Practical carbon–carbon bond formation from olefins through nickel-catalyzed reductive olefin hydrocarbonation

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New carbon–carbon bond formation reactions expand our horizon of retrosynthetic analysis for the synthesis of complex organic molecules. Although many methods are now available for the formation of C(sp²)–C(sp³) and C(sp³)–C(sp³) bonds via transition metal-catalyzed cross-coupling of alkyl organometallic reagents, direct use of readily available olefins in a formal fashion of hydrocarbonation to make C(sp²)–C(sp³) and C(sp³)–C(sp³) bonds remains to be developed. Here we report the discovery of a general process for the intermolecular reductive coupling of unactivated olefins with alkyl or aryl electrophiles under the promotion of a simple nickel catalyst system. This new reaction presents a conceptually unique and practical strategy for the construction of C(sp²)–C(sp³) and C(sp³)–C(sp³) bonds without using any organometallic reagent. The reductive olefin hydrocarbonation also exhibits excellent compatibility with varieties of synthetically important functional groups and therefore, provides a straightforward approach for modification of complex organic molecules containing olefin groups.
Olefins are important synthons in organic chemistry\(^1,2\). They are readily available as stable and inexpensive compounds with great diversity. Simple olefins are both raw materials and products in petrochemical industry. For example, ethylene is produced mostly through steam cracking. They are converted to higher olefins, polyethylene materials and various commodity chemicals\(^3\). On the other hand, olefin groups are also widely represented in natural products with complex structures and many functional groups. Not only the extensive source but also the unique chemical reactivity of olefins attracts chemists, as the olefin moieties are resistant to a good number of synthetic transformations. Some unique transition metal catalyst systems can activate the olefin double bonds leading to highly elegant as well as useful reactions. Famous examples include the Wacker process\(^4\), olefin metathesis\(^1,5\), olefin hydroformylation\(^6\) and Heck reaction\(^7\) that have been extensively used in the preparation of complex organic molecules both in laboratory and in industry. These reactions establish the central role of olefins in modern synthetic organic chemistry as well as fine chemical industry\(^8\).

More recently, unactivated olefins have been used directly as chemical input in some novel cross-coupling reactions (for example, carbon-heteroatom coupling reactions\(^9\)–\(^15\) and few examples of carbon–carbon coupling reactions\(^16\)–\(^20\)). These findings suggest that olefins can be recognized as nucleophilic radical equivalents\(^9\)–\(^10,12,15,17,20\) or alkylmetals equivalents\(^11,13,14,18,19,21–23\) from a novel perspective. In some of these emerging methods that involve transition metal catalysts (Cu (ref. 22), Fe (refs 9,20), Co (ref. 15), Mn (ref. 24) and so on), silanes were used as hydride source as well as reductant. New reactions that use olefins as chemical input are expected to bring new opportunities to organic synthesis. For instance, use of olefins to replace alkylmetallic reagents in traditional cross-coupling reaction fashion\(^25\) (for example, Kumada coupling reaction) with aryl/alkyl electrophiles would have appealing advantages such as better functional group compatibility and broader substrate availability.

We now report the discovery of a new catalytic reaction of olefins, namely, Ni-catalyzed intermolecular reductive olefin hydrocarbonation between olefins and alkyl/aryl halides in an anti-Markovnikov fashion. This reaction provides an efficient strategy for the construction of carbon–carbon bonds\(^26,27\) from more stable and less expensive substrates as compared with the existing methods using organometallic reagents\(^25,26–30\). In terms

| Table 1 | Optimization of reaction conditions for reductive olefin hydrocarbonation reaction. |
|---|---|

1.  0.2 mmol
2.  0.5 mmol
3.  10% NiBr2.diglyme, 15% ligand
4.  3.0 equiv. DEMS, 3.0 equiv. Na2CO3
5.  0.6 ml DMAc, 30 °C, 12 h

Ligands:

- L1*: \([\text{MeN}2\text{N}]\text{NiCl}\)
- L2: \(\text{tBu-Terpy}\)
- L3: \(\text{Pybox}\)
- L4: \(R_1 = \text{Ph}, R_2 = \text{H}, R_3 = \text{H}\)
- L5: \(R_1 = \text{Me}, R_2 = \text{Me}, R_3 = \text{H}\)
- L6: \(R_1 = \text{H}, R_2 = \text{H}, R_3 = \text{Me}\)
- L7: \(R = \text{OMe}\)
- L8: \(R = \text{tBu}\)
- L9*: \(R = \text{Ph}\)
- L10*: \(R = \text{Cy}\)
- L11: \(\text{IPr}\)

