ORGANIC CHEMISTRY

E-Olefins through intramolecular radical relocation

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Full control over the selectivity of carbon–carbon double-bond migrations would enable access to stereochemically defined olefins that are central to the pharmaceutical, food, fragrance, materials, and petrochemical arenas. The vast majority of double-bond migrations investigated over the past 60 years capitalize on precious-metal hydrides that are frequently associated with reversible equilibria, hydrogen scrambling, incomplete *E/Z* stereoselection, and/or high cost. Here, we report a fundamentally different, radical-based approach. We showcase a nonprecious, reductant-free, and atom-economical nickel $(Ni)^{(I)}$-catalyzed intramolecular 1,3-hydrogen atom relocation to yield *E*-olefins within 3 hours at room temperature. Remote installations of *E*-olefins over extended distances are also demonstrated.

The carbon–carbon double bond in olefins serves as a precursor to a rich array of transformations and is a cornerstone in the materials, pharmaceutical, agrochemical arenas, and food industry (*1*, *2*). Its construction in a selective and stereochemically defined manner—i.e., *E* versus *Z* olefin—is of utmost importance, as the geometry is ultimately coupled to function. Although numerous strategies to construct olefins have become established textbook knowledge, the *E/Z* selectivity is frequently incomplete or comes at the expense of valuable functionality in these classical approaches (e.g., Wittig, Julia, Peterson olefinations or Birch reduction). Mixtures of *E* and *Z* isomers are difficult to separate, however. More modern catalytic strategies commonly achieve high selectivity through semihydrogenations, requiring an atmosphere of H_2 or stoichiometric amounts of acid or other H sources (*3*). Olefin metathesis catalysts were developed to selectively access *Z*-olefins, whereas the *E*-isomer is accessible in high selectivity only with certain halogenated or low-functionality compounds (*4*, *5*). Ring-opening strategies via C–C cleavage are elegant alternatives to selectively install *E*-olefins (*6*, *7*).

Double-bond shifts of allyl precursors constitute a potentially powerful alternative strategy, as the allyl group can be installed readily, and the desired *E*-geometry may subsequently be set in a catalytic and atom-economical transformation (*8*, *9*, *10*). This goal cannot be reached through classical synthetic approaches, as direct sigmatropic hydrogen shifts are geometrically inaccessible in the required antarafacial sense. Although base may be used to mediate double-bond migration [at ~200°C, as used on an industrial scale (*9*)], the *E/Z* ratios of the resulting double bonds are modest (~80:20), and the process is incompatible with sensitive functionality and generates stoichiometric amounts of waste. Metal catalysis can potentially circumvent these drawbacks (see below) and may also unleash the possibility for remote functionalization. As such, metal-catalyzed alkene isomerizations have had major societal and industrial impact, e.g., in the large-scale production of gasoline, nylon, detergents, soaps, coatings, lubricants, food, cosmetics, rubbers, and fragrances (*2*).

The past 60 years of research focused primarily on two mechanisms for double-bond transposition (*11*): The vast majority of transformations proceed via metal hydrides. Whereas the precious-metal hydrides deliver an external H through closed-shell polar mechanisms (*9*, *11*), less-precious metal hydrides, such as Co, have been shown to engage in reversible hydrogen atom transfer via biradical pairs (Fig. 1A) (*12*, *13*). These processes make use of external H (that is present as co-reagent). Because of the reversible nature of these reactions, scrambling of hydrogens may occur, and control of *E/Z* selectivity is challenging. The *E*-selectivity is generally much higher for the precious-metal hydride processes that proceed through 1,2-addition, followed by β-hydride elimination (Fig. 1A) (*9*). The latest advance in this area is from Skrydstrup's laboratory employing in situ–generated Pd-H at elevated temperatures (*14*). The possibility for hydride-free binuclear Pd-catalyzed isomerization was recently also reported (*15*). An alternative mechanistic scenario involves the less well-described π-allyl mechanism (Fig. 1B) that proceeds by means of 1,3-addition (*11*). Examples include isomerizations involving zirconocenes (Bu_2ZrCp_2) (*16*) and Grotjahn's highly active Ru catalyst that delivers *E*-olefins with excellent selectivities via a hemilabile ligand that acts as a base (*17*).

