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Olefin Functionalization/Isomerization Enables Stereoselective Alkene Synthesis

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Abstract

Despite tremendous efforts aimed at devising methods for stereoselective alkene synthesis, critical challenges are yet to be addressed. Direct access to a diverse range of 1aryl(boryl)-1-methyl-functionalized tri- and tetrasubstituted *trans* alkenes, entities that are prevalent in many important molecules of interest, through a catalytic manifold from readily available α-olefin substrates remains elusive. Here, we demonstrate that catalytic amounts of a nonprecious *N*-heterocyclic carbene–Ni(I) complex in conjunction with a sterically bulky base promote site- and *trans*-selective union of monosubstituted olefins with a wide array of electrophilic reagents to deliver tri- and tetrasubstituted alkenes in up to 92% yield and >98% regio- and stereoselectivity. The protocol is amenable to the preparation of carbon- and heteroatom-substituted C=C bonds, providing distinct advantages over existing transformations. Utility is highlighted through concise stereoselective synthesis of biologically active compounds.

Developing protocols that afford stereochemically defined acyclic tri- and tetrasubstituted alkenes is a longstanding goal in organic synthesis. These highly substituted C=C bonds (1-aryl(boryl)-1-methyl-substituted in particular) commonly reside in countless molecules of interest including organic materials and biologically active entities (Fig. 1a), and are key intermediates for further derivatization[1,2] to a broader spectrum of high-value compounds (see Supplementary Section 1 for extended bibliography). Although a number of approaches for the preparation of tri- and tetrasubstituted olefins have been introduced,[3–5] crucial drawbacks exist (Fig. 1b). Reactions that convert carbonyl compounds[6–8] or alkynes[9–12] to tri- and tetrasubstituted olefins often involve lengthy synthetic routes, exhibit limited

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Author contributions

C.-F.L., H.W. and H.Z. developed the method and carried out the mechanistic studies. R.M. carried out the DFT calculations. O.G. directed the DFT studies. M.J.K. directed the investigations and wrote the manuscript with revisions provided by the other authors.

Competing interests

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functional group compatibility, suffer from unsatisfactory regio- or stereoselectivity control, and/or are not sufficiently general for applications in complex molecule synthesis (see Supplementary Sections 2 and 3 for extended bibliography). One problematic complication arises from the inappreciable energy difference between the *cis* and *trans* isomers of these highly substituted alkenes[13] (<0.4 kcal/mol; see Supplementary Section 11 for details), which precludes thermodynamic control from delivering products in synthetically useful *E*:*Z* ratios.

Recent advances in catalytic olefin isomerization[14–17] as well as catalytic olefin metathesis[18,19] offer a distinct disconnection strategy starting from stable and more widely available alkenes as substrates, enabling access to certain highly substituted olefins with good control of *E*:*Z* selectivity (Fig. 1b). However, these approaches are also plagued with debilitating shortcomings. Isomerization reactions to trisubstituted olefins typically entail the use of pre-synthesized 1,1-disubstituted substrates which may limit broad utility, particularly in cases where the starting materials are not easily accessible. On the other hand, stereoselective formation of trisubstituted C=C bonds by olefin metathesis relies on the use of trisubstituted substrates through stereoretentive processes, which for 1,1-disubstituted olefins lead to diminished *E*:*Z* ratios.[18] In addition, the second olefin cross-partner has to be 1,2-disubstituted in order to minimize deleterious methylidene formation.[18] This requirement reduces the practicality of this approach especially in cases where the cross-partner is not commercially available. Except for specific substrate-controlled cases[20], olefin metathesis methods that selectively afford tetrasubstituted products are scarce, in part owing to the severe steric strain within the requisite metallacycle intermediates.

A general catalytic manifold that is complementary to the aforementioned systems and provides a myriad of heteroatom- and carbon-functionalized tri- and tetrasubstituted alkenes with exceptional stereoselectivity would be highly desirable. Previous reports in catalytic Mizoroki-Heck reactions of monosubstituted olefins with electrophilic sulfonates/halides[21–23] or boronic acids[24] delivered 1,1-disubstituted alkenes, whereas boryl-Heck transformations[25] of *E*-1,2-disubstituted styrenyl substrates (*Z* isomers are non-selective) with boryl halides offered access to trisubstituted alkenyl boronates with good *trans* selectivity. Notwithstanding these advances, a general strategy that has remained elusive is to *directly* transform abundant and easily accessible monosubstituted α-olefins (vs. the more substituted variants which generally require more steps to be synthesized) to stereodefined tri- and tetrasubstituted products by cross-coupling with a suitable reagent. Such a process will facilitate synthesis of various classes of highly substituted C=C bonds that are otherwise difficult to obtain by other means.