*For L1, NiBr2.diglyme was not added, †For L9 or L10, 20% Ligand was added. DEMS, Diethoxymethylsilane; DMAc, N,N-dimethylacetamide; Diglyme, diethylene glycol dimethyl ether.
of practicality, the reaction shows high levels of 'chemo'- and 'regio'-selectivity, so that a wide range of sensitive functional groups can be tolerated (for example, epoxide, aldehyde and alcohol) in the transformation with minimal substrate protection necessary. As Ni-catalyzed carbon–carbon bond formation processes have enjoyed great success in modern synthesis, the present reaction is expected to find important applications in organic chemistry.
**Results**

**Reaction discovery.** We screened various Ni catalysts, base, silane and solvents for the reductive olefin hydrocarbonation reaction of 1-octene with 1 (see Table 1 and Supplementary Tables 1–5). The pincer complex L1 was tested first, but only trace amount of desired product was obtained with large amount of alkyl iodide recovered. Then we tested the terpyridine ligand L2 and pybox ligand L3. Higher conversion of alkyl iodide was observed but the yield was only slightly improved. To our delight, we observed significant formation of the desired product with the phenanthroline family ligands L4 and L5. We then tested L6 bearing an ortho-methyl group but L6 was inferior. On the other hand, a bipyridine ligand L7 exhibited much better reactivity. Remarkably, when 4,4′-di-tert-butyl-2,2′-bipyridine (L8) was used, the GC yield increased to 96% with an isolated yield of 93% for the desired product. We also tested some monodentate phosphine ligands (L9 & L10) and carbene ligand (L11), but they were not effective.

**Substrates scope.** The substrate scope of the reductive olefin hydrocarbonation reaction was shown in Table 2. A variety of carbon electrophiles and olefins with different functional groups could be readily converted to the desired products with modest to excellent yields (30–93%). Not only alkyl iodides (for example, 3), bromides (for example, 13) and tosylates (for example, 30) were good substrates, but also aryl iodides (for example, 28) could be transformed successfully. With respect to olefins, both mono-substituted (for example, 26) and 1,1-di-substituted alkenes (for example, 31) could be used. Because of the mild reaction conditions, a wide range of synthetically relevant functional groups could survive the transformation. For instance, ether (4–6), ester (7), fluoride (8), trifluoromethyl (9), carbamate (10–11), sulfonamide (12–13), amine (14), aryl chloride (15) and bromide (16) were well tolerated. Heterocycles such as thiophene (17), furan (18), and pyridine (19) could also be used in the reaction. Several base-sensitive groups, such as nitrile (20) and ketone (29, 32) posed no problem. Even more active groups, such as unprotected benzaldehyde (21) and azo groups (22), were compatible with the reaction. As an interesting substrate, 23 containing a pinacol boronate ester (35) could selectively undergo the reductive olefin hydrocarbonation reaction with its carbon–boron bond intact. To our surprise, the reaction could even be conducted in the presence of an epoxide group (36) (24) or an unprotected OH group (25). Noteworthy, an internal alkene (11, 14) (for example, 33) could have been converted in the reaction, although further ligand optimization was needed to improve the yields.

**Modification of complex molecules.** To further demonstrate the high degree of functional group compatibility of the reductive olefin hydrocarbonation reaction (Fig. 1), we exploited its use as a novel tool for the modification of complex biologically interesting molecules (Fig. 2). As an example, a cholesterol derivative (34) could react with 35 to produce 36 without affecting either the internal alkene or alcohol groups (Fig. 2a). Hecogenin derivative (37), which contained both ketal and ketone groups, was also a good substrate for the modification process (Fig. 2b). Furthermore, calciferol (40) was converted to 42 selectively in the presence of the hydroxyl, internal alkene and even 1,3-diene groups (Fig. 2c).

Modification of a cinchonidine derivative (43) resulted in the 'chemo'-selective formation of 44, while tolerating both the amino group and quinoline structure (Fig. 2d, left). Single-crystal XRD analysis of 44 confirmed that the skeleton of cinchonidine was fully maintained during the modification process. In addition, the coupling of quinine (46) and a fructose derivative (45) enabled the production of highly complex molecules in a convergent fashion (Fig. 2d, right).