In light of the ever-increasing demands for greater sustainability, particularly for processes of societal and industrial relevance, a key challenge in this arena is to overcome the need for precious-metal catalysts and/or stoichiometric additives (and waste) (*9*, *18*). Ru has an Earth abundance of only 10^{-7}% and a considerable associated cost (*19*). By contrast, nickel is nonprecious, relatively cheap and abundant (~90,000 times more than Ru), and capable of triggering double-bond migration, albeit in varying *E/Z* ratios and so-far limited generality (*20*). This reactivity has been linked to $Ni^{(II)}$-H as active species.

We envisioned that a simplified mechanistic scenario that minimizes co-reagents and intermediates may increase the likelihood for *E/Z* control under nonprecious Ni catalysis in double-bond migrations. Arguably, the simplest scenario involves the direct delivery of a hydrogen from position 1 to 3 in the allylic framework. Given that radicals are not subject to the Woodward–Hoffmann orbital symmetry restrictions, we hypothesized that a radical-induced 1,3-H shift could deliver a solution to the *E/Z* selection challenge. The intermediacy of high-energy free organic radicals would need to be avoided in this context, as additional challenges, such as intermolecular H atom transfer events for radical termination and chain propagation, would arise, and these scenarios are known to deliver moderate selectivities (see Fig. 1A). We envisioned instead that if the substrate were coupled to a nonprecious metalloradical complex, such as a low-coordinate $Ni^{(I)}$ (*21*)—e.g., via π-coordination—the resulting metalloradical-substrate complex might have an inherent driving force for internal reorganization.

As part of our ongoing program in odd-oxidation-state metal reactivity, we also studied the propensity of dimeric metal complexes in the +1 oxidation state to generate open-shell monomers (*22*). Our findings suggest that for certain complexes of suitable ligand environment, such as the dinuclear *N*-heterocyclic carbene (NHC)–derived $Ni^{(I)}$ dimer **1** (Fig. 2) (*23*), which is readily accessible at low cost from commercially available precursors, a double bond or solvent could function as a trigger to generate an open-shell metal complex.

When we subjected $[Ni(\mu\text{-}Cl)IPr]_2$ dimer **1** to 4-methoxyallylbenzene **2**, selective generation of the corresponding isomerized *E*-alkene **3** was observed. After evaluating different reaction parameters, we found that *E*-olefin **3** was generated quantitatively and exclusively (*24*) within 3 hours at room temperature in chlorobenzene (Fig. 2A).

To gain further insight, we subjected $Ni^{(I)}$ catalyst **1** to a mixture of substrate **4** and the deuterium-labeled **5-d_1** (containing >98% deuterium enrichment). We did not observe isotopic scrambling and instead formed **6** and **7-d_1** as the exclusive products, regardless of whether the reaction was run in deuterated or nondeuterated solvent (Fig. 2B and fig. S11 to S14). These data provide strong support that the solvent does not act as a source of hydrogen/deuterium and that the 1,3-H shift proceeds exclusively intramolecularly. Our further investigation of the catalytic reaction with paramagnetic proton nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) spectroscopic analyses showed clear indications of radicals being present (see figs. S19 to S22 for details). We

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therefore next performed a radical clock experiment and subjected catalyst **1** to *cis*-diphenylcyclopropenyl olefin **8**. The stereochemical integrity of **8** is highly sensitive to transient radical character (*25*). Although free organic phenylcyclopropylcarbinyl radicals are known to undergo rapid ring opening (*26*), this is not necessarily expected for the $Ni^{(I)}$-induced radical character at the olefin. Our calculations suggest the opening to be endergonic and hence reversible under $Ni^{(I)}$ coordination. Our ^{1}H-NMR spectroscopic analysis indicated that 28% of the *trans*-olefin (*trans*-**8**) was formed in a mixture with the cis-isomer, which is a strong indication of radical intermediates. All our additional tests with probe **8** and alternative metal species that are known to isomerize double bonds or could potentially be derived from $Ni^{(I)}$ dimer **1** [i.e., $Ni^{(II)}$ or $Ni^{(0)}$] did not show cis-to-trans isomerization (see Fig. 2B, fig. S18, and table S1).

