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Nickel-catalyzed alkene *ipso*-selective reductive hydroamination with nitroarenes

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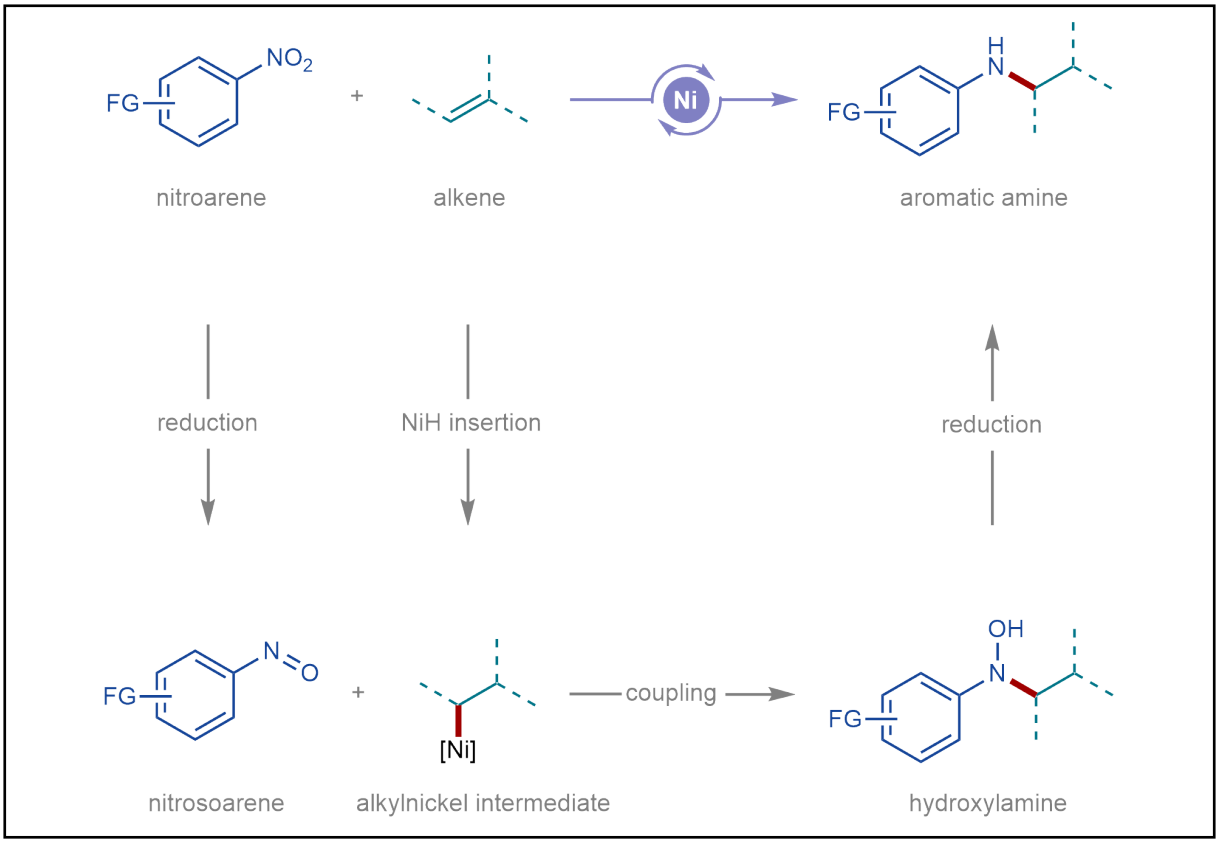
Graphical abstract



Aromatic amines with primary and secondary alkyl groups could be accessed through nickel-catalyzed ipso-selective alkene hydroamination with nitroarenes.

Public summary

- A nickel-catalyzed *ipso*-selective alkene hydroamination with nitroarenes under mild reductive conditions was developed.
- Repaid preparation of aromatic amines with primary and secondary alkyl groups and compatibility with many functional groups were demonstrated.
- Based on the literature and mechanistic investigation, a plausible reaction mechanism involving in situ generation of alkylnickel intermediates and reaction with in situ generated nitrosoarenes was proposed.

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SI Supporting Information

Abstract: Aromatic amine synthesis via reductive coupling between alkenes and nitroarenes is attractive; however, it remains underdeveloped. Herein, we report a nickel-catalyzed alkene hydroamination with nitroarenes under mild reductive conditions. This reaction exhibited an *ipso*-selectivity and enabled repaid preparation of aromatic amines with primary and secondary alkyl groups. Many functional groups were well tolerated, providing an efficient approach for drug-like arylamine synthesis.

