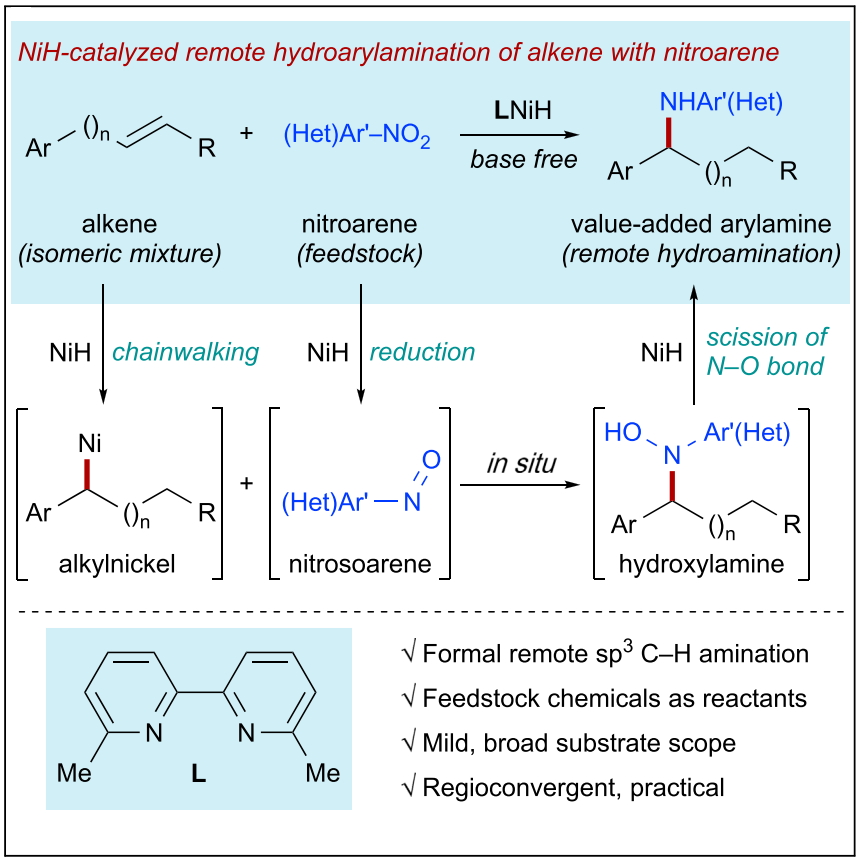
Chem

CellPress

Article

Remote sp^3 C–H Amination of Alkenes with Nitroarenes



Zhu and colleagues describe the remote hydroamination of alkenes with nitro(hetero)arenes through nickel-catalyzed alkene isomerization and sequential reductive relay hydroamination process. Using two common feedstock chemicals, olefins and nitroaromatics, in an operationally simple procedure, this attractive protocol provides efficient and practical access to a wide range of arylamines under mild conditions.

Jichao Xiao, Yuli He, Feng Ye, Shaolin Zhu

shaolinzhu@nju.edu.cn

HIGHLIGHTS

Direct remote hydroamination of alkenes with nitroarenes

Nickel-catalyzed alkene isomerization and sequential reductive relay hydroamination

Readily available reactants and catalysts, mild conditions, and broad substrate scope

Practical, scalable, and regioconvergent for arylamine synthesis

Xiao et al., Chem 4, 1–13
July 12, 2018
https://doi.org/10.1016/j.chempr.2018.04.008

Please cite this article in press as: Xiao et al., Remote sp^3 C–H Amination of Alkenes with Nitroarenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.04.008

Chem

CellPress

Article

Remote sp^3 C–H Amination of Alkenes with Nitroarenes

Jichao Xiao,[1] Yuli He,[1] Feng Ye,[1] and Shaolin Zhu[1,2,*]

SUMMARY

Direct installation of a functional group at remote, unfunctionalized sites in an alkyl chain is a synthetically valuable but rarely reported process. The remote relay hydroarylamination of distal and proximal olefins, and of olefin isomeric mixtures, has been achieved through NiH-catalyzed alkene isomerization and sequential reductive hydroarylamination with nitroarenes. This provides an attractive approach to the direct installation of a distal arylamino group within alkyl chains. The single-step conversion of simple olefins and nitro(hetero)arenes to value-added arylamines is a practical strategy for amine synthesis as well as the remote activation of sp^3 C–H bonds. The value of this transformation is further supported by the regioconvergent arylamination of isomeric mixtures of olefins.

INTRODUCTION

Arylamines are commonly encountered in pharmaceuticals, natural products, agrochemicals, and other chemicals.[1–3] Classical methods for arylamine synthesis include Buchwald-Hartwig amination,[4–6] amine-carbonyl reductive amination,[7] and nucleophilic substitution.[8] Recently, direct amination of the ubiquitous sp^3 C–H bond has emerged as an attractive strategy for amine synthesis. However, to discriminate between the many structurally similar aliphatic C–H bonds in an alkyl chain and to achieve high regio- and chemoselectivity, a local pre-installed polar directing group is often required. This makes the strategy inefficient and limits its wide application.[9–11] Therefore, undirected strategies that allow C–H functionalization at remote, unfunctionalized sites could be valuable for the synthesis of complex molecules and will allow access to structures that would otherwise be difficult to synthesize.[12,13] Given the abundance and availability of alkenes, olefin hydroamination has in recent years been presented as a direct and attractive alternative with which to access amines.[14–29] However, this elegant approach has generally been restricted to installation of an amino group at a C=C double bond. Remote functionalization of olefins remains a formidable challenge in organic synthesis and in recent years has attracted considerable interest from the chemistry community.[30–52] More specifically, the direct installation of an amino group by remote hydroamination of olefins at an sp^3 carbon distant from a double bond (Figure 1A) is a valuable but unexplored process.[53,54]

Nitro(hetero)arenes are stable, inexpensive, and readily available starting materials. They are also precursors of anilines, one of the most popular nitrogen sources, which are usually prepared in advance by hydrogenation of the corresponding nitroarenes. Because of these potential advantages, there is an impetus to discover chemical transformations that directly utilize nitroarenes in synthetically valuable C–N bond-forming reactions.[55–65] Recently, Baran et al.[26] developed a straightforward

The Bigger Picture

Modern organic synthesis requires more efficient strategies, such as C–H functionalization, with which to construct complex molecules from readily available chemicals. Undirected functionalization of remote aliphatic C–H bonds is a synthetically valuable but largely unknown process. Synergistic combination of metal-catalyzed chainwalking (migration of a double bond along the hydrocarbon chain, a process involving repeated migratory insertions and β-hydride eliminations) and cross-coupling chemistry offers a general approach to the remote functionalization of easily accessed unsaturated hydrocarbon substrates. In this paper, we demonstrate that direct installation of a distal arylamino group can be achieved from two common feedstock chemicals (olefins and nitroarenes) via nickel hydride chemistry. It is anticipated that the strategy could inspire the development of other remote functionalizations with different regioselectivity as well as asymmetric transformations.