With these experimental data in strong support of a radical mechanism, we turned to computational studies (*27*). The bulky $Ni^{(I)}$ dimer was found to be too shielded to allow for direct reactivity with the alkene. Instead, a substrate- or solvent-assisted homolytic cleavage of the dimer to a substrate-$Ni^{(I)}$ monomer complex is favored. This generates a metal-substrate complex with overall radical character (Fig. 2C). A relatively facile H atom transfer to the Ni center then takes place, generating a shallow intermediate that rapidly relocates the H atom to the organic moiety so as to generate the more stable Ni-substrate radical complex. No movement of the metal occurs while the H atom migrates. The pathway leading to the *E*-olefin is calculated to be favored (by $\Delta\Delta G^{\ddagger}$ = 6.6 kcal/mol) over the *Z*-pathway. These findings are in line with the excellent *E*-selectivity, EPR-activity, and the observed lack of H/D scramblings, as no stable intermediates are generated and, therefore, no sufficient time is available for exchange processes. This mechanism is therefore in stark contrast to established metal-hydride reactivity.

With the fundamentally different mechanism established, we set out to explore the generality of the process. Our isomerization shows a wide scope with short reaction times and excellent selectivities (Fig. 3). We succeeded in efficiently isomerizing the methoxyarene-derived anethole, eugenol, and safrole in excellent yield and *E*-selectivity (>98:2) at room temperature to the corresponding trans-products (**3, 6, 9** to **11**). These substrate classes are in considerable industrial demand, with anethole alone being produced on a million-ton scale per year.

Our protocol is efficient toward substrates with electron-withdrawing functional groups such as ketone or ester (**14**, **15**), the pharmaceutically relevant trifluoromethyl, and potentially coordinating amine groups (**16**, **17**). Functional groups that are frequently reactive in typical precious-metal catalysis—e.g., nitrile (**20**), bromide (**13**), or boronic ester (**23**)—were also tolerated (Fig. 3). These groups are of utmost value for further orthogonal manipulations and build-up of molecular complexity. Multiple migrations