Keywords: nickel; alkene; nitroarene; reductive hydroamination; C-N coupling

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1 Introduction

Aromatic amines are necessary organic chemicals in many fields, such as the chemical industry, materials, medicines, and agricultural and veterinary medicines[1]. For example, the small-molecule pharmaceuticals palbociclib, apixaban, elexacaftor, and tofacitinib were among the top 200 drugs by retail sales in 2021 (Fig. 1a). Classical methods for synthesizing aryl or heteroaryl amines include amine-carbonyl reductive amination[2], nucleophilic substitutions of amines with alkyl halides[3–5], Buchwald–Hartwig C-N coupling reactions[6–8], and Ullmann-Ma-type amination reactions[9–14] (Fig. 1b). The methods mentioned above for synthesizing aromatic amines via C–N bond formation require primary aromatic amines as starting materials. However, primary aromatic amines are usually prepared by nitroarene derivative hydrogenation reduction[15,16]. Therefore, the direct synthesis of aromatic amines using large industrial nitroarenes shortens the synthesis steps and improves the synthetic efficiency[16–20]. On the other hand, the stable features and extensive sources of alkenes[21–28] have promoted alkene hydroamination as an attractive alternative for amine synthesis[29–35]. In 2015, Baran et al.[36] reported a practical arylamine synthesis via alkene hydroamination with nitroarenes, which combines iron-promoted hydrogen atom transfer, radical addition, and zinc reduction. In 2016, Hu et al.[15] realized an elegant single-step (hetero)aryl amine synthesis via iron-catalyzed reductive coupling between alkyl halides and nitroarenes. In 2018, Zhu et al.[37] developed an efficient benzylic arylamine synthesis via sequential nickel-catalyzed chain-walking and hydroamination processes. In 2021, Wang and Zhu et al.[38] extended this efficient alkene hydroamination reaction to an asymmetric version. Very recently, Wang and Zhu et al.[39] developed a useful method to access α-aminoboronates via hydroamidation of alkenyl boronates. Despite these achievements in synthesizing aromatic amines with tertiary or benzylic alkyl groups (Fig. 1c), general methods for synthesizing aromatic amines with primary and secondary alkyl groups from nitroarenes with alkenes remain underdeveloped.

Our group systematically researched base-metal-catalyzed alkene functionalization reactions, catalytic mechanistic studies and applications in functional organic molecule synthesis[40–44]. Based on our research interests in alkene hydroalkylation reactions (Fig. 1d) [45–51], we envisioned that nickel-promoted reductive hydroamination of alkenes and nitroarenes might be suitable for achieving our amine synthesis goal. Herein, we report a nickel-catalyzed alkene *ipso*-selective reductive hydroamination with nitroarenes to access aromatic amines with primary and secondary alkyl groups (Fig. 1e).

2 Materials and methods

2.1 Materials

The following chemicals were purchased and used as received: nickel(II) bromide 2-methoxyethyl ether complex (CAS: 312696-09-6, Aldrich, 459674-5G); triethoxysilane (CAS: 998-30-1, TCI, T1040); diethoxymethylsilane (CAS: 27176-10-9, Adamas, 35415E); tetrahydrofuran (CAS: 109-99-9, Energy Chemical, W3100755000); 1,4-dioxane (CAS: 123-91-1, Adamas, 01375906); methanol (CAS: 67-56-1, Sinopharm, 10014118); *N*,*N*-dimethylacetamide (CAS: 127-19-5, Adamas, 011342855); potassium fluoride (CAS: 7789-23-3, Acros, 01163384); and sodium carbonate anhydrous (CAS: 497-19-8, Sinopharm, 10019260).

2.2 Analytical methods

^{1}H NMR, ^{13}C NMR, ^{11}B NMR and ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer and a Bruker 500 MHz spectrometer at 295 K in $CDCl_3$ unless otherwise noted.