Please cite this article in press as: Xiao et al., Remote sp^3 C–H Amination of Alkenes with Nitroarenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.04.008

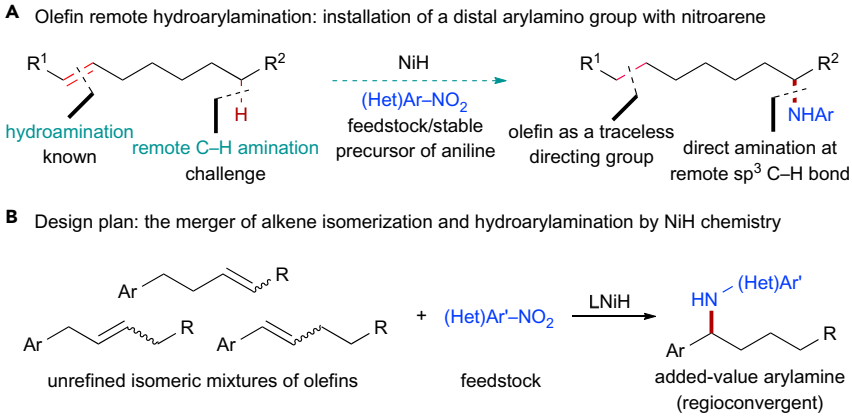


Figure 1. Design Plan: Remote sp^3 C–H arylamination Enabled by Alkene Isomerization and a Sequential Reductive Hydroarylamination Relay Process

hydroamination approach to the construction of arylamines from nitroarenes by combining a FeH-mediated radical reaction followed by a zinc reduction in a one-pot fashion. A recent focus of our laboratory has been the development of NiH-catalyzed olefin remote functionalization as a general strategy with which to achieve inert sp^3 C–H bond functionalization through NiH-catalyzed alkene isomerization and subsequent cross-coupling.[47,50,51] We recently sought to learn whether metal hydride[66–69]-catalyzed chainwalking chemistry could be used to enable remote aliphatic C–H amination through the direct use of nitroarenes as amination reagents. Herein, we report the successful implementation of this strategy and demonstrate the direct conversion of two simple feedstock chemicals, olefins and nitro(hetero) arenes, to useful benzylic arylamines under mild conditions with high functional-group tolerance (Figure 1B). In addition, some insights gleaned from preliminary mechanistic studies are reported.

RESULTS

Reaction Optimization

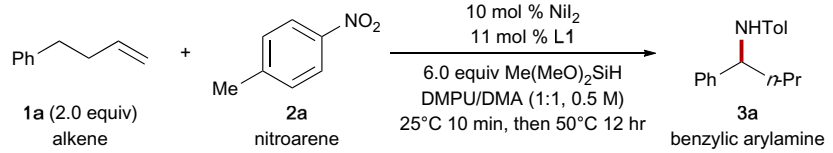
Our initial investigation was focused on the remote hydroarylamination of 4-phenyl-1-butene (**1a**) with 4-nitrotoluene (**2a**) (Figure 2; see also Tables S1 and S2). Investigation of a variety of reaction parameters showed that high (99%) regioselectivity of the benzylic arylamination product can be obtained in good yield at 50°C with a combination of NiI_2 and the C2-substituted bipyridine ligand **L1** (6,6′-dimethyl-2,2′-bipyridine) without extra base (Figure 2, entry 1). Control experiments revealed that the nickel catalyst was necessary for the reaction to proceed, and substitution of NiI_2 with another nickel source ($NiBr_2$) led to only a moderate yield and significant diminution in the regioisomeric ratio (entry 2). Furthermore, replacement of the solvent, a mixture of 1,3-dimethyl-3.4.5.6-tetrahydro-2(1H)-pyrimidinone (DMPU) and *N*,*N*-dimethylacetamide (DMA) with another solvent (tetrahydrofuran) led to a substantial decrease in the yield, and use of a single solvent was also less efficient (entries 3–5). Use of 1,1,1,3,5,5,5-heptamethyltrisiloxane or polymethylhydrosiloxane results in decreased yield and regioisomeric ratio (rr), but trimethoxysilane is comparably effective (entries 6–8). Conducting the reaction at room temperature also leads to a diminished yield (entry 9). Interestingly, the desired migratory amination also proceeds in the absence of the ligand **L1**, although the yield is very low (entry 10). In addition, absence of the methyl groups from **L1** reduces the yield (entry 11), whereas a phosphine ligand, 2′-(diphenylphosphino)-*N*,*N*′-dimethyl-(1,1′-biphenyl)-2-amine, is ineffective (entry 12).[70–73] The use of lower catalyst loading leads to a modest decrease in yield (entry 13) and finally, monitoring the

[1]State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China

[2]Lead Contact

*Correspondence: shaolinzhu@nju.edu.cn

https://doi.org/10.1016/j.chempr.2018.04.008



entry	deviation from standard conditions	yield of **3a** (%)	rr
1	none	96(87)	>99:1
2	$NiBr_2$, instead of NiI_2	23	68:32
3	THF, instead of DMPU/DMA	42	97:3
4	DMPU only	79	98:2
5	DMA only	75	98:2
6	$Me(TMSO)_2SiH$, instead of $Me(MeO)_2SiH$	38	92:8
7	PMHS, instead of $Me(MeO)_2SiH$	60	90:10
8	$(MeO)_3SiH$, instead of $Me(MeO)_2SiH$	95	>99:1
9	25°C for 12 hr	71	>99:1
10	no **L1**	16	76:24
11	bpy, instead of L1	23	85:15
12	PhDavePhos, instead of L1	10	67:33
13	5 mol % NiI_2, 6 mol % L1	70	>99:1
14	25°C 10 min, then 50°C 10 min	83	>99:1

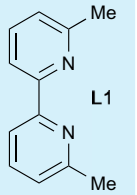


Figure 2. Variation of Reaction Parameters

Yields were determined by GC with *n*-tetradecane as the internal standard. The yield in parentheses is the isolated yield and is an average of two runs (0.2-mmol scale). rr refers to regioisomeric ratio, representing the ratio of the major (benzylic amine) product to the sum of all other isomers as determined by GC analysis (see Supplemental Information). DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; DMA, *N*,*N*-dimethylacetamide; THF, tetrahydrofuran; Tol, *p*-tolyl; PMHS, polymethylhydrosiloxane; PhDavePhos, 2-(diphenylphosphino)-*N*,*N*-dimethyl-(1,1′-biphenyl)-2-amine.

reaction by gas chromatography (GC) shows that the reaction rate is very fast in the first 20 min (entry 14). Notably, no extra reduction step[26] is needed in this protocol to produce the final arylamine product.

Substrate Scope

We sought to define the scope of alkene coupling partners under the optimal conditions. As illustrated in Figure 3A (see also Figures S36–S44 and S83–S102), terminal aliphatic alkenes bearing a wide variety of substituents on the remote aryl ring can undergo isomerization-hydroamination smoothly (**1c–1g**). Heteroaromatic substrates, common scaffolds in medicinally relevant targets, such as those containing a pyridine linked aryl ring (**1g**), a furan (**1h**), or a thiophene (**1i**; Figures S200 and S201), in place of the aryl group are likewise suitable for this reaction.

Unactivated internal olefins are also suitable partners under these conditions (Figure 3B; see also Figures S45–S50 and S103–S118). Consistent with our expectations, both *E* (**1o** and **1p**) and *Z* (**1n**) alkenes, as well as *E*/*Z* mixtures (**1j–1m**) are accommodated perfectly, yielding benzylic amines exclusively in comparable yields, regardless of the position of the C=C bond in the starting material. Notably, even with a heteroatom substituent at the other terminus of the alkyl chain such as the Boc carbamate in **1o** or the ether in **1p** (Figures S202 and S203), migration toward the aryl group and subsequent benzylic amination are still preferred. Interestingly, a trisubstituted internal alkene (**1q**; Figures S204 and S205), a challenging substrate for transition-metal catalysis, also undergoes remote hydroamination, although with diminished yield and rr.

