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Authors: Qi-Lin Zhou, Li-Jun Xiao, Chao-Yue Zhao, Lei Cheng, Bo-Ya Feng, Wei-Min Feng, Jian-Hua Xie, and Xiu-Fang Xu

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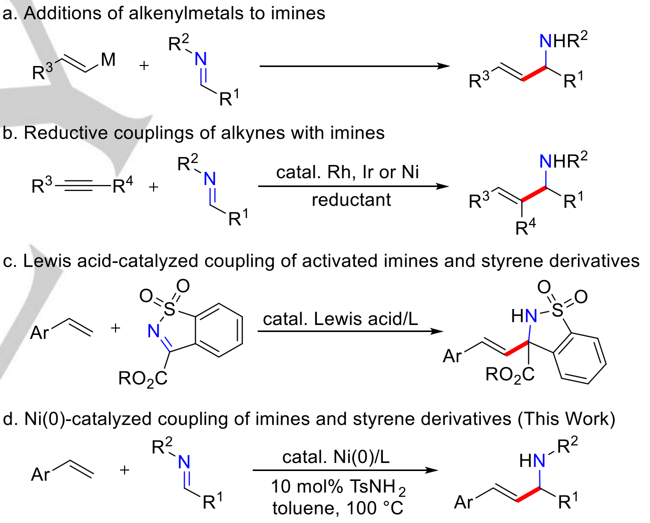
Nickel(0)-Catalyzed Hydroalkenylation of Imines with Styrene and Derivatives

Li-Jun Xiao,[a] Chao-Yue Zhao,[b] Lei Cheng,[a] Bo-Ya Feng,[b] Wei-Min Feng,[a] Jian-Hua Xie,[a] Xiu-Fang Xu,*[b] and Qi-Lin Zhou*[a,c]

Abstract: We have developed a Ni(0)-catalyzed hydroalkenylation of imines with styrene and derivatives. A wide range of aromatic and aliphatic imines directly coupled with styrene and derivatives, providing various synthetically useful allylic amines with up to 95% yield. The reaction offers a new atom- and step-economical approach to allylic amines by using abundant alkenes instead of alkenyl-metallic reagents. Experiments and DFT calculations showed that the $TsNH_2$ promotes the proton transfer from the coordinated olefin to imine, accompanied by a new C–C bond formation.

Allylic amine moieties not only widely exist in a large number of important naturally occurring nitrogen-containing compounds, agrochemicals and pharmaceutical but also act as a versatile building block in organic synthesis.[1] In this context, the development of general and efficient methods for the synthesis of allylic amines has been a topic of considerable interest.[2] Among various potential methods, direct C–C coupling of imines and π-compounds represents one of the most attractive pathways because it allows two smaller carbon skeletons to be joined together, meaning that more abundant and inexpensive starting materials could be used.[3] Traditional strategy for such couplings mainly relies on nucleophilic additions of alkenylmetals to imines (Scheme 1a), in which alkenylmetals are generally in situ prepared from alkenyl halides[4] or alkynes[5] with organometallic reagents. To avoid the use of sensitive alkenylmetals, some alternative methods are developed. One is reductive coupling[6] or alkylative coupling[7] of alkynes with imines in the presence of various reductants or alkylmetallic reagents (Scheme 1b). Another is the coupling of activated alkenes with imines such as in the Morita–Baylis–Hillman reaction[8] and C–H addition reaction[9]. Despite these progresses, the coupling of abundantly available alkenes such as styrene and α-olefins with imines remains a challenge.[10] Recently, Jia and co-workers developed a Lewis acid-catalyzed direct coupling of styrene and derivatives with highly-activated imines bearing two electron-deficient groups,[11] providing allylic amines in atom-economical fashion (Scheme 1c). However, the common aldimines are inert in the reaction. Herein we report a nickel-catalyzed direct coupling of aldimines with styrene and derivatives, producing allylic amines (Scheme 1d). The presence of catalytic amount of $TsNH_2$ proved to be critical for the reaction efficiency. The experiments and density functional theory (DFT) calculations showed that the $TsNH_2$ acts as a Brønsted acid to aid the ring opening of nickellacycle and facilitates the coupling reaction.