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JUSTC, **2022**, 52(12): 1

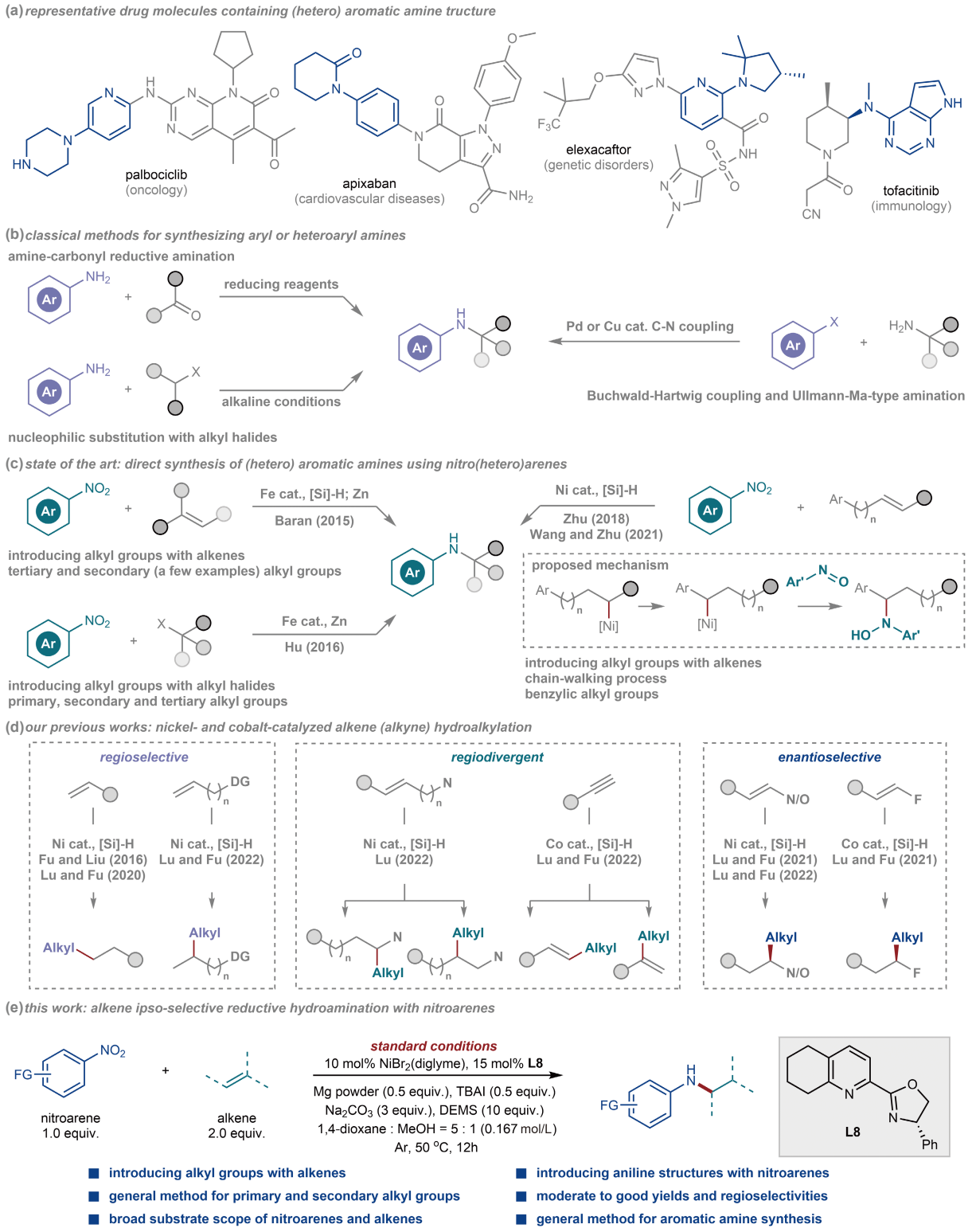

Fig. 1. State-of-the-art aromatic amine synthesis and our strategy. DG = directing group; FG = functional group; DEMS = diethoxymethylsilane; diglyme = 2-methoxyethyl ether; TBAI = tetrabutylammonium iodide.

Data for ^{1}H NMR were reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR were reported as follows: chemical shift (δ ppm), multiplicity, and coupling constant (Hz). Data for ^{11}B NMR were reported as follows: chemical shift (δ ppm), multiplicity, and coupling constant (Hz). Data for ^{19}F NMR were reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz). Chemical shifts were reported using the residual solvent $CHCl_3$ as the internal reference for ^{1}H NMR (δ = 7.260 ppm) and the $CDCl_3$ peak as the internal reference for ^{13}C NMR (δ = 77.160 ppm). High-resolution mass spectral analysis (HRMS) data were acquired on a Water

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XEVO G2 Q-TOF (Waters Corporation). Gas chromatographic (GC) analysis was acquired on a Shimadzu GC-2010 plus Series GC system equipped with a flame-ionization detector. Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Column chromatographic purification of the products was accomplished using forced-flow chromatography on silica gel (300–400 mesh).

2.3 General procedure

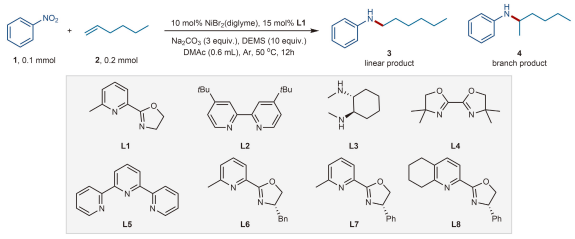
In air, a 10 mL screw-cap test tube equipped with a magnetic stirrer was charged with **L8** (0.03 mmol, 15 mol%), $NiBr_2$(diglyme) (0.02 mmol, 10 mol%), Na_2CO_3 (0.6 mmol, 3.0 equiv.), TBAI (0.1 mmol, 0.5 equiv.), and Mg powder (0.1 mmol, 0.5 equiv.) (if the nitroarene or the alkene was solid, they were added at this step). The test tube was evacuated and backfilled with argon three times. Then, solvent (1,4-dioxane ∶ MeOH = 5 ∶ 1, 1.20 mL) was added, followed by alkene (0.4 mmol, 2.0 equiv.) and nitroarene (0.2 mmol, 1.0 equiv.). Then, DEMS (2.0 mmol, 10.0 equiv.) was added dropwise via a syringe, and the solution was stirred for 5 min at 25 °C, followed by stirring at 50 °C for 12 h. The reaction mixture was diluted with H_2O followed by extraction with EtOAc, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to obtain the target product. The yield represents the isolated yield of the major product. The reaction regioselectivity was determined by GC analysis of the reaction mixture. In a few cases, the reaction regioselectivity could not be determined by GC analysis; ^{1}H NMR determined regioisomeric ratios after chromatography purification.

3 Results and discussion

3.1 Screening of reaction conditions

As shown in Table 1, we began this study with the synthesis of *N*-hexylaniline (**3**) from nitrobenzene (**1**) and hex-1-ene (**2**) using the hydroalkylation reaction conditions reported in our early works[45]. With a merely increased amount of silane (entry 1), we obtained a mixture of linear product **3** and branched product **4** in a 39% GC (gas chromatography) yield and a 3.4 ∶ 1.0 regioselectivity (*l* ∶ *b*, linear ∶ branched). Then, we screened the influence of all reaction parameters, such as nickel catalysts, ligands, silanes as hydride sources, bases, additives, and solvents. Other nitrogen- or phosphine-containing ligands were examined: bipyridine (**L2**, entry 2), bioxazoline (**L4**, entry 4), and terpyridine (**L5**, entry 5) yielded only trace amounts of cross-coupling products; the ethylenediamine-structured ligand (**L3**, entry 3) provided a better 5.0 ∶ 1.0 regioselectivity with a decreased total yield; and the phosphine ligand 1,2-bis(diphenylphosphino)ethane (dppe, entry 6) could be used with a decreased 29% GC yield and 1.9 ∶ 1.0 regioselectivity. In solvent screening (entries 7–11), a low polarity solvent (entry 8) led to improved coupling efficiency; a 1,4-dioxane/MeOH mixed solvent further improved the yield (entry 11). The selection of $NiBr_2$(diglyme), Na_2CO_3, and diethoxymethylsilane (DEMS) was critical to this reaction: other nickel catalysts, bases, and silanes were much less effective (entries 12–18). Next, we tried to add additives to the reaction: the addition of tetrabutylammonium iodide (TBAI, entries 19 and 20) could significantly improve the coupling efficiency; additional zinc (entry 21) or magnesium