Our approach to achieve this goal is to design a catalytic regime as illustrated in Fig. 1c. We postulated that a suitable transition metal-based catalyst may first react with an electrophilic reagent **B** (e.g. through oxidative addition or ligand substitution) to form an intermediate that subsequently undergoes branched-selective Heck-type functionalization[21–23] with terminal alkenes **A** to afford **D**. This is followed by a kinetically controlled stereoselective C–C double bond transposition, to generate the desired product **C**. However, identifying an appropriate catalyst that is capable of promoting both steps in a tandem sequence is a formidable challenge, given that multiple levels of selectivity (chemo-, regio- and stereo-)

have to be exquisitely controlled in order to minimize generation of side products arising from competitive isomerization of **A** as well as undesired isomeric products of **D** and **C**. Adding to these complications is the need for mild reaction conditions that tolerate diverse functional groups for broad applicability in chemical synthesis. Of the few instances of olefin functionalization/isomerization that afforded trisubstituted enoates and enol ethers, an acid or base was presumably involved to drive C=C bond migration (see Supplementary Section 2.3 for extended bibliography).

Results

Optimization of reaction conditions.

We commenced our studies by evaluating conditions to merge unactivated alkene **5a** with electrophilic aryl triflate **6a** to give trisubstituted **7a** using stoichiometric amounts of sodium *tert*-pentoxide as base and anhydrous toluene as solvent at 80 °C for 12 hours under a N_2 atmosphere (Table 1). A survey of different ligands (12 mol %) in the presence of 10 mol % of $Ni(cod)_2$ (cod, 1,5-cyclooctadiene) revealed that *N*-heterocyclic carbenes (NHCs) were noticeably superior to phosphine and bipyridine ligands (entries 1–3) in promoting the desired transformation. With **L6** as the ligand (entry 4), **7a** and its olefin isomers (**7a'** and **7a"**) were isolated as a 15:85 mixture in 65% yield. Changing the ligand to the more sizeable **L7** (entry 5) increased the ratio of the desired product, and **7a** was obtained in 90% *E* selectivity (72% yield of mixture, ~31% **7a'** and **7a"**). There was appreciable improvement (90:10 **7a**:**7a'**+**7a"**) when a pre-synthesized $(IPr)_2Ni(0)$ complex **Ni-1**[26] was employed (entry 6), although yield for **7a** (85:15 *E*:*Z*) was moderate. For entries 4–6, significant amounts of **5a** regioisomers (~25–40% from olefin migration) were detected as side products.

Replacing $Ni(cod)_2$ with other commercially available Ni(II) salts was ineffective (<2% conversion (conv.) to desired product; see Supplementary Table 1). We surmised that a more selective catalyst was necessary to promote efficient C–C bond formation/isomerization, which led us to examine the dinuclear IPr–derived Ni(I) dimeric complex **Ni-2**.[27] Using 5 mol % of **Ni-2** (entry 7), **7a** could be secured in 83% yield, 93% *E* selectivity and 95:5 regioisomeric ratio within two hours (vs. 12 hours for entries 1–6) with minimal **5a** isomerization by-products (<10%). Notably, prolonging the reaction was detrimental to stereoselectivity (80:20 *E*:*Z* ratio after 12 hours), presumably due to post-reaction isomerization. It merits mention that switching **6a** to other classes of aryl electrophiles (e.g. bromides, iodides) or changing the base/solvent all led to inferior results. On the other hand, lowering the reaction temperature gave poor conv. to mixtures of **7a**, **7a'** and **7a"** (see Supplementary Table 1 for details).

Mechanistic investigations.

The remarkable enhancement in catalytic efficiency and selectivity with a Ni(I)-based catalyst prompted us to conduct a series of experimental and computational studies to shed light on the mechanism and origin of selectivity (Fig. 2). Control studies revealed that 1,2-dialkyl-substituted olefins are incompetent substrates under the established conditions, suggesting that the present transformation likely proceeds through sequential

functionalization to a 1,1-disubstituted alkene followed by isomerization (cf. Fig. 1c). Given that **Ni-2** was previously shown to promote radical-based alkene isomerizations,[15] it remains for us to elucidate whether olefin migration in our reaction system follows a similar radical pathway. Studies were first carried out by subjecting 1,1-disubstituted **7b'** to **Ni-2** under various isomerization conditions (Fig. 2a, i). With our established system, 67% conv. to **7b** (94:6 *E*:*Z*) was observed. 65% Isomerization could also be achieved in the absence of phenyl triflate and base, although **7b** was generated in appreciably lower selectivity (87:13 *E*:*Z*). A similar result was obtained (65% conv., 91% *E* selectivity) when the transformation was conducted in PhCl under previously established 1,3-hydrogen atom relocation conditions,[15] albeit a higher catalyst loading (10 mol %) was required. These observations provided hints that C=C bond migration in our system could follow a pathway distinct from that reported by Schoenebeck and co-workers.[15]