Scheme 1. The synthesis of allylic amines by C–C couplings of imines with π-compounds

The Ni(0)-catalyzed coupling reaction of π-components and carbonyls or imines is one of the most efficient protocols for their join via C–C bond formation.[12] Jamison and co-workers pioneered in achieving a Ni(0)-catalyzed coupling of aromatic aldehydes with α-olefins in the presence of Et_3SiOTf and Et_3N, providing allylic alcohol silyl ethers.[13] We recently developed a Ni(0)-catalyzed hydroacylation of alkenes with aldehydes, delivering ketones.[14] When the aldehyde was switched into an imine, surprisingly, we obtained a small amount of allylic amine, instead of ketimine as expected. Encouraged by this result, we decided to investigate the reaction of imines with alkenes in detail.

We found that the Ni(0) complexes with monophosphine ligands catalyzed the hydroalkenylation of imine **2a** with styrene (**1a**) (Table 1, entries 1–6) and that PCy_3 was the best ligand, providing allylic amine **3a** in 56% yield (entry 4). The use of diphosphine ligands such as 1,2-bis(diphenylphosphaneyl)-

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[a] L.-J. Xiao, L. Cheng, W.-M. Feng, Prof. J.-H. Xie, Prof. Q.-L. Zhou
State Key Laboratory and Institute of Elemento-organic Chemistry
College of Chemistry, Nankai University
Tianjin 300071, China
E-mail: qlzhou@nankai.edu.cn
Homepage: http://zhou.nankai.edu.cn
[b] C.-Y. Zhao, B.-Y. Feng, Prof. X.-F. Xu
Department of Chemistry, Key Laboratory of Advanced Energy Materials Chemistry (Ministry of Education)
College of Chemistry, Nankai University
Tianjin 300071, China
E-mail: xxfang@nankai.edu.cn
[c] Prof. Q.-L. Zhou
Collaborative Innovation Center of Chemical Science and Engineering (Tianjin)
Tianjin 300071, China

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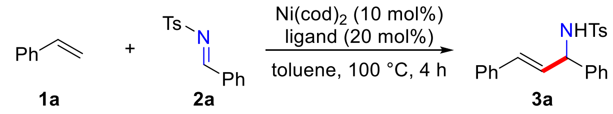
ethane (dppe), 1,3-bis(diphenylphos-phaneyl)propane (dppp) gave no reaction. To improve the yield of the hydroalkenylation product, various additives were evaluated. In the presence of a Brønsted acid, such as H_2O, PhOH, the yield of allylic amine **3a** was slightly increased (entries 7–11). Surprisingly, the $TsNH_2$ dramatically promoted the reaction. When 10 mol % $TsNH_2$ was added, the yield of **3a** increased to 97% (entry 11).

Table 1. Optimization of reaction conditions[a]



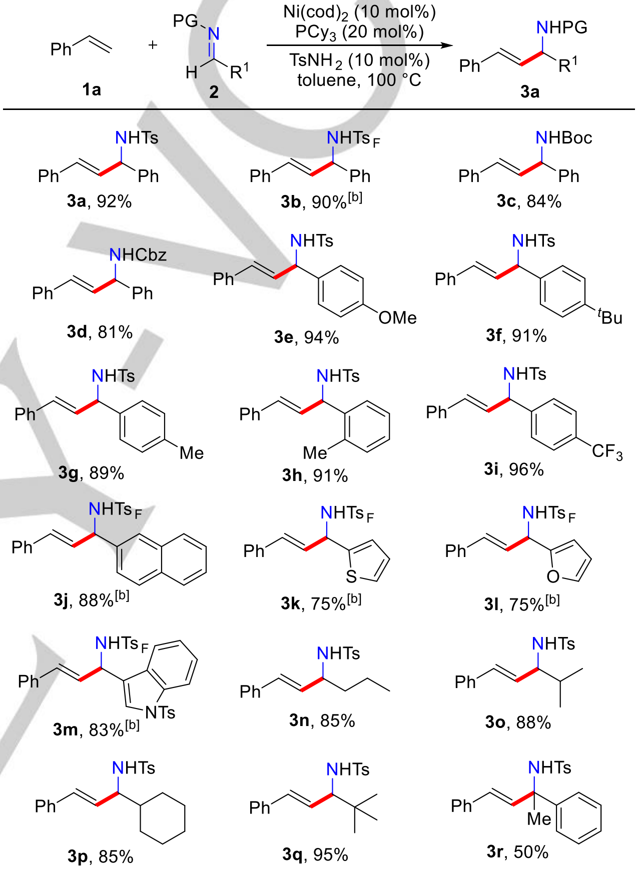
entry	ligand	additive (mol%)	yield (%)[b]
1	PPh_3	–	12
2	PPh_2Cy	–	16
3	$PPhCy_2$	–	35
4	PCy_3	–	56
5	P^nBu_3	–	8
6	P^tBu_3	–	5
7	PCy_3	$TfNH_2$ (10)	33
8	PCy_3	H_2O (10)	62
9	PCy_3	PhOH (10)	60
10	PCy_3	$PhCO_2H$ (10)	51
11	PCy_3	$TsNH_2$ (10)	**97 (92)**
12	PCy_3	$TsNH_2$ (5)	84
13	PCy_3	$TsNH_2$ (20)	74