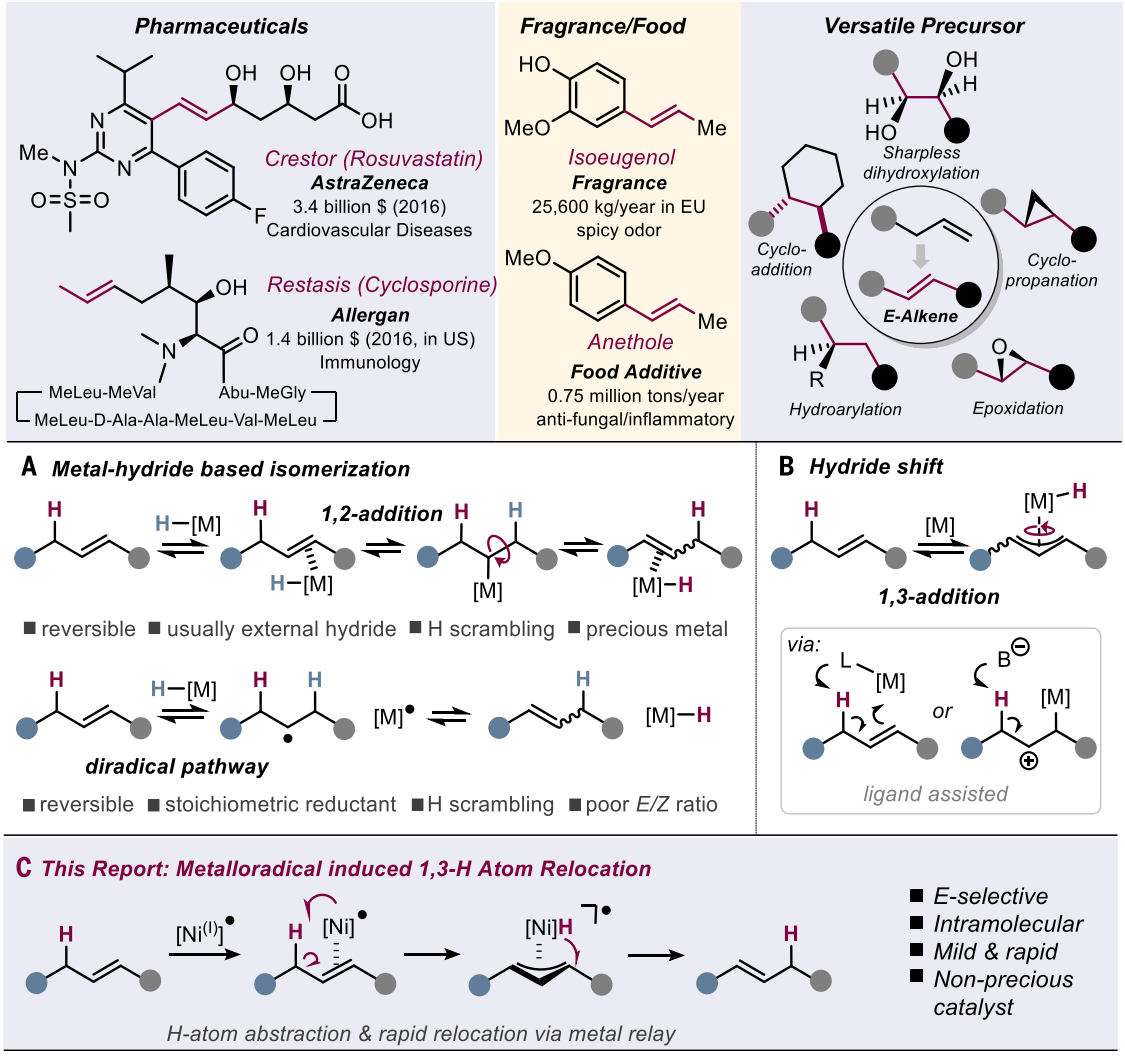


Fig. 1. Prevalence of *E*-olefins and isomerization-based methods to access them. Top: Importance of *E*-alkene in pharma, food, and fragrance industries and synthesis (*36*–*38*). Middle (**A** and **B**) Known mechanisms for metal-catalyzed isomerization. (**C**) This work. EU, European Union.

can also be executed in the same molecule (**25**). Moreover, selected oxygen-containing substrates (**14**, **34**) reacted in higher yields in the presence of a catalytic amount of $Ti(O^iPr)_4$.

The migration proceeds equally selectively and efficiently at a 1-g scale (with **13**), and the product is amenable to straightforward purification. A quantitative conversion is seen in only 3 hours at room temperature at 5 mol % catalyst loading (*28*); however, a lowering to 1 to 2 mol % is also possible but requires longer time at room temperature (24 hours). The *E*-selectivity remains unchanged and is independent of the catalyst loading. Moreover, for those substrates that are liquids, the reactions may also be run solvent-free. In this context, we isomerized neat estragole (a naturally occurring liquid) to the industrially produced anethole **3** in >99:1 *E/Z* selectivity [>99% conversion, 96% yield] in 16 hours using 5 mol % of catalyst. Considering that solely the nonprecious catalyst and the substrate are required, the process should have considerable potential also in an industrial context.