Please cite this article in press as: Xiao et al., Remote sp^3 C–H Amination of Alkenes with Nitroarenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.04.008

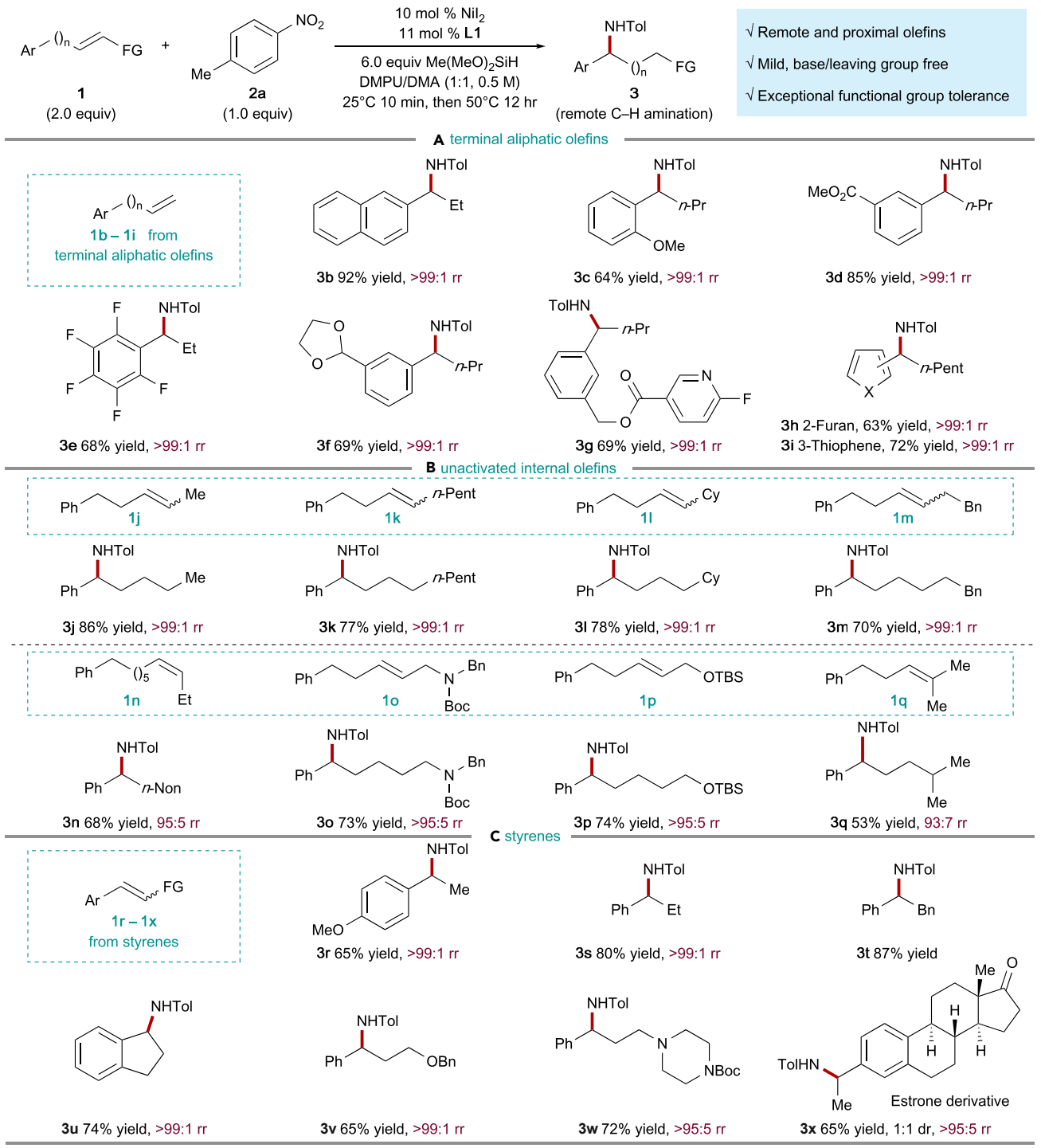


Figure 3. Scope of Alkene Coupling Component

Isolated yields on 0.20-mmol scale (average of two runs). rr refers to regioisomeric ratio, representing the ratio of the major (benzylic amine) product to the sum of all other isomers as determined by GC analysis. Ratios reported as >95:5 were determined by crude ^{1}H NMR analysis. FG, functional group.

Perhaps less surprising, but equally useful, is the hydroamination of styrenes containing various substituents to produce the desired benzylic amine exclusively (Figure 3C, **3r–3x**; see also Figures S51–S55, S119–S132, S206, and S207). Although this

Please cite this article in press as: Xiao et al., Remote sp^3 C–H Amination of Alkenes with Nitroarenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.04.008

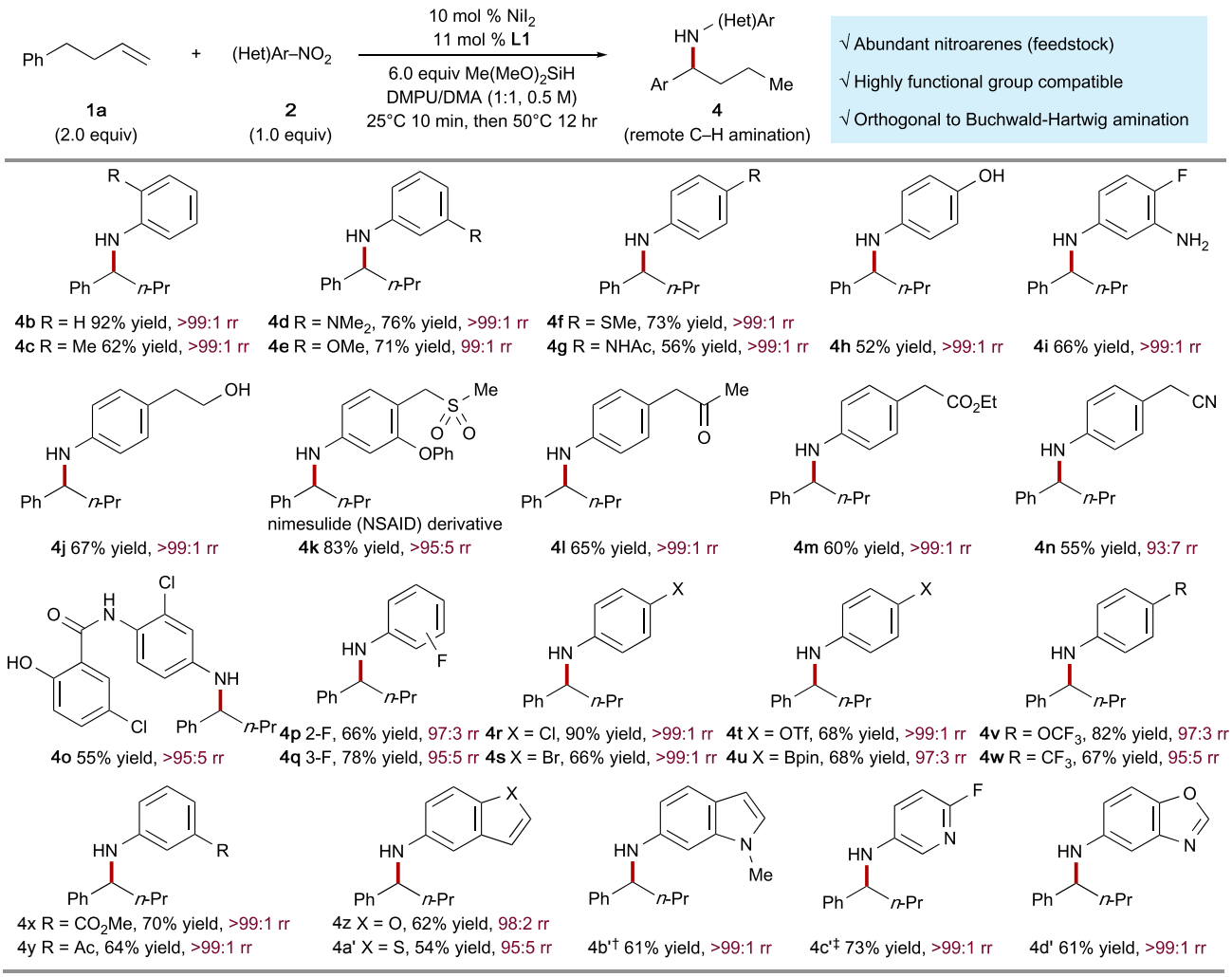


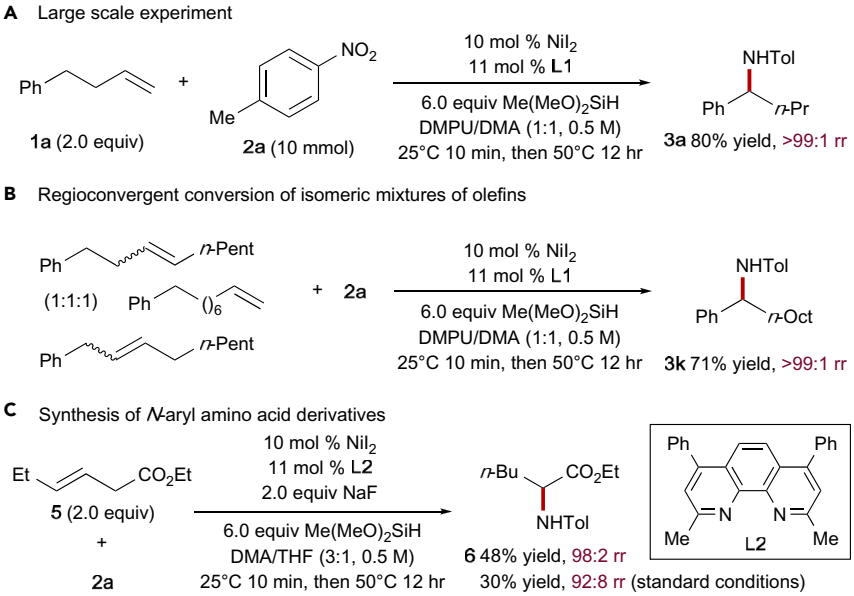
Figure 4. Scope of Nitroarene Component

Yield and rr are as defined in Figure 3. †7.0 equiv silane. ‡24 hr.