[a] Reaction condition: **1a** (1.0 mmol), **2a** (0.5 mmol), toluene (1 mL). [b] Determined by ^1H NMR analysis using an internal standard.

Using the above-described optimal reaction conditions, we evaluated a wide variety of aldimines **2** in the reaction with styrene (Table 2). The protecting group on the imine N atom proved to be necessary, and various frequently used protecting groups were suitable, providing 81–92% yield (**3a**–**3d**). Aromatic aldimines derived either from aromatic aldehydes bearing substituents with various electronic and steric property (**3e**–**3j**), or from heteroaromatic aldehydes (**3k**–**3m**), are suitable substrates, affording the products in good to high yields (75%–96%). In addition, we successfully carried out the reaction of aliphatic aldimines, which are challenging substrates under traditional addition reaction conditions owing to competing side-reactions such as imine–enamine tautomerization, decomposition and self-condensation. All the tested aliphatic aldimines bearing different steric alkyl group gave the desired products in high yield (**3n**–**3q**, 85–95%). It was delighted to find that the ketimine, which often displays extremely low reactivity in coupling reaction, can also react with styrene, affording the allylic amine **3r** with a tertiary carbon in 50% yield.

Next, we investigated various alkenes **1** in the reaction with benzaldimine **2a** (Table 3). Aryl alkenes bearing substituents with various steric and electronic property provided corresponding products **4a**–**4j** in high yields (80–95%). In addition, the heteroaryl alkenes reacted with **2a** smoothly to give desired products **4k**–**4n** in 80–85% yield. It is worth noting that vinylsilanes were also suitable substrates, affording useful silane-terminated allylic amines **4o** and **4p** in moderate yields. However, the reactions of aliphatic alkenes with aldimines produced a mixture of allylic and homoallylic amines, and sometimes the homoallyic amine became the main product (**4q**–**4t**).[15]

Table 2. Nickel-catalyzed hydroalkenylation of imines **2** with styrene[a]

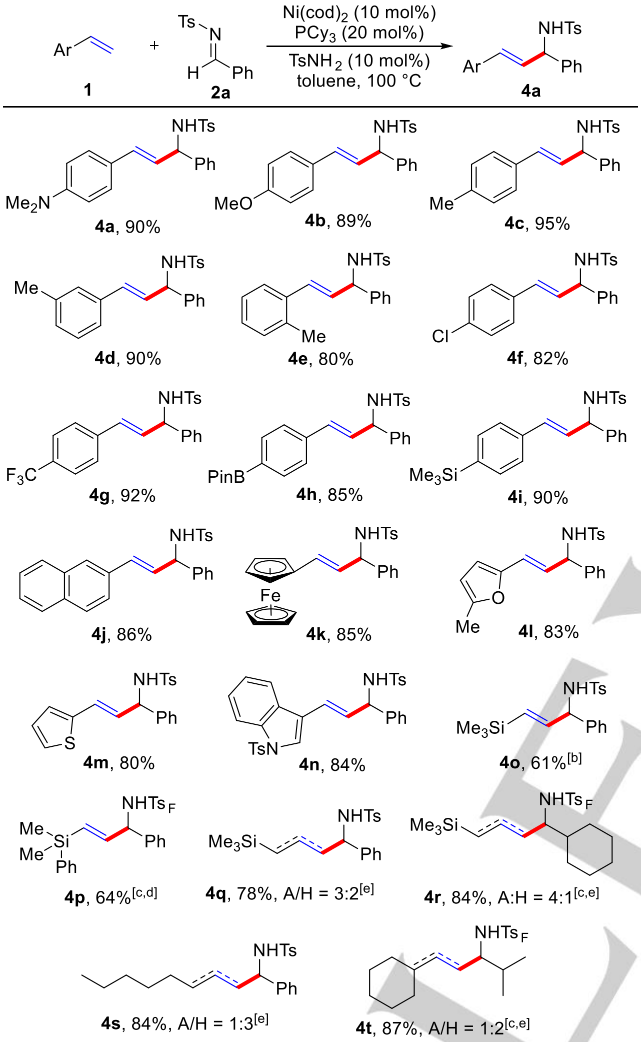


[a] Isolated yield, Ts_F = 4-$CF_3C_6H_4SO_2$. [b] 4-$CF_3C_6H_4SO_2NH_2$ (10 mol%) was added.