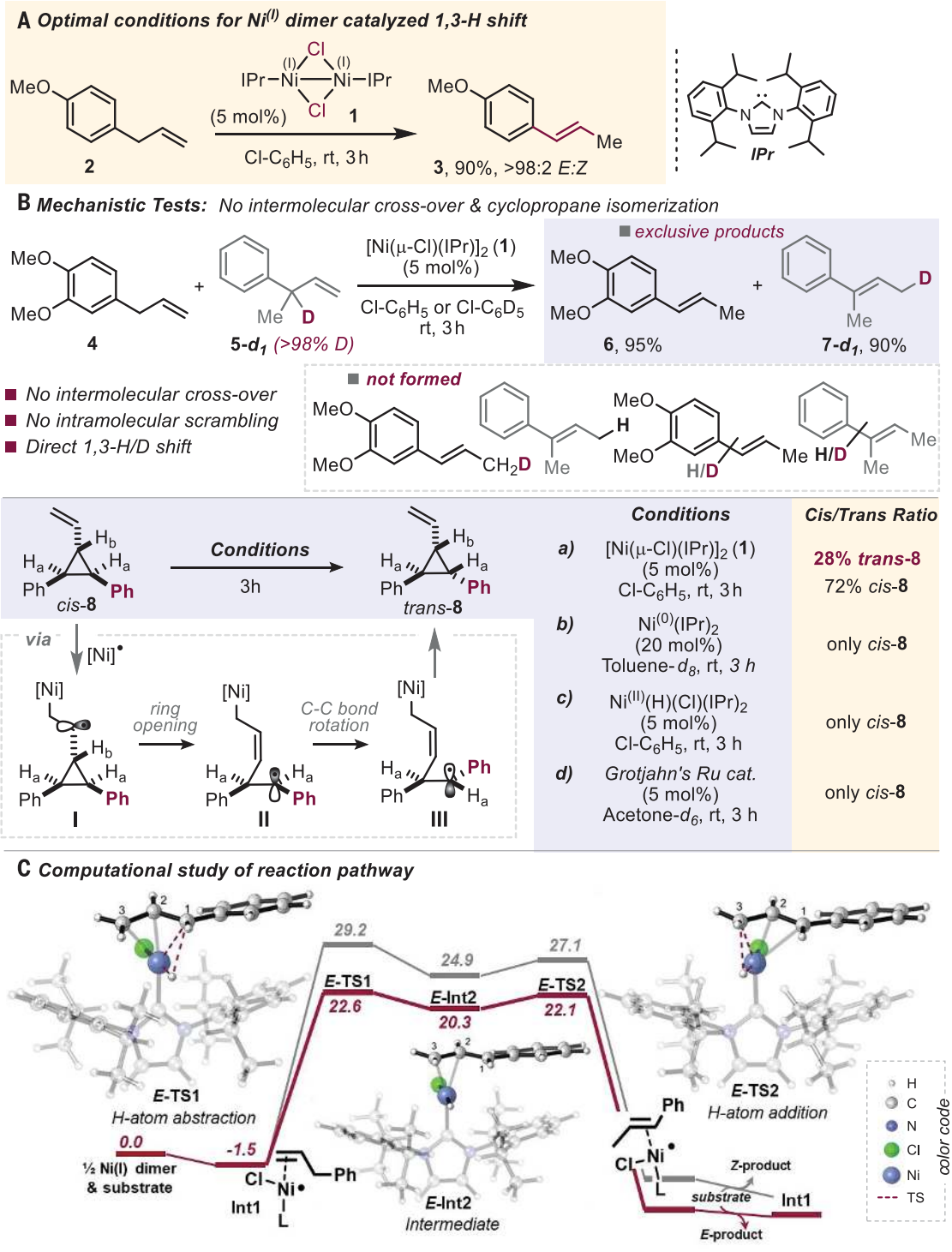


Fig. 2. Ni(I)-catalyzed 1,3-H atom shift. (**A**) Test reaction. (**B**) Experimental mechanistic studies. (**C**) Computational studies. Free-energy diagram in kcal/mol, calculated at CPCM(chlorobenzene) M06L/def2-TZVP//ωB97XD/6-31G(d)(SDD) at room temperature (*27*). cat., catalyst; TS, transition state.