The reductive olefin hydrocarbonation reaction of sclareol (48) proceeded smoothly in the presence of different two tertiary
Figure 2 | Modification of complex molecules. (a) 10% NiBr$_2$.diglyme, 15% L8, 3.0 equiv. DEMS, 3.0 equiv. Na$_2$CO$_3$, 2 ml DMAc, 30 °C, 12 h. (b) The same conditions as in a, the newly formed carbon–carbon bond was between C10 and C11. (c) 20% NiBr$_2$.diglyme, 30% L8, 3.0 equiv. DEMS, 3.0 equiv. Na$_2$CO$_3$, 2 ml DMAc, 30 °C, 12 h. (d) conditions for compound 44: 20% NiBr$_2$.diglyme, 30% L8, 3.0 equiv. DEMS, 2.0 equiv. Na$_2$CO$_3$, 2 ml THF/DMAc (v/v = 1/3), 30 °C, 12 h, the newly formed carbon–carbon bond was between C19 and C20; conditions for compound 47: same conditions as in c. (e) Same conditions as in c. (f) 20% NiBr$_2$.diglyme, 30% L8, 4.0 equiv. DEMS, 4.0 equiv. Na$_2$CO$_3$, 2 ml DMAc, 30 °C, 12 h. Bn, benzyl; Bz, benzoyl; TMS, trimethylsilyl.
alcohol groups (Fig. 2e). In a more complex example with pleuromutilin (50) (Fig. 2f), we obtained the desired product (52) in 28% yield (with 40% recovery of starting material) despite the presence of carbamate, ester, ketone, unprotected primary and secondary alcohol groups in the reactant. Therefore, the reductive olefin hydrocarbonation reaction presents attractive opportunities for the modification of natural products or other complex molecules.

Other applications. Ethylene, as the simplest and most abundant olefin, has been attracting increasing attentions in synthetic organic chemistry. We were delighted that ethylene as C2 source in olefin, has been attracting increasing attentions in synthetic applications. Other applications for the modification of natural products or other complex molecules.

To gain more insights into the reaction mechanism, radical clock experiments were carried out (Fig. 3c). Compound 61 containing a cyclopropyl ring was used as radical clock substrate (Fig. 3c, top). In this coupling reaction, we obtained only the ring-opened product 62 in 34% isolated yield. We also tested the reaction with (Z)-8-iodooct-3-ene (63) (Fig. 3c, bottom). A mixture of linear coupling product (64a) and ring-cyclized product (64b) was obtained with a ratio of 3:1. The formation of ring-cyclized product (64b) revealed that this reaction proceeds through a radical cyclization process. Finally, we took advantage of optical pure secondary alkyl bromide (65) to study the stereochemistry of this reductive olefin hydrocarbonation reaction (Fig. 3d). When (S)-65 was alkylated with 1-hexene, we obtained a racemic product (67) in 37% yield. Furthermore, radical inhibiting experiment using TEMPO (2,2,6,6-tetramethylpiperidinoxyl) as a radical trap was carried out (see Supplementary Discussion). The reaction was largely inhibited when 0.2 equiv. TEMPO was added, indicating a radical type reaction mechanism. Nonetheless, details for the mechanism of this reaction are not clear at present. Further investigations are ongoing in our lab.

In summary, we have developed a practical and user-friendly method for the formation of carbon–carbon bonds through Ni-catalyzed intermolecular coupling of aryl or alkyl electrophiles with olefins under reductive conditions. This newly developed reductive olefin hydrocarbonation reaction provides a useful and general approach for the construction of carbon–carbon bonds by directly using olefins as nucleophile precursors. This reaction exhibited excellent compatibility with varieties of synthetically important functional groups and therefore, provided an efficient...
new approach for the modification of complex molecules. Our next challenge was the development of asymmetric version of this new carbon–carbon bond forming reaction and its extension to internal olefins.

**Methods**

**Materials.** For NMR and high-performance liquid chromatography spectra of compounds in this manuscript, see Supplementary Figs 1–119. For details of the synthetic procedures, see Supplementary Methods. For X-ray data see Supplementary Data 1.

**Procedure.** NiBr₂-diglyme (7.0 mg, 0.02 mmol, 10 mol%), 4,4′-di-tert-butyl-2′-hippuridine (8.0 mg, 0.03 mmol, 15 mol%) and Na₂CO₃ (42.4 mg, 0.4 mmol, 2.0 equiv.) were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with argon (three cycles). To these solids, 0.6 ml DMAC was added under argon atmosphere. The reaction mixture was stirred at room temperature for 30 s. To the reaction mixture, electrophile (0.2 mmol, 1.0 equiv.), alkene (0.3 mmol, 1.5 equiv.) and DMS (0.4 mmol, 2.0 equiv.) were added under a positive flow of argon. The reaction mixture was stirred at 30 °C for 12 h. To remove the DMAC, the reaction mixture was poured into 50 ml of ice water and the resulting mixture was extracted with ethyl acetate (4 × 30 ml). The combined organic layer was dried over Na₂SO₄, filtered, concentrated in vacuum and purified by column chromatography on silica gel.

