trans.* **2019**, *48*, 6501–6512.

(16) (a) Ramesha, A. R.; Bhat, S.; Chandrasekaran, S. Reaction of Azides with Tetrathiomolybdate: Reduction and Imine Formation. *J. Org. Chem.* **1995**, *60*, 7682–7683. (b) Martinez-Sarti, L.; Diez-Gonzalez, S. On the Unique Reactivity of Pd(OAc)₂ with Organic Azides: Expedient Synthesis of Nitriles and Imines. *ChemCatChem* **2013**, *5*, 1722–1724.

(17) Sindhuja, E.; Ramesh, R. Direct synthesis of imines from primary alcohols and amines using an active ruthenium(II) NNN-pincer complex. *Tetrahedron Lett.* **2014**, *55*, 5504–5507.

(18) (a) Gunanathan, C.; Milstein, D. Bond Activation and Catalysis by Ruthenium Pincer Complexes. *Chem. Rev.* **2014**, *114*, 12024–12087. (b) Li, H.; Zheng, B.; Huang, K.-W. A new class of PN³-pincer

ligands for metal-ligand cooperative catalysis. *Coord. Chem. Rev.* **2015**, *293–294*, 116–138 and references therein. (c) Gonçalves, T. P.; Huang, K.-W. Metal-Ligand Cooperative Reactivity in the (Pseudo)-Dearomatized PN³(P) Systems: The Influence of the Zwitterionic Form in Dearomatized Pincer Complexes. *J. Am. Chem. Soc.* **2017**, *139*, 13442–13449. (d) Li, H.; Wang, Y.; Lai, Z.; Huang, K.-W. Selective Catalytic Hydrogenation of Arenols by a Well-Defined Complex of Ruthenium and Phosphorus-Nitrogen PN³-Pincer Ligand Containing a Phenanthroline Backbone. *ACS Catal.* **2017**, *7*, 4446–4450. (e) Li, H.; Al-Dakhil, A.; Lupp, D.; Gholap, S. S.; Lai, Z.; Liang, L.-C.; Huang, K.-W. Cobalt-Catalyzed Selective Hydrogenation of Nitriles to Secondary Imines. *Org. Lett.* **2018**, *20*, 6430–6435. (f) Li, H.; Gonçalves, T. P.; Zhao, Q.; Gong, D.; Lai, Z.; Wang, Z.; Zheng, J.; Huang, K.-W. Diverse catalytic reactivity of a dearomatized PN³P*-nickel hydride pincer complex towards CO₂ reduction. *Chem. Commun.* **2018**, *54*, 11395–11398. (g) Li, H.; Gonçalves, T. P.; Hu, J.; Zhao, Q.; Gong, D.; Lai, Z.; Wang, Z.; Zheng, J.; Huang, K.-W. A Pseudodearomatized PN³P*Ni-H Complex as a Ligand and σ -Nucleophilic Catalyst. *J. Org. Chem.* **2018**, *83*, 14969–14977. (h) Li, H.; Gonçalves, T. P.; Lupp, D.; Huang, K.-W. PN³(P)-Pincer Complexes: Cooperative Catalysis and Beyond. *ACS Catal.* **2019**, *9*, 1619–1629. (i) Zhou, C.; Munkerup, K.; Wang, Y.; Das, P. K.; Chakraborty, P.; Hu, J.; Yao, C.; Huang, M.-H.; Huang, K.-W. J. I. C. F. Ligand-centered reactivity of a pseudo-dearomatized phosphorus-nitrogen PN³P* rhodium complex towards molecular oxygen at room temperature. *Inorg. Chem. Front.* **2020**, *7*, 2017–2022.

(19) (a) Milstein, D. Discovery of Environmentally Benign Catalytic Reactions of Alcohols Catalyzed by Pyridine-Based Pincer Ru Complexes, Based on Metal-Ligand Cooperation. *Top. Catal.* **2010**, *53*, 915–923. (b) Das, U. K.; Ben-David, Y.; Diskin-Posner, Y.; Milstein, D. N-Substituted Hydrazones by Manganese-Catalyzed Coupling of Alcohols with Hydrazine: Borrowing Hydrogen and Acceptorless Dehydrogenation in One System. *Angew. Chem., Int. Ed.* **2018**, *57*, 2179–2182. (c) Das, U. K.; Ben-David, Y.; Leitius, G.; Diskin-Posner, Y.; Milstein, D. Dehydrogenative Cross-Coupling of Primary Alcohols To Form Cross-Esters Catalyzed by a Manganese Pincer Complex. *ACS Catal.* **2019**, *9*, 479–484.

(20) (a) Chen, T.; Li, H.; Qu, S.; Zheng, B.; He, L.; Lai, Z.; Wang, Z.-X.; Huang, K.-W. Hydrogenation of Esters Catalyzed by Ruthenium PN³-Pincer Complexes Containing an Aminophosphine Arm. *Organometallics* **2014**, *33*, 4152–4155. (b) Qu, S.; Dang, Y.; Song, C.; Wen, M.; Huang, K.-W.; Wang, Z.-X. Catalytic Mechanisms of Direct Pyrrole Synthesis via Dehydrogenative Coupling Mediated by PNP-Ir or PNN-Ru Pincer Complexes: Crucial Role of Proton-Transfer Shuttles in the PNP-Ir System. *J. Am. Chem. Soc.* **2014**, *136*, 4974–4991.

(21) (a) Liang, L.-C.; Chien, P.-S.; Lee, P.-Y.; Lin, J.-M.; Huang, Y.-L. Terminal nickel(ii) amide, alkoxide, and thiolate complexes containing amido diphosphine ligands of the type [N(o-C₆H₄PR₂)₂]- (R = Ph, iPr, Cy). *Dalton Trans.* **2008**, 3320–3327. (b) Liang, L.-C.; Li, C.-W.; Lee, P.-Y.; Chang, C.-H.; Man Lee, H. A terminal nickel(ii) anilide complex featuring an unsymmetrically substituted amido pincer ligand: synthesis and reactivity. *Dalton Trans.* **2011**, *40*, 9004–9011.