Table 1. Optimization of reaction conditions.



entry	variation from standard conditions	yield/%[a]	3 ∶ 4 (*l* ∶ *b*)[b]
1	none	39	3.4 ∶ 1.0
2	**L2** instead of **L1**	<2	—
3	**L3** instead of **L1**	12	5.0 ∶ 1.0
4	**L4** instead of **L1**	<2	—
5	**L5** instead of **L1**	<2	—
6	dppe instead of **L1**	29	1.9 ∶ 1.0
7	CH_3CN instead of DMAc	24	1.4 ∶ 1.0
8	toluene instead of DMAc	50	2.8 ∶ 1.0
9	THF instead of DMAc	25	2.5 ∶ 1.0
10	1,4-dioxane instead of DMAc	45	3.6 ∶ 1.0
11	1,4-dioxane ∶ MeOH = 5 ∶ 1 instead of DMAc	57	3.4 ∶ 1.0
12	NiI_2 instead of $NiBr_2$(diglyme)	49[c]	2.5 ∶ 1.0
13	$Ni(acac)_2$ instead of $NiBr_2$(diglyme)	8[c]	1.0 ∶ 1.0
14	$Ni(cod)_2$ instead of $NiBr_2$(diglyme)	18[c]	1.0 ∶ 3.5
15	KF instead of Na_2CO_3	38[c]	1.9 ∶ 1.0
16	NaOH instead of Na_2CO_3	<2[c]	—
17	PMHS instead of DEMS	35[c]	2.8 ∶ 1.0
18	$(MeO)_3SiH$ instead of DEMS	29[c]	2.9 ∶ 1.0
19	1.0 equiv. TBAI added	66[c]	1.9 ∶ 1.0
20	0.5 equiv. TBAI added	66[c]	2.3 ∶ 1.0
21	0.5 equiv. TBAI and 0.5 equiv. Zn powder added	68[c]	4.2 ∶ 1.0
22	0.5 equiv. TBAI and 0.5 equiv. Mg powder added	78[c]	4.6 ∶ 1.0
23	**L6** instead of **L1**	38[d]	6.7 ∶ 1.0
24	**L7** instead of **L1**	56[d]	12 ∶ 1.0
25	**L8** instead of **L1**	85 (70)[d,e]	6.3 ∶ 1.0
26	5.0 equiv. DEMS used	42	6.9 ∶ 1.0
27	3.0 equiv. DEMS used	10	6.4 ∶ 1.0

[a]Conditions: **1** (0.10 mmol, 1.0 equiv.), **2** (0.20 mmol, 2.0 equiv.), nickel catalyst (0.01 mmol, 10 mol%), ligand (0.015 mmol, 15 mol%), silane (1.0 mmol, 10.0 equiv.), base (0.30 mmol, 3.0 equiv.), additives, solvent (0.60 mL, 0.167 mol/L), 50 °C, 12 h. GC (gas chromatography) yield. [b]Yields and regioisomeric ratios were determined by GC analysis with triphenylmethane as an internal standard. The yield refers to total yield for the mixture of the linear product (**3**) and branched product (**4**). [c]1,4-Dioxane ∶ MeOH = 5 ∶ 1 as solvent. [d]1,4-Dioxane ∶ MeOH = 5 ∶ 1 as solvent, 0.5 equiv. TBAI and 0.5 equiv. Mg powder were added. [e]Isolated yield for the linear product in parentheses. DEMS = diethoxymethylsilane; PMHS = polymethylhydrosiloxane; DMAc = *N*,*N*-dimethylacetamide; THF = tetrahydrofuran; acac = acetylacetonate; cod = 1,5-cyclooctadiene; dppe = 1,2-bis(diphenylphosphino)ethane; Bn = benzyl; TBAI = tetrabutylammonium iodide.

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JUSTC, **2022**, 52(12): 1

(entry 22) powder could simultaneously improve the coupling yield and regioselectivity. The iodine ion might have a protective effect on the nickel catalyst. Another alternative is the formation of alkyl iodides in the presence of iodine ions. Finally, we tried to fine-tune the ligand under the conditions of entry 22 to seek better results (entries 23–25). To our delight, the use of pyridine-oxazoline ligand (**L8**) delivered satisfactory results (entry 25): a combination of $NiBr_2$(diglyme) and **L8**, Na_2CO_3 as the base, DEMS as silane, TBAI and Mg powder as additives, in a 1,4-dioxane/MeOH mixed solvent delivered linear product **3** with 85% GC yield for the linear and branched product, 70% isolated yield for the linear product, and good regioselectivity profile (6.3 ∶ 1.0 *l* ∶ *b*). If the DEMS loading could be reduced, it would greatly improve the synthetic utility of this methodology. Unfortunately, the low loadings (5.0 equiv. in entry 26 and 3.0 equiv. in entry 27) DEMS led to decreased coupling yields.