In another set of experiments, a separately synthesized **8'** isomerized to **8** with 68% conv. and 86% *E* selectivity under the standard reaction conditions, but there was only 11% conv. (71:29 *E*:*Z*) when triflate/base were absent (<5% conv. in PhCl at ambient temperature[15]). Minimal cyclopropane ring rupture (<2%) was found in all cases, suggesting that hydrogen atom transfer via long-lived radical intermediates[28] is not involved. Further, we surmised that the conversion of **8'** to **8** in the presence of triflate/base is less likely to proceed through metalloradical-induced 1,3-hydrogen atom shift,[15] since this process is inefficient in promoting C=C bond migration. Rather, a non-radical 1,3-hydrogen shift[29,30] through an allylnickel species might be operative during the course of olefin isomerization. The allyl isomerization could be promoted by a Ni(I) species or, to a certain degree, by an in situ-formed Ni(0) species in the presence of base.[31] In order to probe the possibility of adventitiously-generated Ni(0) species[32] in our **Ni-2** catalytic system, we relied on the propensity of NHC–Ni(0) complexes to promote vinylcyclopropane rearrangements to cyclopentenes.[33] Specifically, vinylcyclopropane **9** was independently treated with **Ni-2** as well as the IPr–Ni(0) species derived from $Ni(cod)_2$ and **L7** (with and without tiflate/base) in toluene at 80 °C (Fig. 2a, ii). Indeed, ≥35% ring cleavage to cyclopentene **10** was obtained in the Ni(0)-mediated systems, whereas only 10% conv. to **10** was found in the presence of **Ni-2**. <5% Olefin isomerization to cyclopropene was detected in all cases, presumably due to the resulting product's ring strain that inadvertently raised the energy barrier. Even though it cannot be completely excluded, these control experiments intimate that any formation of Ni(0) species from **Ni-2** is probably not significant under our established reaction conditions. Further investigations are ongoing to obtain more insights on the nature of the organonickel species generated in the reaction mixture.

More evidence to support our proposed non-radical 1,3-hydrogen shift mechanism could be derived from deuterium labelling and crossover studies (Fig. 2a, iii). Treatment of ***d*-5c** with **6a** under the standard conditions afforded ***d*-7c** in 53% yield with ~1.0 D incorporation at the methyl group. Furthermore, intermolecular crossover between ***d*-5c** and non-deuterated **5d** was not detected (<2% deuterium incorporation within expected product **7d**). These results as well as the lack of deuterium content erosion within ***d*-7c** in both experiments, suggest that a free nickel-hydride species is less likely involved in the C=C bond isomerization

step. Instead, the observations are more consistent with an intramolecular Ni-promoted 1,3-hydrogen shift leading to the observed stereoselectivity.

Electron paramagnetic resonance (EPR) analysis of the reaction mixture (**Ni-2**, NaO*t*-Am, **5a** and **6a** in toluene) indicated the presence of paramagnetic organometallic species generated in the system (see Supplementary Section 6 for details). To gain further insights into the mechanism, unrestricted open-shell dispersion-corrected DFT calculations (UB3LYP-D3, PBE0-D3, and UM06L) were employed and, overall, supported a catalytic pathway as shown in Fig. 2b (see Supplementary Section 11 for full computational details). Specifically, initial dissociation of **Ni-2** to the monomeric Ni(I) chloride species is followed by a thermodynamically favorable ligand substitution with sodium *tert*-pentoxide to afford the catalytically active Ni(I)-alkoxide I. In the presence of an aryl triflate and monosubstituted alkene **A**, a branched-selective Mizoroki-Heck reaction proceeds through initial oxidative addition of In the presence of an aryl triflate and monosubstituted alkene **A**, a branched-selective Mizoroki- with the electrophile followed by regioselective arylnickelation and β-H elimination to deliver Ni(III)-hydride **IV**. All attempts to locate the energetically less favored linear-selective arylnickelation transition state were unsuccessful, presumably due to the inherent steric strain that substantially raised the energy. Finally, reductive elimination of **IV** facilitated by sodium *tert*-pentoxide base generates olefin-coordinated Ni(I)-alkoxide **V**. At this juncture, contrary to the radical-based isomerization detailed recently by Schoenebeck and co-workers[15], computations support a *stereoselective non-radical allyl isomerization sequence* (see Supplementary Section 11 for further details and justification of this assertion). Specifically, Ni(I) **V** undergoes an inner-sphere *trans*-selective allylic C–H insertion (Fig. 2c) to furnish an η^1-allylnickel(III) intermediate **VI** that subsequently undergoes migration to yield **VII**. Finally, *irreversible* reductive elimination regenerates the catalytically active species **I** and releases the desired trisubstituted product **B**, overall −58.1 kcal/mol downhill in energy. An alternative minor Ni(0)/Ni(II) pathway for the tandem Heck reaction/isomerization, which cannot be entirely ruled out, was also computed (see Supplementary Section 11 for full computational details).