To gain mechanistic insight into the hydroalkenylation reaction, we carried out control experiments. When 10 mol % $NiBr_2$(dme) and 20 mol % PCy_3 were used as catalyst, no reaction occurred under standard reaction conditions. However, when Zn (40 mol %) was added as a reductant, the hydroalkenylation reaction proceeded in high yield (92%) (Scheme 2a). This result indicated that the reaction was catalyzed by Ni(0) instead of Ni(II). We found that the yield of hydroalkenylation reaction in the absence of $TsNH_2$ can be increased from 56% (Table 1, entry 4) to 96% by prolonging reaction time to 24 h. We speculated that a trace amount of $TsNH_2$ was produced by hydrolysis of imine **2a** in the reaction, which promotes the reaction. To confirm that, we conducted the hydroalkenylation reaction with cyclic ketimine **2s** (Scheme 2b), which is stable and difficult to produce $TsNH_2$ by hydrolysis. Without adding $TsNH_2$, only trace amount of hydroalkenylation product was observed even in the presence of

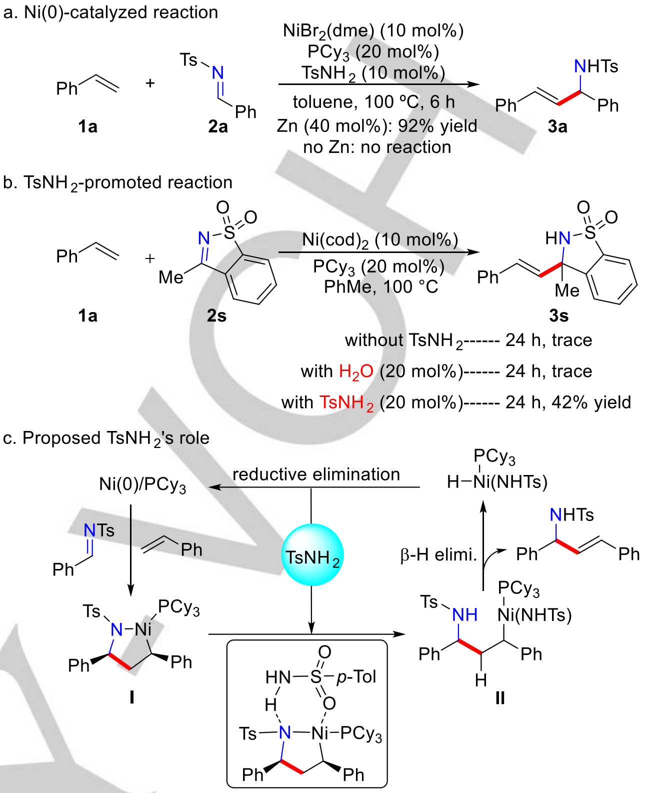
H_2O. However, by adding 10 mol% $TsNH_2$, the hydroalkenylation product was obtained in 42% yield. These results suggested that the presence of catalytic amount of $TsNH_2$ is critical for the reaction.

Table 3. Nickel-catalyzed hydroalkenylation of imine **2a** with alkenes*ᵃ*



[a] Isolated yield, Ts_F = 4-$CF_3C_6H_4SO_2$. [b] 10.0 equiv. of **1o** (neat). [c] 4-$CF_3C_6H_4SO_2NH_2$ (10 mol%) was added. [d] 5.0 equiv. of alkene **1**. [e] Yield of mixture of two isomers; A/H = ratio of allylic amine to homoallylic amine; The *E*/*Z*-selectivity was determined by coupling constant of the olefinic hydrogens in NMR spectra,[16] and only *E* isomer was observed.