is a reductive process, the sensitive ketone group in an estrone-derived styrene is retained intact (**3x**). In contrast, the classical reductive amination of a carbonylamines requires the protection of the ketone.

We next demonstrated the generality of this reaction with respect to the nitroarene component (Figure 4; see also Figures S56–S82 and S133–S197). Substrates with either electron-rich (**2d–2g**) or electron-deficient (**2o–2y**) substituents cross-couple efficiently. Such mild and base-free reaction conditions potentially allow the use of a range of nitroarene components with sensitive functional groups, including ethers (**2e** and **2v**), amines (**2d** and **2i**), esters (**2m** and **2x**), amides (**2g** and **2o**), a sulfone (**2k**), a thiolether (**2f**), and a nitrile (**2n**). Free phenol (**2h**), amine (**2i**), and alcohol (**2j**) are well tolerated. Of particular interest are potential coupling motifs, including aryl halides (**2o–2s**), an aryltriflate (**2t**), and a boronic acid pinacol ester (**2u**), which are left intact and utilizable for further cross-coupling transformations. A series of heterocycles including benzofuran (**2z**), benzothiophene (**2a′**), indole (**2b′**), pyridine (**2c′**), and benzooxazole (**2d′**), which are frequently found in medicinally active chemicals, were also shown to be competent coupling partners.

Please cite this article in press as: Xiao et al., Remote sp^3 C–H Amination of Alkenes with Nitroarenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.04.008



Scheme 1. Large-Scale, Regioconvergent, and Expanded Alkene Scope Experiments

Applications

As a demonstration of the robustness and practicality of this protocol, we carried out a 10-mmol-scale experiment and found that **3a** could be isolated from the reaction in 80% yield without a decrease in the rr (Scheme 1A; see also Scheme S1). Moreover, this process is also sufficiently effective to allow conversion of isomeric mixtures of olefins into value-added arylamines in a regioconvergent fashion. This includes positional and geometrical isomers, which are generally much more readily available and substantially cheaper than pure isomers. To provide proof of concept, we used a mixture of equimolar amounts of three olefin isomers under the standard conditions. Consistent with expectations amination was highly selective, occurring at the benzylic position and producing only a single regioconvergent amination product (Scheme 1B; see also Scheme S2). Additionally we extended this chemistry to olefins with a remote ester group on the alkyl chain (Scheme 1C; see also Scheme S3). Under slightly modified reaction conditions, migratory amination with excellent selectivity at the carbon α to the ester is obtained, producing the *N*-aryl amino acid derivative (**6**; Figures S2 and S3).

DISCUSSION

Proposed Catalytic Cycle

A detailed description of the proposed pathway is outlined in Figure 5. It was envisioned that a nickel hydride species, LNiH (**I**) generated from silane, could be used to initiate a rapid and reversible sequential β-hydride elimination and β-migratory reinsertion and iterative process from an olefin isomer (**1a**) to access a series of alkylnickel(I) intermediates (**II**, **IV**, etc.) along the alkyl chain. If nickel migration along the alkyl chain is rapid and the reaction of benzylnickel(I) intermediate (**IV**) with the amination reagent, the nitrosoarene (**V**) generated *in situ* from the nitroarene (**2a**), is favorable, it will provide rapid access to the remote hydroxylamine intermediates (**VI**) rather than hydroamination at the original C=C double bond. Further reduction of hydroxylamine (**VI**) will provide the final hydroamination product (**3a**). The nickel hydride species (**I**) is regenerated *in situ* by a stoichiometric amount of a hydrosilane to achieve a net catalytic, remote hydroarylamination reaction.

Please cite this article in press as: Xiao et al., Remote sp^3 C–H Amination of Alkenes with Nitroarenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.04.008