The proposed mechanistic model in Fig. 2b is also consistent with the observed stereochemical outcome. This is noteworthy because the discrepancy in energy between the two potential products, **(*E*)-B** and **(*Z*)-B**, is nowhere near large enough to explain the observed high *trans* selectivity. Instead, as seen in Fig 2c., the difference in energy between the diastereomeric transition states ***trans*-TS-V-VI** and ***cis*-TS-V-VI** correlates well with our stereoselectivity results. This difference is attributed to the shift in geometry of the *tert*-pentoxide that must occur in order to accommodate formation of the minor *cis* isomer. In the transition state leading to the *cis* isomer, the sizeable *tert*-pentoxide is forced down, pushing the bulky IPr ligand outwards which raises the energy dramatically (such steric repulsion is absent in the transition state leading to the major *trans* isomer). Taken together, these DFT results reveal the crucial roles played by the sterically encumbered *tert*-pentoxide and IPr ligand in inducing high stereoselectivity, a shift in C=C bond isomerization mechanism that arises from ligand substitution of Ni(I)-chloride with the bulky *tert*-pentoxide, as well as the need for high reaction temperatures to overcome the barrier for olefin migration (in accordance with our experimental observations).

Substrate scope.

With the established **Ni-2**-catalyzed conditions in hand, we proceeded to examine the scope with a variety of functionalized monosubstituted alkenes using phenyl triflate as cross-partner (Fig. 3a). These include substrates that gave rise to aryl-, amino- and alkoxy-substituted products **7e**–**i** in 61–90% yield and 83:17–96:4 *E*:*Z* ratios. Notably, alternative methods to access heteroatom-functionalized trisubstituted olefins such as **7g**–**i** are insufficiently general or lead to poor yields and/or stereoselectivities.[34–36] The reaction to obtain **7g** could be performed on gram scale without a significant diminution in yield or selectivity.

Terminal olefins with a functional group installed at the allylic or homoallylic site could be transformed to the corresponding trisubstituted C=C bonds, furnishing **7j**–**q** in 51–73% yield and 83% to >98% *E* selectivity. Products that contain an amide (**7j**), an ester (**7n**), a silane (**7k**), a cyanide (**7m**) as well as a sterically hindered α-branched olefin (**7l**) could be secured. Longer-chain alkenes that bear a phthalimide (**7t**), a Lewis basic amine (**7u**), an electrophilic epoxide (**7x**; susceptible to ring cleavage with zirconocene-catalysed carbometallation[3,37]) and heterocyclic motifs (**7v**, **w**) were efficiently generated. **7r**, an olefin that is appended to a reactive unprotected hydroxyl unit, was isolated in 58% yield and 89:11 *E*:*Z* ratio by treating the substrate with tetramethyl-1,3,2-dioxaborolane[38] prior to the ensuing Ni-catalyzed reaction in a single pot.

Functionalized aryl and heteroaryl triflates were also evaluated in our Ni-catalyzed protocol (Fig. 3b). Triflates carrying electron-rich or electron-deficient aryl moieties were found to serve as effective reagents, delivering the desired products **7y**–**ai** in 55–92% yield and up to 96:4 *E*:*Z* ratio. Synthesis of polycyclic **7ad** demonstrates compatibility with an electrophilic ketone group. The X-ray structure of **7d** confirms the predominant formation of the *trans* isomer. Besides trisubstituted alkenes, we speculated whether α-branched monosubstituted alkenes could be utilized as substrates to afford the corresponding fully substituted C=C bonds. The increased steric demand would inevitably raise the steric strain inherent within the catalytic intermediates during the course of the Heck reaction and subsequent isomerization (cf. Fig. 2c). Accordingly, a higher **Ni-2** loading (10–15 mol % vs. 5–10 mol % for trisubstituted products) was required, allowing efficient access to exocyclic and acyclic tetrasubstituted **7aj**–**7an** in 30–65% yield (Fig. 3c). These include pharmaceutically important scaffolds such as piperidine- and azetidine-containing[39,40] **7aj**–**7al** as well as triarylethylenes[41] **7am–7an**.