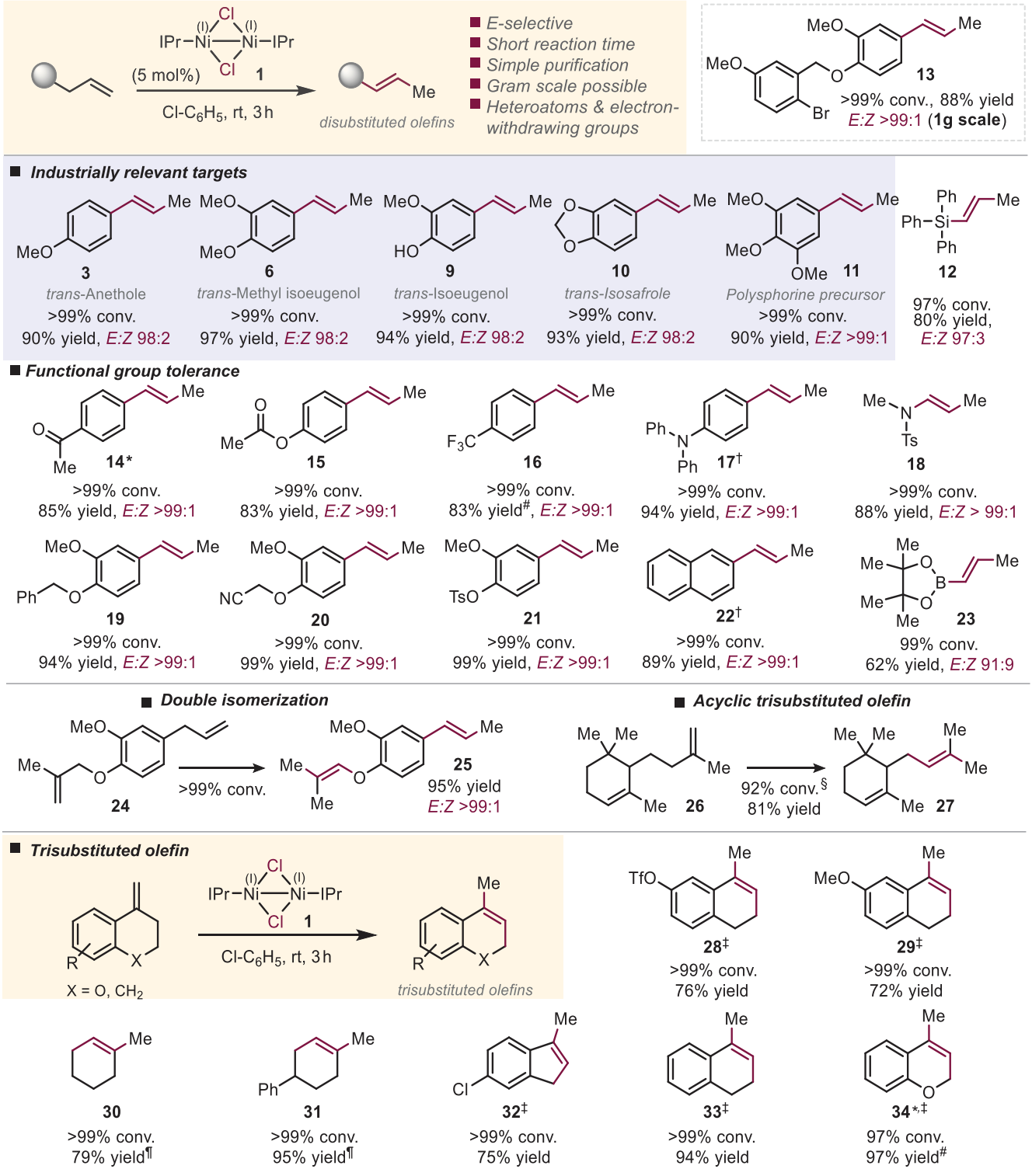
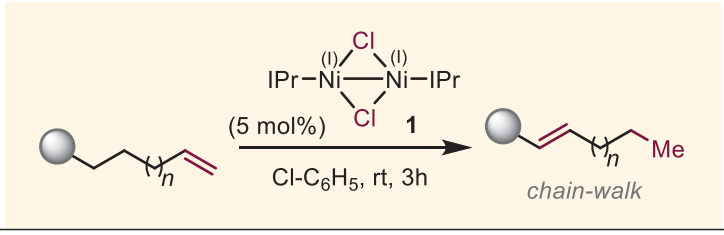
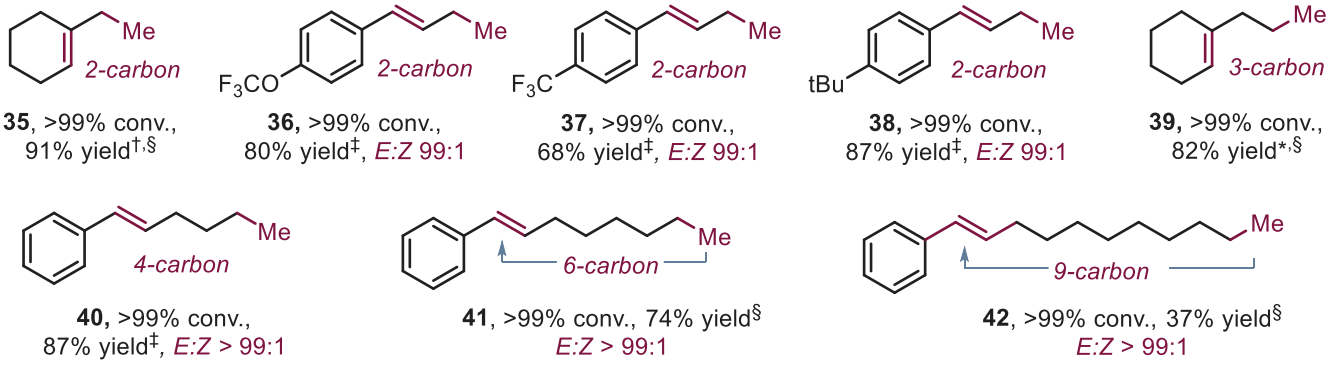


Fig. 3. Scope of 1,3-H atom shift. Conditions: **1** (5 mol %), olefin (1.0 equiv.) in chlorobenzene (0.4 M) (except **30** in CH_2Cl_2) (*24*), *10 mol % $Ti(O^iPr)_4$, †48 hours, ‡10 mol % catalyst, §20 mol % catalyst. ¶Small amount (≤5%) of inseparable alternative isomer was also detected. #Yield determined by ^{1}H-NMR against added internal standard. conv., conversion; equiv., equivalent; rt, room temperature.