A plausible reaction path is proposed in Scheme 2c based on the aforementioned experimental results and previous reports[17]. Oxidative cyclization of imine and alkene resulted in the formation of a five-membered azanickellacycle intermediate **I**. The Brønsted acid $TsNH_2$ promoted the ring-opening of azanickellacycle to the intermediate **II** through protonation to the N atom and coordination to the Ni atom in the azanickellacycle. Subsequent β-hydride elimination of the intermediate **II** would be feasible to release an allylic amine product and regenerate the nickel catalyst and $TsNH_2$.



Scheme 2. Control experiments and proposed $TsNH_2$'s role

To understand the reaction mechanism, DFT study was performed using the reaction of imine **2a** with styrene.[18] As shown in Figure 1, the substrate-coordinated complex **A1** undergoes oxidative cyclization to form the azanickellacycle intermediate **B1** through transition state **TS1**. Then, the reaction can proceed along three distinct pathways: direct β-hydride elimination of **B1** via transition state **TS6** (in red); H_2O promoting the ring-opening of **B1** via transition state **TS4** (in blue); and $TsNH_2$ promoting the ring-opening of **B1** via transition state **TS2** (in black). **TS2** is more stable than **TS4** and **TS6** by lowering the overall barrier of the catalytic cycle to 30.9 kcal/mol, which means that the rate-limiting step is the oxidative cyclization. The KIE study (k_H/k_D = 1.1, see SI for details) also showed that the hydrogen transfer process is not involved in rate-limiting step.

In summary, we have developed a protocol for direct hydroalkenylation of imines with alkenes catalyzed by a Ni(0)/PCy_3 complex. This protocol offers a straightforward method for the synthesis of allylic amines. The alkenes function like the alkenylmetal reagents that are used in conventional methods for the synthesis of allylic amines. The experimental and computational studies showed that the $TsNH_2$ promotes ring-opening of azanickellacycle intermediate and facilitates the proton transfer from olefin to imine. Further investigations on the asymmetric version of the reaction and its applications in organic synthesis is in progress in our laboratory.

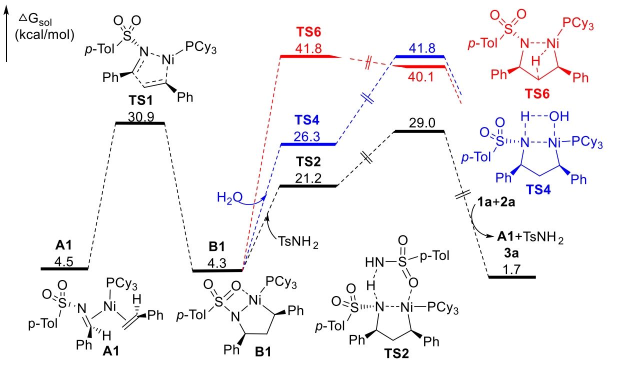


Figure 1. DFT-computed Gibbs free energy changes of the [Ni(PCy$_3$)]-catalyzed hydroalkenyaltion of imine **2a** with styrene.

Experimental Section

In an argon-filled glove-box, an oven-dried sealed tube was charged with a stir bar, Ni(cod)$_2$ (14 mg, 0.05 mmol), PCy$_3$ (28 mg, 0.1 mmol), TsNH$_2$ (0.05 mmol), alkene **1**, (1.0 mmol) aldimine **2** (0.50 mmol) and toluene (1.0 mL). The tube was then sealed with a Teflon-lined screw cap, removed from the glove box, stirred at room temperature for 5 min and then 100 °C for 4 h. After being cooled to room temperature, the mixture was added aqueous HCl (1 N, 0.1 mL) and ethyl acetate, and filtered over a short plug of silica gel (ethyl acetate eluent). The filtrate was concentrated in *vacuo* and the residue was purified by column chromatography on silica gel (PE/EA = 8:1, v/v) to afford the corresponding product.

Acknowledgements

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Keywords: Nickel Catalyst • hydroalkenylation • Imine• Alkene • Allylic Amine

[1] a) G. Petranyi, N. S. Ryder, A. Stűtz, *Science* **1984**, *224*, 1239. b) R. C. Schnur, M. L. Corman, *J. Org. Chem.* **1994**, *59*, 2581. c) M. B. Haidoune, I. Raynaud, N. O'Connor, P. Richomme, R. Mornet, M. Laloue, *J. Agric. Food Chem.* **1998**, *46*, 1577. d) T. Hartmann, C. Theuring, T. Beuerle, L. Ernst, M. S. Singer, E. A. Bernays, *J. Chem. Ecol.* **2004**, *30*, 229. e) E. M. Skoda, G. C. Davis, P. Wipf, *Org. Process Res. Dev.* **2012**, *16*, 26.