With terminal alkenes bearing two different allylic groups, predominant formation of the *E* isomer was observed but selectivities were somewhat diminished (~80% for **7ao**, **ap**). This is probably due to the smaller energy difference between the competing transition states leading to opposite stereoisomers during the course of C=C bond transposition (cf. Fig. 2c for trisubstituted olefins). Nevertheless, the major tetrasubstituted isomer could be readily purified by conventional silica gel chromatography, and pure *E*-**7ao**–**7ap** were isolated in 46–47% yield. This strategy is markedly attractive when the use of stoichiometric reducing agents[42] or addition of pre-synthesized organometallic reagents to unsymmetrical ketones followed by dehydration[43] constitute less practical options.

Replacing triflates with boron-based electrophiles such as bis(pinacolato)diboron enables access to the corresponding boron-substituted alkenes in the presence of lithium *tert*-butoxide and DMPU (Fig. 4a). Synthesis of tri- and tetrasubstituted alkenyl boronates **11a**–**e** in up to 67% yield and 95% *Z* (*trans*) selectivity underscores the versatility of our Ni-catalyzed functionalization/isomerization strategy. As illustrated in Extended Data Fig. 1, preliminary mechanistic studies indicated that these transformations likely proceed through sequential boryl-Heck-type reaction[25] (via a putative nickel-boryl[44] species **IX**) followed by olefin isomerization that is reminiscent of the process depicted in Fig. 2c.

Applications to chemical synthesis.

The Ni-catalyzed protocol offers new opportunities to devise more concise preparative routes for various important biologically active molecules (Fig. 4b). The first application relates to the *E*-selective synthesis of trisubstituted **7aq**, a compound that can be elaborated to protein tyrosine phosphatase inhibitor **1**.[45] The required triflate **13** was synthesized from commercially available phenol **12** and subjected to the established **Ni-2**catalyzed cross-coupling conditions with 1-heptene to deliver **7aq** in 63% yield and 92% *E* selectivity. The two-step route obviates the unsatisfactory regioselectivity issues that would arise from hydroboration of an internal alkyne[46] as reported in a previous disclosure.[45]

In another formal synthesis of the signal transducer and activator of transcription 6 inhibitor **2**[47], the alcohol appendage within *N*-Boc-L-prolinol **14** was converted to an olefin in two steps to afford **15** in 78% overall yield. Following a site- and stereoselective cross-coupling with phenyl triflate, fragment **7ar**, a precursor of **2**, was secured in 71% yield and 95:5 *E*:*Z* ratio. Temarotene and arotinoid acid, diaryl-substituted alkenes with cancer chemopreventive and anti-cancer properties[48], respectively, can be readily accessed using the developed Ni-catalyzed method as a key step. Friedel-Crafts dialkylation of phenol with dichloride **16** followed by trifylation furnished triflate **17** in 79% overall yield. Temarotene was isolated in 58% yield and 90% *E* selectivity from the cross-coupling of **17** and allylbenzene, whereas the analogous reaction of **17** with methyl 4-allylbenzoate followed by alkaline hydrolysis gave arotinoid acid in 39% overall yield and 91:9 *E*:*Z* ratio. The present sequences are more concise than a previously reported eight-step synthesis (for arotinoid acid)[48] and four-step synthesis (for temarotene).[49]

Besides carbon-substituted olefins, borylated building blocks can be efficiently obtained by employing the borylation/isomerization conditions developed in Fig. 4a. In one instance, prokineticin receptor I antagonist **3**[50] was prepared from commercially available **18** and bis(pinacolato)diboron through two catalytic processes via tetrasubstituted alkenyl boronate **11a** and **7ak** in 52% overall yield. By cross-coupling of **11a** with different reaction partners, this approach allows facile derivatization to a wider assortment of analogues. In contrast to previous reports[50,51] that relied on synthesis of advanced ketone intermediates en route to the alkene target molecules, our devised sequence is more convenient for the expeditious generation of structural diversity. Alternatively, **7ak** could be obtained by reaction of **18** with 4-chlorophenyl triflate in a single step using 10 mol% of **Ni-2** and sodium *tert*-pentoxide in toluene, albeit in diminished yield (30%; cf. Fig. 3c). Preparation of trisubstituted **11f** from commercially available and inexpensive 4-bromobenzyl bromide **19** in 41% yield and

92% *Z* (*trans*) selectivity over three steps showcases another application directed towards the synthesis of kinase inhibitor **21**.[52] The overall route is shorter compared to previous procedures[52,53] that involved formation of an internal alkyne from **19** followed by catalytic hydroboration.