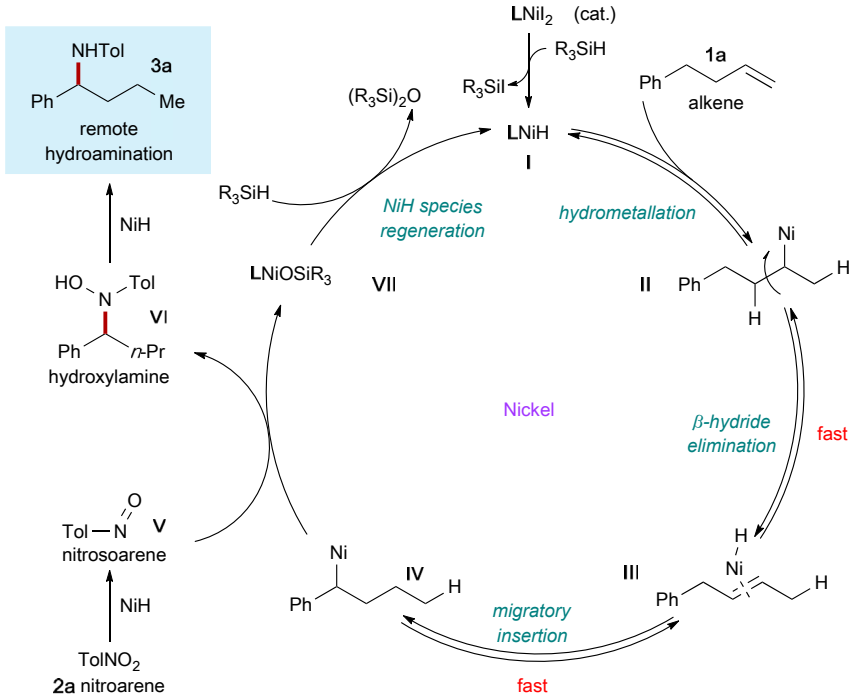


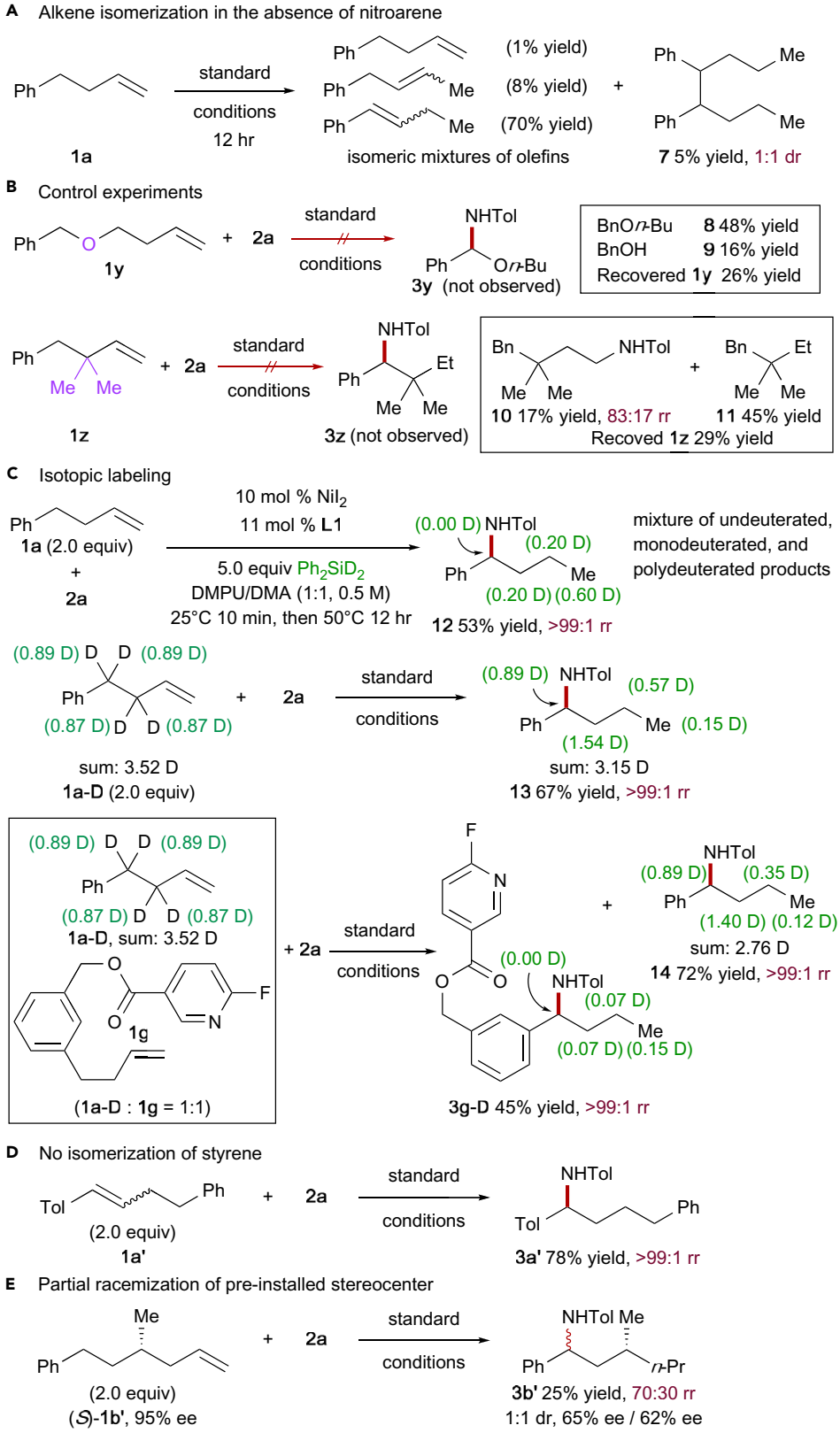
Figure 5. Proposed Mechanism for Reductive Relay Hydroamination

Mechanistic Studies

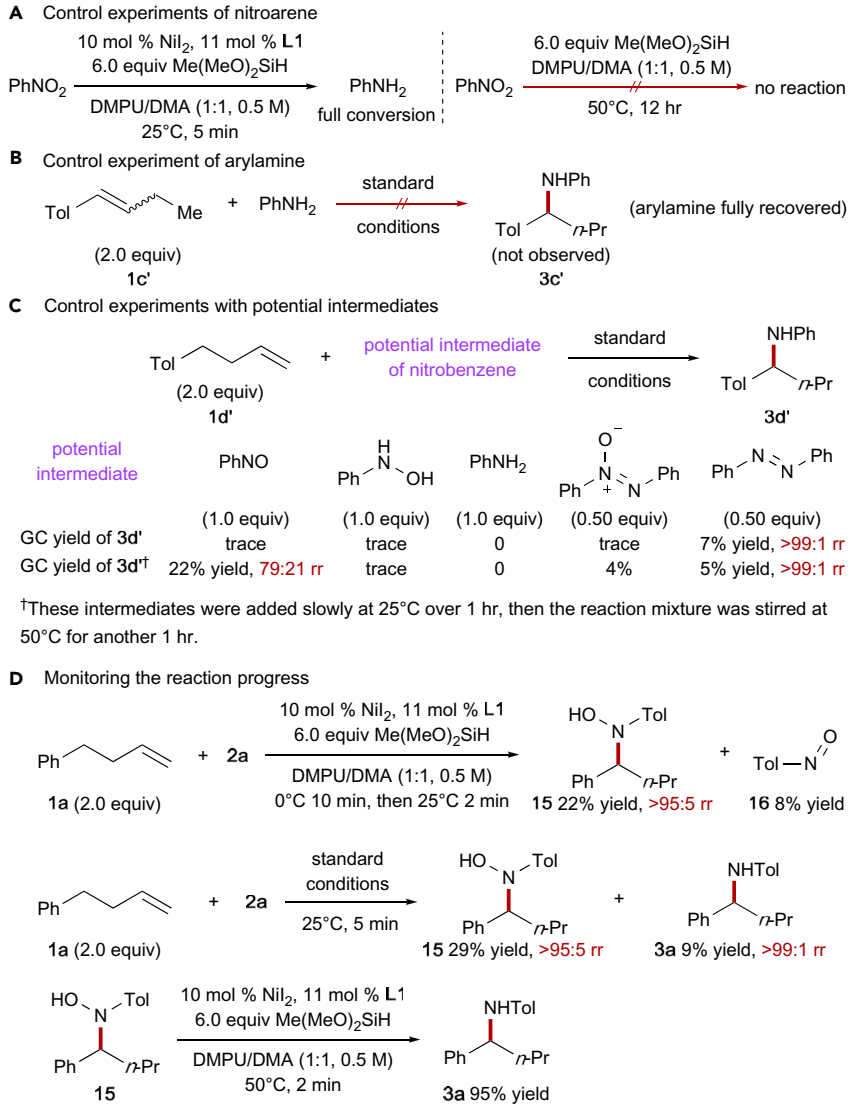
A series of experiments were conducted to gain insight into the mechanism of the reaction. The fact that olefin **1a** itself, in the absence of nitroarene, can isomerize to other positional isomers under standard conditions suggests that alkene isomerization is unrelated to C–N bond formation, and also indicates that the nitroarene is not involved in the chainwalking step (Scheme 2A; see also Table S3 and Figures S208 and S209). Furthermore, no desired isomerization-hydroarylamination reaction occurs when an oxygen atom or a gem-dimethyl spacer lacking a β-hydrogen is introduced into the hydrocarbon chain between the benzylic position and double bond (Scheme 2B; see also Scheme S4 and Figures S4 and S5). This is consistent with the hypothesis that olefin isomerization occurs through rapid and reversible β-hydrogen elimination and reinsertion steps.[74–77] An isotope labeling experiment of a model reaction was carried out with deuterodiphenylsilane. Deuterium scrambling and deuterium incorporation at all the positions except the benzylic position along the hydrocarbon chain were observed. As revealed by mass spectrometric analysis, a mixture of undeuterated, monodeuterated, and polydeuterated products was obtained. This supports a mechanism whereby chainwalking occurs with dissociation and reassociation of free NiH/NiD from the NiH/NiD-olefin complex (Scheme 2C; see also Scheme S5 and Figures S6–S8).[50] Furthermore, when deuterium-labeled olefin **1a-D** is used in both standard and crossover reactions, deuterium scrambling and deuterium incorporation at all the positions along the hydrocarbon chain are also observed (Scheme 2C; see also Schemes S6 and S7 and Figures S9–S18). Deuterium incorporation in **3g-D** further supports the dissociation and reassociation of NiH/NiD from the olefin during the chainwalking process. Interestingly, no deuterium scrambling at the benzylic position in either **12** or **3g-D** is observed, suggesting that β-migratory insertion with a styrenic intermediate is highly regiospecific and forms the benzylic nickel species. This hypothesis is further supported by experiments using a styrene substrate (**1a′**) (Scheme 2D; see also Scheme S8). Only one

Chem

CellPress



Scheme 2. Mechanistic Studies Concerning Chainwalking



Scheme 3. Studies of the Mechanism of Reductive Hydroarylamination

regioisomer (**3a′**, Figures S19 and S20) is obtained and no isomerization of **1a′** is observed during the partial conversion. To explore the chainwalking process further, we evaluated an olefin substrate (*S*)-**1b′** (Figures S210 and S211), with a pre-installed stereogenic center (95% enantiomeric excess [ee]) in the alkyl chain, under the standard conditions (Scheme 2E; see also Scheme S9). In contrast to the preservation of the chiral integrity in the PdH-catalyzed chainwalking process,[33,37] in the corresponding product (**3b′**, 1:1 diastereomeric ratio; Figures S21–S26), partial racemization of this stereocenter is observed (the ee of this stereocenter drops from 95% to 65% and 95% to 62%). This again implies that NiH disengages during the chainwalking process.