Another challenge in double-bond migrations is application to higher substitution patterns, such as disubstituted and cyclic olefins (*29*). Our $Ni^{(I)}$ radical-based isomerization proved to be efficient to transform acyclic 1,1-disubstituted olefins (**27**) and to afford various cyclic olefin derivatives containing functional groups (-Cl, -OMe, -OTf) or heteroatoms (**34**) with high yield and exclusive regioselectivity (**28**, **29**, **32** to **34**). Only for **30** and **31** could small amounts (≤5%) of an alternative isomer be detected by gas chromatography–mass spectrometry (GC-MS). Although chlorobenzene generally proved to be an excellent solvent, it may be inconvenient for the preparation of volatile products, such as **30**.





35, >99% conv., 91% yield†,§

36, >99% conv., 80% yield‡, *E:Z* 99:1

37, >99% conv., 68% yield‡, *E:Z* 99:1

38, >99% conv., 87% yield‡, *E:Z* 99:1

39, >99% conv., 82% yield*,§

40, >99% conv., 87% yield‡, *E:Z* > 99:1

41, >99% conv., 74% yield§ *E:Z* > 99:1

42, >99% conv., 37% yield§ *E:Z* > 99:1

Fig. 4. Chain walking. Conditions: 0.4 M olefin in chlorobenzene (or *in CH_2Cl_2), 5 mol % **1** (†10 mol %). ‡Small amount (≤5%) of inseparable alternative internal isomer was also detected. §Yields were determined by ^{1}H-NMR against added internal standard (*24*).

We found dichloromethane to be a suitable alternative in this case, allowing **30** to be isolated in 83% yield.

Our mechanistic analysis suggested that a double-bond migration over more than one bond should also be feasible. Migrations of double bonds over extended carbon skeletons are more generally termed chain walking (*30*, *31*) and constitute a strategy in relation to remote functionalizations (*32*, *33*). Upon subjection of catalyst **1** to various substrates (Fig. 4), double-bond migrations occurred efficiently and with exclusive *E*-selectivity in 3 hours at room temperature, showing that *E*-olefins can also be installed remotely. Whereas for the two-, three-, or four-carbon chain walks (**35** to **38**, **40**) the benzylic olefin was formed in high yield (with ≤5% of alternative internal isomers according to uncalibrated GC-MS analysis), when moving to longer chains (>4 carbons, i.e., **41**, **42**) or nonaromatic driving forces (**39**), significant amounts of alternative internal double-bond isomers were observed (*34*). Whereas Pd-catalysis such as [(Cl)(H)Pd$^{(II)}$($PtBu_3$)$_2$] (*14*) primarily yields one-bond isomerizations, *E*-selective chain walks are otherwise achieved under Ru catalysis (*35*) (with similar or lower driving force) (see fig. S23).

Overall, our protocol combines operational simplicity, ease of purification, sustainability (no additional reagents, nonprecious metal, potential for solvent-free reactivity), and scalability with functional group tolerance, short reaction times, and mild conditions.