Conclusions

We have devised a robust Ni-catalyzed system that enables reliable conversion of a wide array of readily available monosubstituted olefins to value-added tri- and tetrasubstituted alkenes through efficient union with appropriate electrophilic reagents. Mechanistic and computational studies provided insights to support a non-radical tandem transformation involving a site-selective Heck-type reaction, followed by a stereoselective C=C bond migration. The proposed involvement of a Ni(I)/Ni(III) catalytic pathway[54–56] provided a plausible rationale for the observed regio- and stereochemical outcome of the transformations, although a Ni(0)/Ni(II) cycle cannot be completely excluded. The present study is expected to enhance the way in which many important molecules are synthesized, and inspire further development of catalytic tandem transformations for the selective construction of high-value molecules from easily accessible and non-precious materials.

Methods

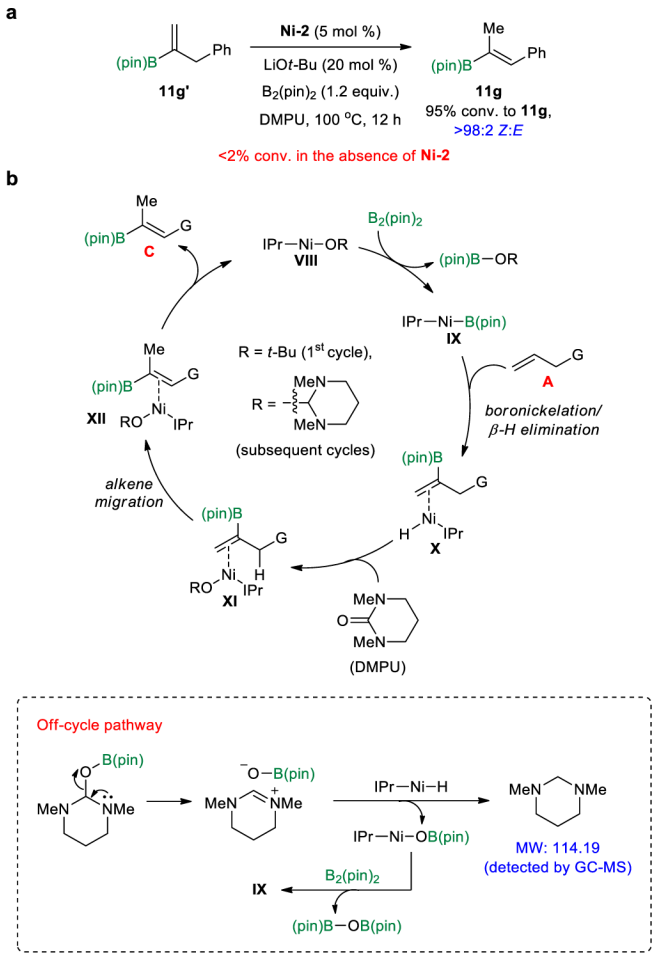
General procedure for tandem Mizoroki-Heck reaction/isomerization:

In a N_2-filled glove box, an oven-dried 4 mL vial equipped with a stir bar was charged with Ni-2 (5.0–15 mol %), NaO*t*-Am (1.0 eq) and toluene (1.0 mL). Alkene substrate (0.10 mmol, 1.0 eq) and aryl triflate (1.2 eq) were then added to the system. The vial was sealed and the reaction mixture was allowed to stir at 80 °C or 100 °C for 2–20 h. After cooling to ambient temperature, the crude mixture was purified by silica gel chromatography.

General procedure for tandem boryl-Heck reaction/isomerization:

In a N_2-filled glove box, an oven-dried 4 mL vial equipped with a stir bar was charged with **Ni-2** (5.0 mol %), LiO*t*-Bu (20 mol %), $B_2(pin)_2$ (1.2 equiv.) and DMPU (0.2 mL). Alkene substrate (0.10 mmol, 1.0 eq) was then added to the system. The vial was sealed and the reaction mixture was allowed to stir at 100 °C for 12 h. After cooling to ambient temperature, the crude mixture was washed with water and extracted with EtOAc (twice). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography.