Next, we set out to identify the active species of nitroarene. As shown in Scheme 3A (see also Schemes S10 and S11), no reaction happens in the absence of nickel, and nitrobenzene is easily reduced to aniline in the absence of olefin under standard conditions. However, no desired hydroarylamination reaction occurs when aniline is

Please cite this article in press as: Xiao et al., Remote sp^3 C–H Amination of Alkenes with Nitroarenes, Chem (2018), https://doi.org/10.1016/j.chempr.2018.04.008

resubjected to the standard conditions with the styrene (**1c′**), suggesting that aniline is not involved in the hydroamination step (Scheme 3B; see also Scheme S12). Additionally, a series of potential intermediates were used directly in place of nitrobenzene (Scheme 3C; see also Scheme S13 and Figures S27 and S28). Under standard conditions, none of them give product **3d′** in any considerable yield. Considering that the actual intermediate is generated *in situ* at low concentration under the standard reaction conditions, we next added these potential intermediates slowly over a period of 1 hr. Indeed, the desired product **3d′** (Figures S29, S198, and S199) is obtained in 22% GC yield in case of nitrosobenzene, suggesting that the nitrosoarene is likely the actual intermediate. Due possibly to the relative high concentration of nitrosobenzene compared with the alkylnickel intermediate, low regioselectivity is observed and aniline is the major side product. As suggested in our proposed mechanism, the final amination product presumably forms by reduction of hydroxylamine intermediate (Figure 5). Indeed, hydroxylamine **15** (Figures S31–S34) and nitrosobenzene **16** (Figures S30 and S35) could be monitored, isolated, and confirmed at the early stage of the reaction (Scheme 3D; see also Scheme S14). As anticipated, the final product **3a** is obtained quantitatively from hydroxylamine **15** under standard conditions. Additional studies to fully elucidate the reaction pathway are currently in progress.

Conclusion

We have developed a practical, operationally simple, and selective reductive remote hydroamination process via a sequential NiH-catalyzed chainwalking-reductive hydroarylamination relay process. This mild and efficient protocol utilizes two readily available reactants, inexpensive silane reductants, and earth-abundant nickel salt catalysts. Excellent regio- and chemoselectivity are observed for a wide range of both alkene and nitroarene coupling partners. The practical value of this process is further highlighted by large-scale synthesis and regioconvergent amination of unrefined isomeric mixture of olefins. Studies toward a catalytic asymmetric version of this transformation are continuing.[78]

EXPERIMENTAL PROCEDURES

Representative Procedure for NiH-Catalyzed Remote Hydroarylamination

6,6′-Dimethyl-2,2′-bipyridine (**L1**, 4.1 mg, 11 mol %) was added to an oven-dried 8-mL screw-cap vial (Figure S1) equipped with a magnetic stir bar. The vial was introduced into a nitrogen-filled glovebox and NiI_2 (6.3 mg, 10 mol %), anhydrous DMPU (0.10 mL) and anhydrous DMA (0.10 mL) were added. The mixture was then stirred for 10 min, at which time dimethoxymethylsilane (147 μL, 1.2 mmol, 6.0 equiv) was added and the stirring was continued for another 10 min at room temperature before 4-phenyl-1-butene (60 μL, 0.40 mmol, 2.0 equiv) was added. The tube was sealed with a Teflon-lined screw cap, removed from the glovebox and stirred at 0°C before a solution of 4-nitrotoluene (27.4 mg, 0.20 mmol, 1.0 equiv) in anhydrous DMPU (0.10 mL) and anhydrous DMA (0.10 mL) was added dropwise by syringe. The reaction mixture was then stirred at 25°C for 10 min and stirred at 50°C for up to 12 hr. After the reaction was complete, the reaction mixture was immediately filtered through a short pad of silica gel (using EtOAc in hexanes) to give the crude product. Tetradecane (20 μL) was added as an internal standard for GC analysis. 1,1,2,2-Tetrachloroethane (10.5 μL, 0.10 mmol) was added as internal standard for ^{1}H NMR analysis of the crude material. The product was purified by chromatography on silica gel for each substrate. The yields reported are the average of at least two experiments, unless otherwise indicated. See Supplemental Information for more detailed Experimental Procedures and characterization data for all products.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 211 figures, 3 tables, and 15 schemes and can be found with this article online at https://doi.org/10.1016/j.chempr.2018.04.008.

ACKNOWLEDGMENTS

Support was provided by the 1000-Youth Talents Plan, the National Natural Science Foundation of China (21772087 and 21702102), the Fundamental Research Funds for the Central Universities (020514380095 and 020514380086), and the National Science Foundation of Jiangsu Province (BK20160642). Y.H. thanks the Postgraduate Research & Practice Innovation Program of Jiangsu Province (KYCX17_0021) and the Nanjing University Innovation and Creative Program for PhD Candidates (CXCY17-16) for support. We are grateful to Yun Du and Pei Hu for GC-MS analysis. This paper is dedicated to Professor David W.C. MacMillan on the occasion of his 50th birthday.

AUTHOR CONTRIBUTIONS

Conceptualization, S.Z.; Methodology, J.X., Y.H., and S.Z.; Investigation, J.X., Y.H., and F.Y.; Writing – Original Draft, J.X.; Writing – Review & Editing, S.Z.; Supervision, S.Z.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: December 4, 2017
Revised: February 11, 2018
Accepted: April 10, 2018
Published: May 17, 2018

REFERENCES AND NOTES

1. Lawrence, S.A. (2004). Amines: Synthesis, Properties and Applications (Cambridge University Press).
2. Ricci, A. (2008). Amino Group Chemistry, from Synthesis to the Life Sciences (Wiley-VCH Verlag GmbH).
3. Roughley, S.D., and Jordan, A.M. (2011). The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. J. Med. Chem. *54*, 3451–3479.
4. Ley, S.V., and Thomas, A.W. (2003). Modern synthetic methods for copper-mediated C(aryl)-O, C(aryl)-N, and C(aryl)-S bond formation. Angew. Chem. Int. Ed. *42*, 5400–5449.
5. Surry, D.S., and Buchwald, S.L. (2008). Biaryl phosphane ligands in palladium-catalyzed amination. Angew. Chem. Int. Ed. *47*, 6338–6361.
6. Hartwig, J.F. (2008). Evolution of a fourth generation catalyst for the amination and thioetherification of aryl halides. Acc. Chem. Res. *41*, 1534–1544.
7. Baxter, E.W., and Reitz, A.B. (2001). Reductive aminations of carbonyl compounds with borohydride and borane reducing agents. Org. React. *59*, 1.
8. Guillena, G., Ramón, D.J., and Yus, M. (2010). Hydrogen autotransfer in the N-alkylation of amines and related compounds using alcohols and amines as electrophiles. Chem. Rev. *110*, 1611–1641.
9. Gutekunst, W.R., and Baran, P.S. (2011). C-H functionalization logic in total synthesis. Chem. Soc. Rev. *40*, 1976–1991.
10. McMurray, L., O'Hara, F., and Gaunt, M.J. (2011). Recent developments in natural product synthesis using metal-catalysed C-H bond functionalisation. Chem. Soc. Rev. *40*, 1885–1898.
11. Yamaguchi, J., Yamaguchi, A.D., and Itami, K. (2012). C-H bond functionalization: emerging synthetic tools for natural products and pharmaceuticals. Angew. Chem. Int. Ed. *51*, 8960–9009.
12. Choi, G.J., Zhu, Q., Miller, D.C., Gu, C.J., and Knowles, R.R. (2016). Catalytic alkylation of remote C-H bonds enabled by proton-coupled electron transfer. Nature *539*, 268–271.
13. Chu, J.C.K., and Rovis, T. (2016). Amide-directed photoredox-catalysed C–C bond formation at unactivated sp^3 C-H bonds. Nature *539*, 272–275.
14. Huang, L., Arndt, M., Gooßen, K., Heydt, H., and Gooßen, L.J. (2015). Late transition metal-catalyzed hydroamination and hydroamidation. Chem. Rev. *115*, 2596–2697.
15. Pirnot, M.T., Wang, Y.-M., and Buchwald, S.L. (2016). Copper hydride catalyzed hydroamination of alkenes and alkynes. Angew. Chem. Int. Ed. *55*, 48–57.
16. Lepori, C., and Hannedouche, J. (2017). First-row late transition metals for catalytic (formal) hydro-amination of unactivated alkenes. Synthesis *49*, 1158–1167.
17. Kawatsura, M., and Hartwig, J.F. (2000). Palladium-catalyzed intermolecular hydroamination of vinylarenes using arylamines. J. Am. Chem. Soc. *122*, 9546–9547.
18. Utsunomiya, M., Kuwano, R., Kawatsura, M., and Hartwig, J.F. (2003). Rhodium-catalyzed anti-Markovnikov hydroamination of vinylarenes. J. Am. Chem. Soc. *125*, 5608–5609.
19. Waser, J., Gaspar, B., Nambu, H., and Carreira, E.M. (2006). Hydrazines and azides via the metal-catalyzed hydrohydrazination and hydroazidation of olefins. J. Am. Chem. Soc. *128*, 11693–11712.
20. Zhang, Z., Lee, S.D., and Widenhoefer, R.A. (2009). Intermolecular hydroamination of