**References**

1. Hoveyda, A. H. & Zhugraln, A. R. The remarkable metal-catalyzed olefin hydroamination reaction. Nature 450, 243–251 (2007).
2. Williams, J. M. I. Preparation of Alkenes: A Practical Approach (Oxford University Press, 1996).
3. Saini, V., Stokes, B. J. & Sigman, M. S. Transition-metal-catalyzed laboratory-scale carbon-carbon bond-forming reactions of ethylene. Angew. Chem. Int. Ed. 52, 11206–11220 (2013).
4. Takacs, J. M. & Jiang, X. The Wacker reaction and related alken oxide reactions. Curr. Org. Chem. 7, 369–396 (2003).
5. Connon, S. J. & Blecher, S. Recent developments in olefin cross-metathesis. Angew. Chem. Int. Ed. 42, 1900–1923 (2003).
6. Evans, P. A. Modern Rhodium-Catalyzed Organic Reactions 93–110 (Wiley-VCH, 2005).
7. Meijere, A. D. & Diederich, F. Metal-Catalyzed Cross-Coupling Reactions 2nd edn 217–315 (Wiley-VCH, 2005).
8. Corey, E. J. & Chen, X.-M. The Logic of Chemical Synthesis (John Wiley & Sons, Inc., 1995).
9. Leggans, E. K., Barker, T. J., Duncan, K. K. & Boger, D. L. Iron(III)/NaBH₄-mediated addition to unactivated alkenes: synthesis of novel 20′-Vinblasting analogues. Org. Lett. 14, 1428–1431 (2012).
10. Gaspar, B. & Carreira, E. M. Catalytic hydrochlorination of unactivated olefins with para-toluensulfonyl chloride. Angew. Chem. Int. Ed. 47, 5758–5760 (2008).
11. Yang, Y., Shi, S.-L., Niu, D., Liu, P. & Buchwald, S. L. Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. Science 349, 62–66 (2015).
12. Gui, J. et al. Practical olefin hydroamination with nitroarenes. Science 348, 886–891 (2015).
13. Sakae, R., Hirano, K. & Miura, M. Ligand-controlled regiodivergent Cu-catalyzed amination of unactivated terminal alkynes. J. Am. Chem. Soc. 137, 6460–6463 (2015).
14. Xi, Y., Butcher, T. W., Zhang, J. & Hartwig, J. F. Regioselective, asymmetric formal hydroamination of unactivated internal alkenes. Angew. Chem. Int. Ed. 55, 776–780 (2016).
15. Waser, J. & Carreira, E. M. Convenient synthesis of alkylhydrazides by the Cobalt-catalyzed hydrodrazinolysis reaction of olefins and azodicarbonylates. J. Am. Chem. Soc. 126, 5676–5677 (2004).
16. Gaspar, B. & Carreira, E. M. Mild cobalt-catalyzed hydrosilylation of olefins with tosyl cyanide. Angew. Chem. Int. Ed. 46, 4519–4522 (2007).
17. Lo, J. C., Gui, J., Yabe, Y., Pan, C. M. & Baran, P. S. Functionalized olefin cross-coupling to construct carbon-carbon bonds. Nature 516, 343–348 (2014).
18. Yang, Y.-M., Atkinson, N. C., Placeves, A. L., Zhu, S. & Buchwald, S. L. Enantioselective synthesis of carbonyl- and heterocycles through a CuH-catalyzed hydroalkylation approach. J. Am. Chem. Soc. 137, 10524–10527 (2015).
19. Su, W. et al. Ligand-controlled regiodivergent copper-catalyzed alkylation of alkenes. Angew. Chem. Int. Ed. 54, 12957–12961 (2015).
20. Lo, J. C., Yabe, Y. & Baran, P. S. A practical and catalytic reductive olefin coupling. J. Am. Chem. Soc. 136, 1304–1307 (2014).
21. Maksymowicz, R. M., Roth, P. M. C. & Fletcher, S. P. Catalytic asymmetric carbon-carbon bond formation using alkenes as alkylidene equivalents. Nat. Chem. 4, 649–654 (2012).
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Author contributions

X.L. and B.X. contributed equally to this work. X.L. and B.X. designed and carried out the experimental work. Z.Z., T.G., W.S. and J.Y. helped to complete the experimental work. Y.F. and L.L. directed the project and wrote the manuscript.

Additional information

Accession codes: The X-ray crystallographic structures for 39 and 44 reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 1439076 and 1439084, see Supplementary Data 1, the data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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