Extended Data



Extended Data Fig. 1 |. Preliminary studies on the boron variant of the Ni-catalyzed tandem reaction.

a, Control experiments revealed that borylation likely occurs, affording observed intermediate **11g'**, prior to C=C bond migration. **b**, A tentative mechanistic pathway involving formation of a putative nickel-boryl species **IX** to promote boryl-Heck reaction. Under typical circumstances where catalytic amounts of LiO*t*-Bu were used, DMPU likely served as a hydride acceptor to afford the corresponding Ni-alkoxide **VIII** and turn over the catalytic cycle. In other instances, more base might be needed to regenerate the active Ni-*tert*-butoxide species (**VIII**, R = *t*-Bu). G, functional group; pin, pinacolato; DMPU, *N,N'*-dimethylpropyleneurea; IPr, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data availability

All data are available from the corresponding authors upon reasonable request. An X-ray crystal structure data file (CCDC reference number 2018464) has been deposited with the Cambridge Crystallographic Data Centre and is available free of charge from www.ccdc.cam.ac.uk/data_request/cif.

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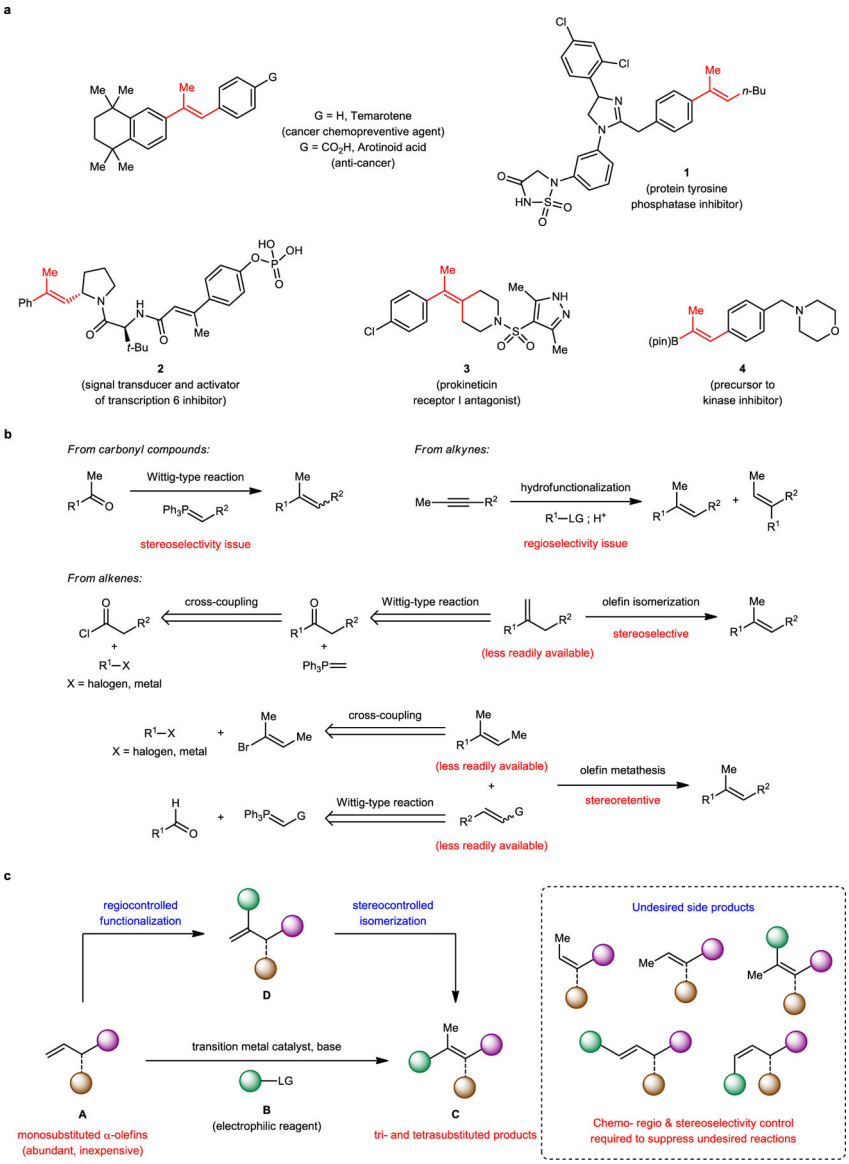


Fig. 1 |. The significance of designing catalytic reactions that deliver stereodefined tri- and tetrasubstituted alkenes.

a, Tri- and tetrasubstituted olefins are ubiquitous entities in biologically active compounds and synthetic intermediates. **b**, Common preparative routes to access trisubstituted alkenes. **c**, An attractive yet unexplored approach involves implementing a catalytic regime that utilizes simple and abundant monosubstituted α-olefins **A** as substrates. In the presence of an appropriate transition metal-based catalyst and an electrophilic reagent **B**, a tandem process featuring a regioselective (net) olefin C–H functionalization followed by stereoselective C=C bond transposition offers an expeditious route to multifunctional tri- and tetrasubstituted alkenes **C**, but formation of multiple undesired side products will have to be suppressed. L, ligand; cat., catalyst; R, G, functional group; Ar, aryl group; LG, leaving group.