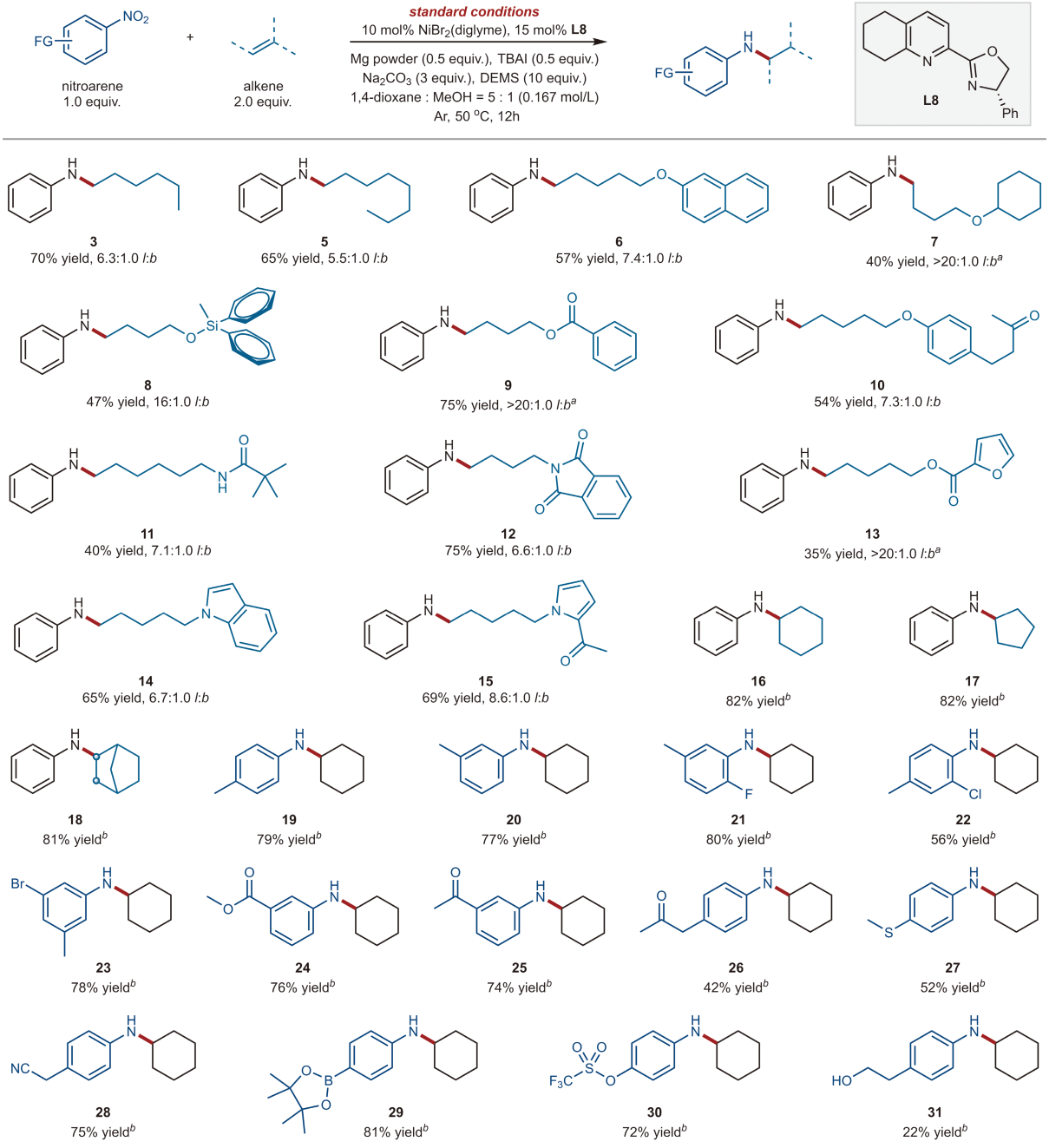

Fig. 2. Scope of substrates. Standard conditions: nitroarene (0.20 mmol, 1.0 equiv.), alkene (0.40 mmol, 2.0 equiv.), $NiBr_2$(diglyme) (0.02 mmol, 10 mol%), **L8** (0.03 mmol, 15 mol%), DEMS (2.0 mmol, 10.0 equiv.), Na_2CO_3 (0.60 mmol, 3.0 equiv.), TBAI (0.10 mmol, 0.5 equiv.), Mg powder (0.10 mmol, 0.5 equiv.), solvent (1,4-dioxane ∶ MeOH = 5 ∶ 1, 1.20 mL, 0.167 mol/L), 50 °C, 12 h. The yield represents the isolated yield of the major product. The reaction regioselectivity was determined by GC analysis of the reaction mixture. [a]For these cases, the reaction regioselectivity could not be determined by GC analysis, ^{1}H NMR determined regioisomeric ratios shown in the table after chromatography purification. [b]**L1** instead of **L8** as ligand. DEMS = Diethoxymethylsilane; TBAI = Tetrabutylammonium iodide.

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JUSTC, **2022**, 52(12): 1

3.2 Scope of reductive hydroamination

With the optimized reaction conditions, we examined the substrate scope of the reductive hydroamination reaction (Fig. 2). In all cases, various alkenes and nitroarenes with different functional groups delivered the desired products in moderate to good yields. This reaction could be applied to terminal (**3**, **5–15**) and internal (**16–18**) alkenes. Cyclic internal alkenes (**16–18**) performed well in this transformation; the ring size of cyclic alkenes did not significantly affect the coupling efficiency, even with extension ring substrates (**18**). Various nitroarenes (**19–31**) were suitable substrates and provided the respective products with satisfactory yields. For the nitroarene coupling partners, electroneutral (**3**), electron-rich (**19**, **20**, **23**, and **27**), and electron-deficient (**24** and **25**) substrates gave moderate to good yields. Under mild reaction conditions, many functional groups were well tolerated, such as ether (**6** and **7**), silyl ether (**8**), ester (**9** and **24**), keto carbonyl (**10**, **25**, and **26**), aryl fluoride (**21**), thioether (**27**), cyano (**28**), and even amide-possessing N–H bonds (**11**). Heterocycles such as phthalimide (**12**), furan (**13**), indole (**14**), and pyrrole (**15**) posed no problem. The compatibility to electrophilic aryl chloride (**22**), aryl bromide (**23**), aryl triflate