ethylene and 1-alkenes with cyclic ureas catalyzed by achiral and chiral gold(I) complexes. J. Am. Chem. Soc. *131*, 5372–5373.

21. Reznichenko, A.L., Nguyen, H.N., and Hultzsch, K.C. (2010). Asymmetric intermolecular hydroamination of unactivated alkenes with simple amines. Angew. Chem. Int. Ed. *49*, 8984–8987.

22. Zhu, S., Niljianskul, N., and Buchwald, S. (2013). Enantio- and regioselective CuH-catalyzed hydroamination of alkenes. J. Am. Chem. Soc. *135*, 15746–15749.

23. Miki, Y., Hirano, K., Satoh, T., and Miura, M. (2013). Copper-catalyzed intermolecular regioselective hydroamination of styrenes with polymethylhydrosiloxane and hydroxylamines. Angew. Chem. Int. Ed. *52*, 10830–10834.

24. Nguyen, T.M., Manohar, N., and Nicewicz, D.A. (2014). anti-Markovnikov hydroamination of alkenes catalyzed by a two component organic photoredox system: direct access to phenethylamine derivatives. Angew. Chem. Int. Ed. *53*, 6198–6201.

25. Shigehisa, H., Koseki, N., Shimizu, N., Fujisawa, M., Niitsu, M., and Hiroya, K. (2014). Catalytic hydroamination of unactivated olefins using a Co catalyst for complex molecule synthesis. J. Am. Chem. Soc. *136*, 13534–13537.

26. Gui, J., Pan, C.-M., Jin, Y., Qin, T., Lo, J.C., Lee, B.J., Spergel, S.H., Mertzman, M.E., Pitts, W.J., Cruz, La, et al. (2015). Practical olefin hydroamination with nitroarenes. Science *348*, 886–891.

27. Zhu, K., Shaver, M.P., and Thomas, S.P. (2016). Chemoselective nitro reduction and hydroamination using a single iron catalyst. Chem. Sci. *7*, 3031–3035.

28. Zhu, K., Shaver, M.P., and Thomas, S.P. (2016). Amine-bis(phenolate) iron(III)-catalyzed formal hydroamination of olefins. Chem. Asian J. *11*, 977–980.

29. Musacchio, A.J., Lainhart, B.C., Zhang, X., Naguib, S.G., Shrewood, T.C., and Knowles, R.R. (2017). Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. Science *355*, 727–730.

30. Sommer, H., Juliá-Hernández, F., Martin, R., and Marek, I. (2018). Walking metals for remote functionalization. ACS Cent. Sci. *4*, 153–165.

31. Vasseur, A., Bruffaerts, J., and Marek, I. (2016). Remote functionalization through alkene isomerization. Nat. Chem. *8*, 209–219.

32. Larionov, E., Li, H., and Mazet, C. (2014). Well-defined transition metal hydrides in catalytic isomerizations. Chem. Commun. *50*, 9816–9826.

33. Singh, S., Bruffaerts, J., Vasseur, A., and Marek, I. (2017). A unique Pd-catalysed Heck arylation as a remote trigger for cyclopropane selective ring-opening. Nat. Commun. *8*, 14200–14209.

34. Lin, L., Romano, C., and Mazet, C. (2016). Palladium-catalyzed long-range deconjugative isomerization of highly substituted α,β-unsaturated carbonyl compounds. J. Am. Chem. Soc. *138*, 10344–10350.

35. Dupuy, S., Zhang, K.-F., Goutierre, A.-S., and Baudoin, O. (2016). Terminal-selective functionalization of alkyl chains by regioconvergent cross-coupling. Angew. Chem. Int. Ed. *55*, 14793–14797.

36. Hamasaki, T., Aoyama, Y., Kawasaki, J., Kakiuchi, F., and Kochi, T. (2015). Chain walking as a strategy for carbon-carbon bond formation at unreactive sites in organic synthesis: catalytic cycloisomerization of various 1,n-dienes. J. Am. Chem. Soc. *137*, 16163–16171.

37. Mei, T.-S., Patel, H.H., and Sigman, M.S. (2014). Enantioselective construction of remote quaternary stereocentres. Nature *508*, 340–344.

38. Mola, L., Sidera, M., and Fletcher, S.P. (2015). Asymmetric remote C-H functionalization: use of internal olefins in tandem hydrometallation-isomerization-asymmetric conjugate addition sequences. Aust. J. Chem. *68*, 401–403.

39. Masarwa, A., Didier, D., Zabrodski, T., Schinkel, M., Ackermann, L., and Marek, I. (2014). Merging allylic carbon-hydrogen and selective carbon-carbon bond activation. Nature *505*, 199–203.

40. Obligacion, J.V., and Chirik, P.J. (2013). Bis(imino)pyridine cobalt-catalyzed alkene isomerization-hydroboration: a strategy for remote hydrofunctionalization with terminal selectivity. J. Am. Chem. Soc. *135*, 19107–19110.

41. Yamakawa, T., and Yoshikai, N. (2014). Alkene isomerization-hydroarylation tandem catalysis: indole C2-alkylation with aryl-substituted alkenes leading to 1,1-diarylalkanes. Chem. Asian J. *9*, 1242–1246.

42. Scheuermann, M.L., Johnson, E.J., and Chirik, P.J. (2015). Alkene isomerization-hydroboration promoted by phosphine ligated cobalt catalysts. Org. Lett. *17*, 2716–2719.

43. Lee, W.-C., Wang, C.-H., Lin, Y.-H., Shih, W.-C., and Ong, T.-G. (2013). Tandem isomerization and C-H activation: regioselective hydroheteroarylation of allylarenes. Org. Lett. *15*, 5358–5361.

44. Bair, J.S., Schramm, Y., Sergeev, A.G., Clot, E., Eisenstein, O., and Hartwig, J.F. (2014). Linear-selective hydroarylation of unactivated terminal and internal olefins with trifluoromethyl-substituted arenes. J. Am. Chem. Soc. *136*, 13098–13101.

45. Busolv, I., Becouse, J., Mazza, S., Montandon-Clerc, M., and Hu, X. (2015). Chemoselective alkene hydrosilylation catalyzed by nickel pincer complexes. Angew. Chem. Int. Ed. *54*, 14523–14526.