[2] M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 1689.

[3] For reviews and examples of hydroalkenylation reactions from two alkenes, see: a) G. Hilt, *Eur. J. Org. Chem.* **2012**, *2012*, 4441. b) T. V. RajanBabu, G. A. Cox, H. J. Lim, N. Nomura; R. K. Sharma; C. R. Smith and A. Zhang, Hydrovinylation Reactions in Organic Synthesis, in *Comprehensive Organic Synthesis*, ed. G. A. Molander and P. Knochel, Elsevier, Oxford, 2nd edn, 2014, Vol. 5, pp. 1582–1620. c) G. Hilt, F.-X. du Mesnil, S. Lüers, *Angew. Chem.* **2001**, *118*, 408; *Angew. Chem. Int. Ed.* **2001**, *40*, 387. d) W.-J. Shi, J.-H. Xie, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2005**, *16*, 705. e) W.-J. Shi, Q. Zhang, J.-H. Xie, S.-F. Zhu, G.-H. Hou, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 2780. f) A. Zhang, T. V. RajanBabu, *J. Am. Chem. Soc.* **2006**, *128*, 5620. g) C.-Y. Ho, L. He, *Angew. Chem.* **2010**, *122*, 9368; *Angew. Chem. Int. Ed.* **2010**, *49*, 9182. h) M. M. P. Grutters, C. Müller, D. Vogt, J. Am. Chem. Soc. 2006, 128, 7414. i) C.-Y. Ho, C.-W. Chan, L. He, *Angew. Chem.* **2015**, *127*, 4595; *Angew. Chem. Int. Ed.* **2015**, *54*, 4512.

[4] a) R. Almansa, D. Guijarro, M. Yus, *Tetrahedron: Asymmetry* **2008**, *19*, 603. b) S. Lou, S. E. Schaus, *J. Am. Chem. Soc.* **2008**, *130*, 6922. c) K. Brak, J. A. Ellman, *J. Am. Chem. Soc.* **2009**, *131*, 3850. d) Y. Luo, A. J. Carnell, H. W. Lam, *Angew. Chem.* **2012**, *124*, 6866; *Angew. Chem. Int. Ed.* **2012**, *51*, 6762. e) B. Gopula, C.-W. Chiang, W.-Z. Lee, T.-S. Kuo, P.-Y. Wu, J. P. Henschke, H.-L. Wu, *Org. Lett.* **2014**, *16*, 632. f) Z. Cui, Y.-J. Chen, W.-Y. Gao, C.-G. Feng, G.-Q. Lin, *Org. Lett.* **2014**, *16*, 1016.

[5] a) S. L. Buchwald, B. T. Watson, M. W. Wannamaker, J. C. Dewan, *J. Am. Chem. Soc.* **1989**, *111*, 4486. b) R. B. Grossman, W. M. Davis, S. L. Buchwald, *J. Am. Chem. Soc.* **1991**, *113*, 2321. c) P. Wipf, C. Kendall, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2003**, *125*, 761.

[6] a) J.-R. Kong, C.-W. Cho, M. J. Krische, *J. Am. Chem. Soc.* **2005**, *127*, 11269. b) E. Skucas, J. R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 7242. c) A. Barchuk, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 8432. d) M.-Y. Ngai, A. Barchuk, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 12644. e) C.-Y. Zhou, S.-F. Zhu, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 10955.

[7] a) S. J. Patel, T. F. Jamison, *Angew. Chem.* **2003**, *115*, 1402; *Angew. Chem. Int. Ed.* **2003**, *42*, 1364. b) S. J. Patel, T. F. Jamison, *Angew. Chem.* **2004**, *116*, 4031; *Angew. Chem. Int. Ed.* **2004**, *43*, 3941.

[8] a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811. b) G. Masson, C. Housseman, J. Zhu, *Angew. Chem.* **2007**, *119*, 4698; *Angew. Chem. Int. Ed.* **2007**, *46*, 4614. c) Y. Wei, M. Shi, *Chem. Rev.* **2013**, *113*, 6659.

[9] Li, Y.; Zhang, X.-S.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4498.

[10] For Pd-catalyzed vinylation of aminals, see: Y. Xie, J. Hu, Y. Wang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 20613.