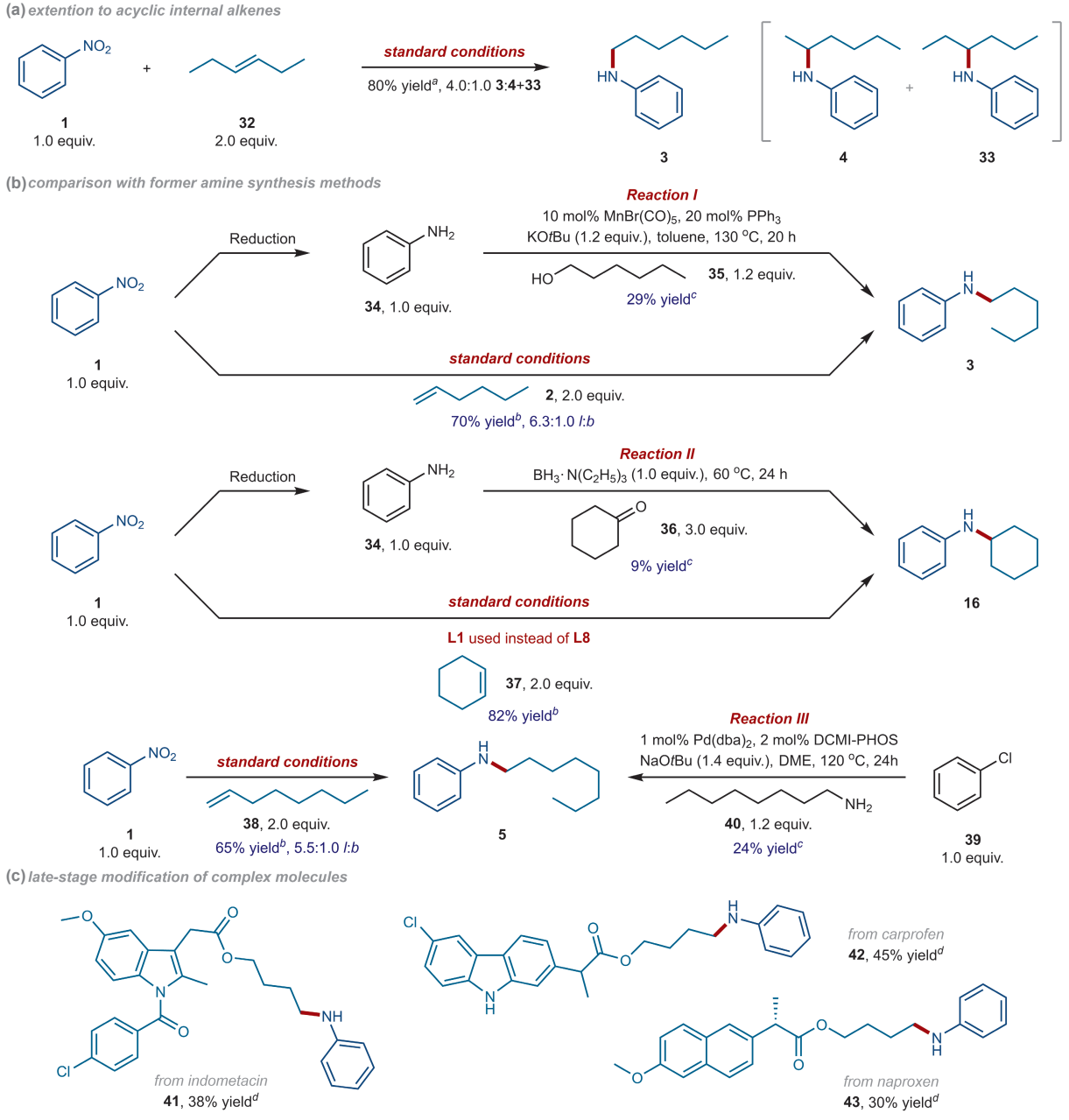

Fig. 3. Synthetic applications. Standard conditions are shown in Fig. 2. [a]The yield represents the total GC yield. The reaction regioselectivity was determined by GC analysis of the reaction mixture. [b]The yield represents the isolated yield of the major product. The reaction regioselectivity was determined by GC analysis of the reaction mixture. [c]Yields reported in reference. [d]The yield represents the isolated yield of the major product. Regioselectivity could not be determined by GC analysis. The regioisomeric ratio was determined to be >20∶1.0 *l*∶*b* by ^{1}H NMR after chromatography purification. DCMI-PHOS = dicyclohexyl(2-mesityl-1*H*-inden-1-yl)phosphine; DME = 1,2-dimethoxyethane; dba = dibenzylideneacetone.

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JUSTC, **2022**, 52(12): 1

(**30**), and nucleophilic arylboronate (**29**) further provided further functionalization possibilities via transition-metal-catalyzed cross-coupling reactions. In addition, this reaction could be conducted in the presence of an alcohol group (**31**) without protection. The good functional group compatibility and the simplicity of operation provided an efficient approach for drug-like arylamine synthesis.

3.3 Synthetic applications

We conducted the reaction between nitrobenzene (**1**) and (*E*)-hex-3-ene (**32**) as a model reaction to examine the reactivity and regioselectivity of acyclic internal alkenes (Fig. 3a). In this case, an isomer mixture was obtained, and linear product **3** was the major isomer. Our approach has a few advantages over former amine synthesis methods (Fig. 3b), such as *N*-alkylation of amines with alcohols via dehydration reaction (Reaction I) [52], amine-carbonyl reductive amination (Reaction II) [53], and Buchwald–Hartwig C-N coupling reactions (Reaction III) [54]. To further demonstrate the synthetic utility, we evaluated the potential of this approach in the late-stage modification of complex molecules (Fig. 3c). Alkenes derived from drug molecules or other biorelevant molecules, such as indomethacin (**41**), carprofen (**42**), and naproxen (**43**), underwent the reductive hydroamination process smoothly.