46. Buslov, I., Song, F., and Hu, X. (2016). An easily accessed nickel nanoparticle catalyst for alkene hydrosilylation with tertiary silanes. Angew. Chem. Int. Ed. *55*, 12295–12299.

47. He, Y., Cai, Y., and Zhu, S. (2017). Mild and regioselective benzylic C-H functionalization: Ni-catalyzed reductive arylation of remote and proximal olefins. J. Am. Chem. Soc. *139*, 1061–1064.

48. Juliá-Hernández, F., Moragas, T., Cornella, J., and Martin, R. (2017). Remote carboxylation of halogenated aliphatic hydrocarbons with carbon dioxide. Nature *545*, 84–88.

49. Gaydou, M., Moragas, T., Juliá-Hernández, F., and Martin, R. (2017). Site-selective catalytic carboxylation of unsaturated hydrocarbons with CO_2 and water. J. Am. Chem. Soc. *139*, 12161–12164.

50. Chen, F., Chen, K., Zhang, Y., He, Y., Wang, Y.-M., and Zhu, S. (2017). Remote migratory cross-electrophile coupling and olefin hydroarylation reactions enabled by in situ generation of NiH. J. Am. Chem. Soc. *139*, 13929–13935.

51. Zhou, F., Zhu, J., Zhang, Y., and Zhu, S. (2018). NiH-Catalyzed reductive relay hydroalkylation: a strategy for the remote C(sp^3)-H alkylation of alkenes. Angew. Chem. Int. Ed. *57*, 4058–4062.

52. Peng, L., Li, Y., Li, Y., Wang, W., Pang, H., and Yin, G. (2018). Ligand-controlled nickel-catalyzed reductive relay cross-coupling of alkyl bromides and aryl bromides. ACS Catal. *8*, 310–313.

53. For a catalytic one-pot reaction consisting of an initial olefin isomerization followed by hydroformylation and reductive amination (hydroaminomethylation), see Seayad, A., Ahmed, M., Jackstell, K.R., Gross, T., and Beller, M. (2002). Internal olefins to linear amines. Science *297*, 1676–1678.

54. For a tandem olefin isomerization-conjugate addition reaction, see Ohlmann, D.M., Gooßen, L.J., and Dierker, M. (2011). Regioselective synthesis of β-aryl- and β-amino-substituted aliphatic esters by rhodium-catalyzed tandem double-bond migration/conjugate addition. Chem. Eur. J. *17*, 9508–9519.

55. For examples using nitroarene in cross-coupling reactions, see references 56–65.

56. Cadogan, J.I.G., Cameron-Wood, M., Mackie, R.K., and Searle, R.J.G. (1965). The reactivity of organophosphorus compounds. Part XIX. Reduction of nitro-compounds by triethyl phosphite: a convenient new route to carbazoles, indoles, indazoles, triazoles, and related compounds. J. Chem. Soc. *1965*, 4831–4837.

57. Gao, H., Ess, D.H., Yousufuddin, M., and Kürti, L. (2013). Transition-metal-free direct arylation: synthesis of halogenated 2-amino-2-hydroxy-1,1-biaryls and mechanism by DFT calculations. J. Am. Chem. Soc. *135*, 7086–7089.

58. Gao, H., Xu, Q.-L., Yousufuddin, M., Ess, D.H., and Kürti, L. (2014). Rapid synthesis of fused N-heterocycles by transition-metal-free electrophilic amination of arene C-H Bonds. Angew. Chem. Int. Ed. *53*, 2701–2705.

59. Bartoli, G., Dalpozzo, R., and Nardi, M. (2014). Applications of Bartoli indole synthesis. Chem. Soc. Rev. *43*, 4728–4750.

60. Tong, S., Xu, Z., Mamboury, M., Wang, Q., and Zhu, J. (2015). Aqueous titanium trichloride promoted reductive cyclization of o-nitrostyrenes to indoles: development and application to the synthesis of rizatriptan and aspidospermidine. Angew. Chem. Int. Ed. *54*, 11809–11812.

61. Cheung, C.W., and Hu, X. (2016). Amine synthesis via iron-catalysed reductive coupling of nitroarenes with alkyl halides. Nat. Commun. *7*, 12494.

62. Cheung, C.W., Ploeger, M.L., and Hu, X. (2017). Direct amidation of esters with nitroarenes. Nat. Commun. *8*, 14878.

63. Yadav, M.R., Nagaoka, M., Kashihara, M., Zhong, R.-L., Miyazaki, T., Sakaki, S., and Nakao, Y. (2017). The Suzuki-Miyaura coupling of nitroarenes. J. Am. Chem. Soc. *139*, 9423–9426.

64. Rauser, M., Ascheberg, C., and Niggemann, M. (2017). Electrophilic amination with nitroarenes. Angew. Chem. Int. Ed. *56*, 11570–11574.

65. Inoue, F., Kashihara, M., Yadav, M.R., and Nakao, Y. (2017). Buchwald-Hartwig amination of nitroarenes. Angew. Chem. Int. Ed. *56*, 13307–13309.

66. Deutsch, C., Krause, N., and Lipshutz, B.H. (2008). CuH-catalyzed reactions. Chem. Rev. *108*, 2916–2927.

67. Crossley, S.W.M., Obradors, C., Martinez, R.M., and Shenvi, R.A. (2016). Mn-, Fe-, and Co-catalyzed radical hydrofunctionalizations of olefins. Chem. Rev. *116*, 8912–9000.

68. Nguyen, K.D., Park, B.Y., Luong, T., Sato, H., Garza, V.J., and Krische, M.J. (2016). Metal-catalyzed reductive coupling of olefin-derived nucleophiles: reinventing carbonyl addition. Science *354*, 300.

69. Eberhardt, N.A., and Guan, H. (2016). Nickel hydride complexes. Chem. Rev. *116*, 8373–8426.

70. Currently, the exact role of methyl substituent in the *ortho* position is still under investigation (although methyl substituent in the *ortho* position most likely accelerates the rate of β-hydride elimination). For selected papers using similar ligands, see references 71–73.

71. Liu, Y., Cornella, J., and Martin, R. (2014). Ni-catalyzed carboxylation of unactivated primary alkyl bromides and sulfonates with CO_2. J. Am. Chem. Soc. *136*, 11212–11215.

72. Qiang, X., Nakajima, M., and Martin, R. (2015). Ni-catalyzed regioselective hydrocarboxylation of alkynes with CO_2 by using simple alcohols as proton sources. J. Am. Chem. Soc. *137*, 8924–8927.

73. Wang, X., Nakajima, M., Serrano, E., and Martin, R. (2016). Alkyl bromides as mild hydride sources in Ni-Catalyzed hydroamidation of alkynes with isocyanates. J. Am. Chem. Soc. *138*, 15531–15534.

74. Binder, J.T., Cordier, C.J., and Fu, G.C. (2012). Catalytic enantioselective cross-couplings of secondary alkyl electrophiles with secondary alkylmetal nucleophiles: Negishi reactions of racemic benzylic bromides with achiral alkylzinc reagents. J. Am. Chem. Soc. *134*, 17003–17006.

75. Cordier, C.J., Lundgren, R.J., and Fu, G.C. (2013). Enantioconvergent cross-couplings of racemic alkylmetal reagents with unactivated secondary alkyl electrophiles: catalytic asymmetric Negishi α-alkylations of N-Boc-pyrrolidine. J. Am. Chem. Soc. *135*, 10946–10949.

76. Pappas, I., Treacy, S., and Chirik, P.J. (2016). Alkene hydrosilylation using tertiary silanes with α-diimine nickel catalysts. redox-active ligands promote a distinct mechanistic pathway from platinum catalysts. ACS Catal. *6*, 4105–4109.

77. Kuang, Y., Anthony, D., Katigbak, J., Marrucci, F., Humagain, S., and Diao, T. (2017). Ni(I)-catalyzed reductive cyclization of 1,6-dienes: mechanism-controlled trans selectivity. Chem *3*, 268–280.

78. Currently, using a chiral pyrox ligand has demonstrated a moderate but not excellent level of enantioselectivity. Progress in this area will be reported in due course.