[11] a) R.-R. Liu, D.-J. Wang, L. Wu, B. Xiang, G.-Q. Zhang, J.-R. Gao, Y.-X. Jia, *ACS Catal.* **2015**, *5*, 6524. b) B. Xiang, T.-F. Xu, L. Wu, R.-R. Liu, J.-R. Gao, Y.-X. Jia, *J. Org. Chem.* **2016**, *81*, 3929.

[12] a) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890. b) J. Montgomery, G. J. Sormunen, *Top. Curr. Chem.* **2007**, *279*, 1. c) C.-Y. Ho, K. D. Schleicher, C.-W. Chan, T. F. Jamison, *Synlett* **2009**, 2565. d) Z. Zeng, D. Yang, *Chin. J. Org. Chem.* **2013**, 33, 2131. e) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299. f) E. A. Standley, S. Z. Tasker, K. L. Jensen, T. F. Jamison, *Acc. Chem. Res.* **2015**, *48*, 1503. g) Y. Hoshimoto, M. Ohashi, S. Ogoshi, *Acc. Chem. Res.* **2015**, *48*, 1746.

[13] a) S.-S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 14194. b) S.-S. Ng, C.-Y. Ho, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 11513. c) C.-Y. Ho, T. F. Jamison, *Angew. Chem.* **2007**, *119*, 796; *Angew. Chem. Int. Ed.* **2007**, *46*, 782.

[14] L.-J. Xiao, X.-N. Fu, M.-J. Zhou, J.-H. Xie, L.-X. Wang, X.-F. Xu, Q.-L. Zhou, *J. Am. Chem. Soc.* **2016**, *138*, 2957.

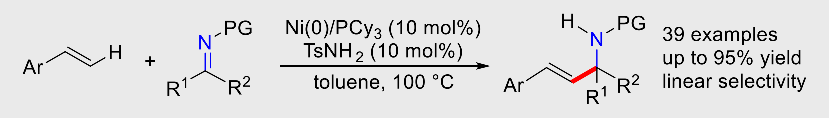
[15] Isomerization of homoallylic amines to allylic amines was observed under the standard reaction conditions (see SI, Scheme S6).

[16] a) M. Karplus, *J. Chem. Phys.* **1959**, *30*, 11. b) R. M. Silverstein, F. X. Webster, D.J. Kiemle, *Spectrometric Identification of Organic Compounds*, 7th ed.; John Wiley & Sons: New York, 2005; pp 171–172.

[17] For examples of Ni-catalyzed multi-component coupling reactions via nickellacycles, see: a) H. Hoberg, E. Hernandez, *J. Chem. Soc., Chem. Commun.* **1986**, 544. b) S. Ogoshi, M.-a. Oka, H. Kurosawa, *J. Am. Chem. Soc*. **2004**, *126*, 11802. c) S. Ogoshi, M. Ueta, T. Arai, H. Kurosawa, *J. Am. Chem. Soc.* **2005**, *127*, 12810. d) S. Ogoshi, T. Haba, M. Ohashi, *J. Am. Chem. Soc*. **2009**, *131*, 10350. e) Y. Hoshimoto, T. Ohata, Y. Sasaoka, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2014**, *136*, 15877. For examples of Brønsted acid to aid the ring opening of nickellacycle, see: f) C.-H. Yeh, R. P. Korivi, C.-H. Cheng, *Angew. Chem.* **2008**, *120*, 4970; *Angew. Chem., Int. Ed.* **2008**, *47*, 4892. g) A. D. Jenkins, A. Herath, M. Song, J. Montgomery, *J. Am. Chem. Soc.* **2011**, *133*, 14460. h) K. Nakai, Y. Yoshida, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2014**, *136*, 7797.

[18] For DFT studies of nickel-catalyzed reactions, see: a) T. Sperger, I. A. Sanhueza, I. Kalvet, F. Schoenebeck, *Chem. Rev.* **2015**, *115*, 9532. b) E. P. Jackson, H. A. Malik, G. J. Sormunen, R. D. Baxter, P. Liu, H. Wang, A.-R. Shareef, J. Montgomery, *Acc. Chem. Res.* **2015**, *48*, 1736. c) All reported free energies are in kcal/mol and calculated using M06/SDD-6-311+G(d,p)/SMD(toluene)//B3LYP/SDD-6-31G(d) at 373.15 K. d) M. J. Frisch, et al. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2013. e) Computational details are in the Supporting Information.

COMMUNICATION



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