3.4 Mechanistic investigation

A series of control and mechanistic experiments were carried out for mechanistic investigation (Fig. 4). In the control experiments with catalysts (Fig. 4a), the model reaction could not occur without nickel catalysts or using cobalt or iron catalysts. We found that in the absence of an alkene, nitrobenzene (**1**) was reduced under the standard conditions (Fig. 4b). However, the reduction of nitrobenzene would not occur in the absence of nickel catalysts. In the control experiments with potential intermediates (Fig. 4c), a series of plausible intermediates, including aniline (**34**), nitrosobenzene (**44**), *N*-phenylhydroxylamine (**45**), azoxybenzene (**46**), and azobenzene (**47**), were subjected to standard conditions instead of nitrobenzene (**1**). Nitrosobenzene (**44**) delivered product **3** in 6% GC yield with a 1.1∶1.0 regioselectivity. In addition, we

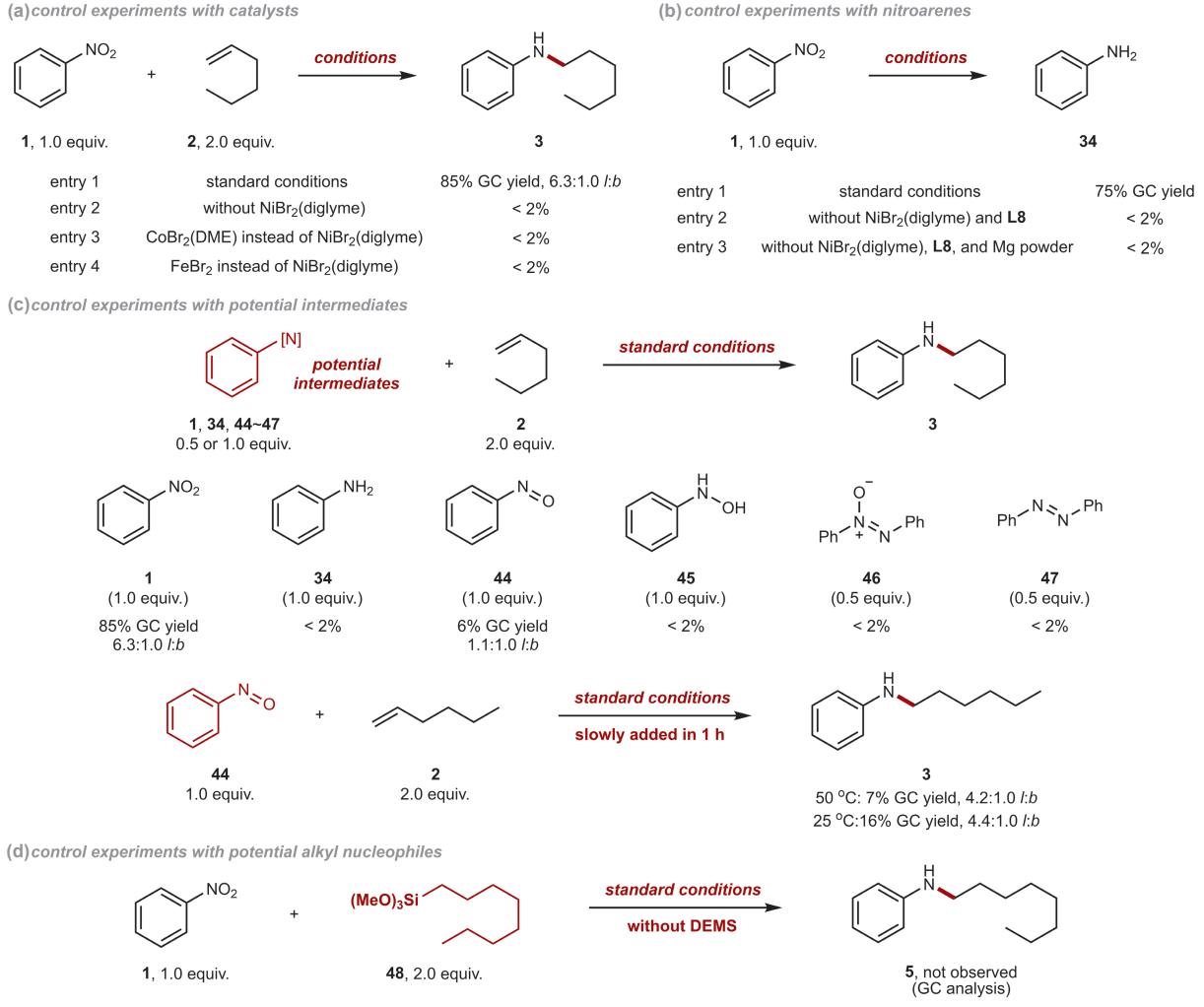

Fig. 4. Mechanistic investigation. Standard conditions: nitroarene or potential intermediate (0.20 mmol, 1.0 equiv. or 0.10 mmol, 0.5 equiv.), alkene (0.40 mmol, 2.0 equiv.), $NiBr_2$(diglyme) (0.02 mmol, 10 mol%), **L8** (0.03 mmol, 15 mol%), DEMS (2.0 mmol, 10.0 equiv.), Na_2CO_3 (0.60 mmol, 3.0 equiv.), TBAI (0.10 mmol, 0.5 equiv.), Mg powder (0.10 mmol, 0.5 equiv.), solvent (1,4-dioxane∶ MeOH = 5∶1, 1.20 mL, 0.167 mol/L), 50 °C, 12 h. Yields and regioisomeric ratios were determined by GC analysis with triphenylmethane as an internal standard. Total yield for the mixture of the linear product and branched product.