REFERENCES AND NOTES

1. R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations* (VCH, ed. 2, 1999).
2. C. R. Larsen, D. B. Grotjahn, "The value and application of transition metal catalyzed alkene isomerization in industry" in *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Four Volumes*, Boy Cornils, Wolfgang A. Herrmann, Matthias Beller, Rocco Paciello, Eds. (Wiley, 2017), pp. 1365–1378.
3. A. Fürstner, *J. Am. Chem. Soc.* **141**, 11–24 (2019).
4. T. T. Nguyen *et al.*, *Science* **352**, 569–575 (2016).
5. T. S. Ahmed, R. H. Grubbs, *J. Am. Chem. Soc.* **139**, 1532–1537 (2017).
6. A. Masarwa *et al.*, *Nature* **505**, 199–203 (2014).
7. P. H. Chen, B. A. Billett, T. Tsukamoto, G. Dong, *ACS Catal.* **7**, 1340–1360 (2017).
8. A. Vasseur, J. Bruffaerts, I. Marek, *Nat. Chem.* **8**, 209–219 (2016).
9. M. Hassam, A. Taher, G. E. Arnott, I. R. Green, W. A. L. van Otterlo, *Chem. Rev.* **115**, 5462–5569 (2015).
10. G. Hilt, *ChemCatChem* **6**, 2484–2485 (2014).
11. E. Larionov, H. Li, C. Mazet, *Chem. Commun. (Camb.)* **50**, 9816–9826 (2014).
12. S. W. M. Crossley, F. Barabé, R. A. Shenvi, *J. Am. Chem. Soc.* **136**, 16788–16791 (2014).
13. G. Li *et al.*, *J. Am. Chem. Soc.* **138**, 7698–7704 (2016).
14. D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **132**, 7998–8009 (2010).
15. E. H. P. Tan, G. C. Lloyd-Jones, J. N. Harvey, A. J. J. Lennox, B. M. Mills, *Angew. Chem. Int. Ed.* **50**, 9602–9606 (2011).
16. E. Negishi, J. P. Maye, D. Choueiry, *Tetrahedron* **51**, 4447–4462 (1995).
17. C. R. Larsen, D. B. Grotjahn, *J. Am. Chem. Soc.* **134**, 10357–10360 (2012).
18. M. Mayer, A. Welther, A. Jacobi von Wangelin, *ChemCatChem* **3**, 1567–1571 (2011).
19. Market price on 20 August 2018 at Infomine.com: Ru (~8200 $/kg), Ni (~13 $/kg)
20. H. J. Lim, C. R. Smith, T. V. RajanBabu, *J. Org. Chem.* **74**, 4565–4572 (2009).
21. C.-Y. Lin, P. P. Power, *Chem. Soc. Rev.* **46**, 5347–5399 (2017).
22. A. B. Dürr, H. C. Fisher, I. Kalvet, K.-N. Truong, F. Schoenebeck, *Angew. Chem. Int. Ed.* **56**, 13431–13435 (2017).
23. B. R. Dible, M. S. Sigman, A. M. Arif, *Inorg. Chem.* **44**, 3774–3776 (2005).
24. The literature does not always clearly specify how *E/Z* ratios were determined. We observe the *E*-isomer exclusively by ^{1}H-NMR for the vast majority of compounds; at best, a trace of the *Z*-isomer is observed in some cases, which quantifies to 1 to 2% in (uncalibrated) GC-MS analysis.
25. E. Cahard *et al.*, *Angew. Chem. Int. Ed.* **51**, 3673–3676 (2012).
26. S.-Y. Choi, P. H. Toy, M. Newcomb, *J. Org. Chem.* **63**, 8609–8613 (1998).
27. T. Sperger, I. A. Sanhueza, I. Kalvet, F. Schoenebeck, *Chem. Rev.* **115**, 9532–9586 (2015).
28. We did not specifically examine the exact reaction time necessary to reach full conversion for each substrate. Grotjahn and co-workers observed several cases of rapid (<30 min) reactions at room temperature with their Ru catalyst.
29. X. Liu *et al.*, *J. Am. Chem. Soc.* **140**, 6873–6882 (2018).
30. H. Sommer, F. Juliá-Hernández, R. Martin, I. Marek, *ACS Cent. Sci.* **4**, 153–165 (2018).
31. H. Schwarz, *Acc. Chem. Res.* **22**, 282–287 (1989).
32. F. Juliá-Hernández, T. Moragas, J. Cornella, R. Martin, *Nature* **545**, 84–88 (2017).
33. L. Lin, C. Romano, C. Mazet, *J. Am. Chem. Soc.* **138**, 10344–10350 (2016).
34. We also examined the isomerization of a mixture of *E/Z* internal double bond isomers, i.e., a 46:54 mixture of (*E*)- and (*Z*)-but-2-en-1-ylbenzene. Using 5 mol % over 24 hours delivered (*E*)-but-1-en-1-ylbenzene in 87% conversion and >98:2 *E/Z* selectivity.
35. D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair, A. Sharma, *J. Am. Chem. Soc.* **129**, 9592–9593 (2007).
36. www.statista.com/markets/412/topic/456/pharmaceutical-products-market/.
37. S. K. Sharma, V. K. Srivastava, R. V. Jasra, *J. Mol. Catal. Chem.* **245**, 200–209 (2006).
38. "HERA Risk Assessment of Isoeugenol 2005".

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/363/6425/391/suppl/DC1
Materials and Methods
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E-Olefins through intramolecular radical relocation

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Olefin shuffle for just a nickel

Controlling the geometry of carbon-carbon double bonds is a central component of chemical manufacturing. One useful trick is to shift hydrogen atoms around to interconvert C=C isomers selectively. However, this approach typically requires precious metals. Kapat *et al.* now report that more-abundant nickel can catalyze rapid conversion of terminal olefins into internal olefins with high selectivity for trans geometry. The odd-electron nickel complex relies on a radical mechanism to shuttle hydrogen to the terminal carbon from the saturated carbon adjacent to the double bond.

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