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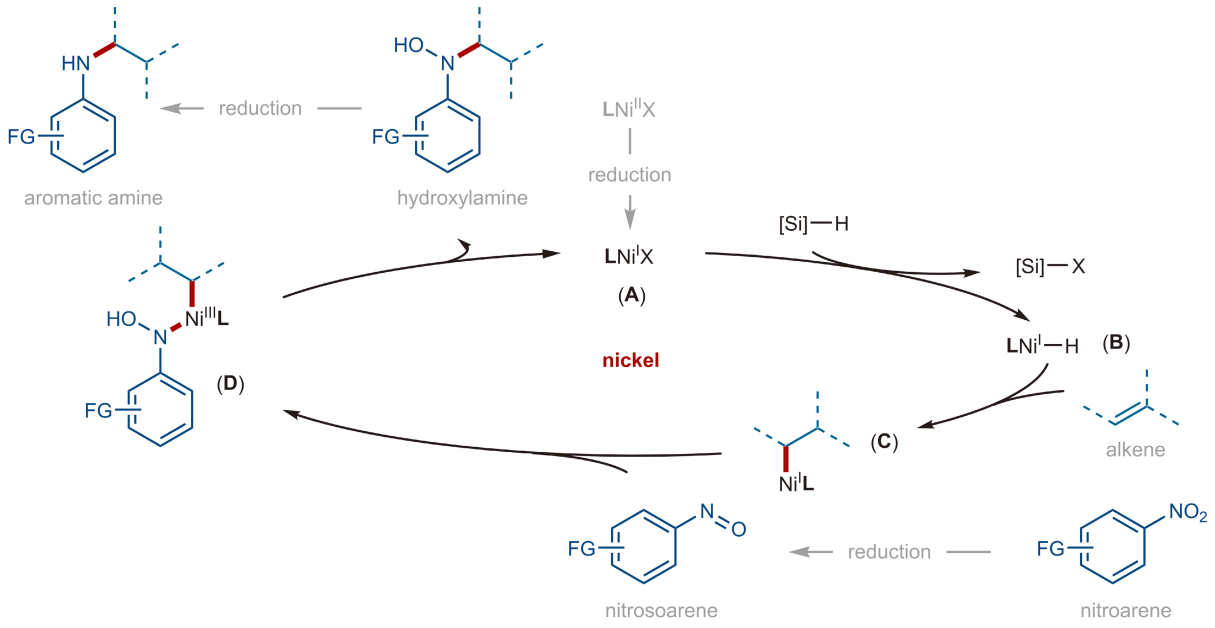

Fig. 5. Plausible reaction mechanism.

conducted a control nitrosobenzene experiment with a slow dropping operation; the yield and regioselectivity of product **3** were improved. Combining the results obtained in Fig. 4c and related literature[15,37], we suggested that the nitrosoarene was a viable reaction intermediate. On the other hand, alkene hydroamination with in situ-generated aniline was less likely because no desired product formed in the control experiment with aniline. We also conducted a control experiment to probe whether alkylsilane acted as an intermediate (Fig. 4d). Trimethoxy(octyl)silane (**48**) was treated with nitrobenzene (**1**) under standard conditions, and the desired product **5** was not observed. This result ruled out the possibility of in situ alkene hydrosilylation and C-N coupling between alkylsilanes and nitroarenes.

3.5 Plausible reaction mechanism

Based on the literature and our mechanistic investigation[15,16,23,37,38,40,45–50], we proposed a plausible reaction mechanism, as outlined in Fig. 5. Active Ni(I)X species (**A**) could be generated from the initial Ni(II) catalysts. Ni(I)X species (**A**) delivered a nickel hydride species Ni(I)H (**B**) after the reaction with silane. Then, alkylnickel(I) intermediates (**C**) were generated through the regioselective migratory insertion of Ni(I)H across the alkene. Reaction of alkylnickel(I) intermediates (**C**) with the nitrosoarenes generated in situ occurred to access the hydroxylamine intermediates and regenerate the active Ni(I)X species (**A**)[37]. Finally, the reduction of hydroxylamines gave aromatic amine products.

4 Conclusions

We developed a nickel-catalyzed alkene hydroamination with nitroarenes under mild reductive conditions. This reaction exhibited an *ipso*-selectivity and enabled the rapid preparation of aromatic amines with primary and secondary alkyl groups. Many functional groups were well tolerated, providing an efficient approach for drug-like arylamine synthesis under protecting-group-free conditions.

Supporting information

The supporting information for this article can be found online at https://doi.org/10.52396/JUSTC-2022-0119. The supporting information includes 65 figures. The characterization of all new compounds is provided in the supporting information.

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Disclosures

Pay caution to eye protection when handling silanes, which might cause potential security risks. Silanes might be disproportionated and form pyrophoric SiH_4. Suitable precautions are needed.

Conflict of interest

The authors declare that they have no conflict of interest.

Biographies

Zhen Li is a master's student under the supervision of Prof. Yao Fu at the University of Science and Technology of China. His research mainly focuses on nickel-catalyzed alkene hydroalkylation.

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JUSTC, **2022**, 52(12): 1

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Yao Fu received his Ph.D. degree from the University of Science and Technology of China in 2005. He is currently a Professor at the University of Science and Technology of China. His research focuses on physical organic chemistry, green organic synthesis, and the biomass chemical industry.

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