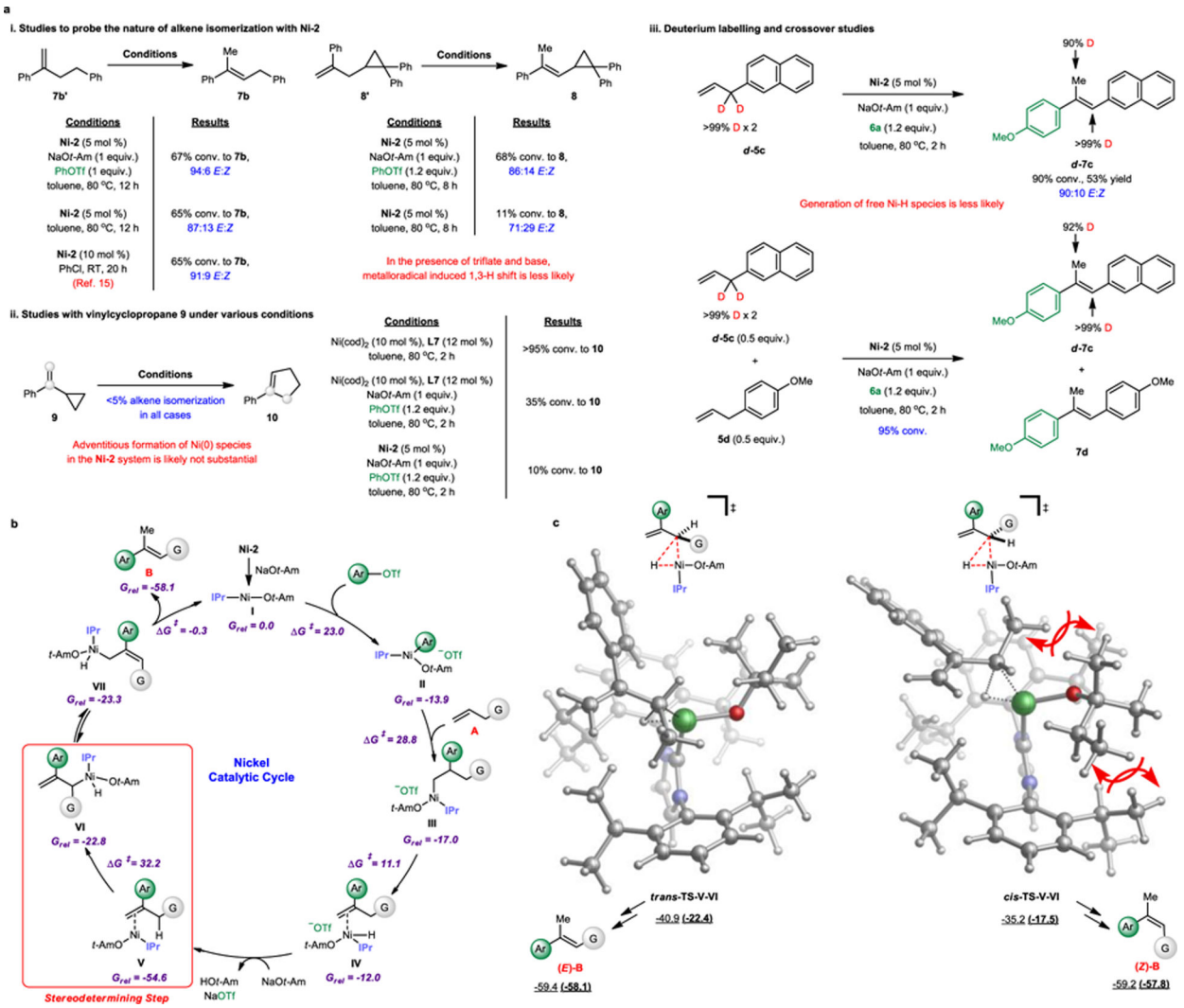


Fig. 2 |. Mechanistic and computational studies.

a, Control experiments rule out the intermediacy of a free nickel-hydride species in the isomerization step to the trisubstituted olefin product. Studies further demonstrate that C=C bond migration is less likely to proceed through metalloradical induced 1,3-hydrogen atom shift. **b**, Proposed Ni-catalyzed mechanism for tandem Mizoroki-Heck reaction/isomerization. The catalytic cycle is supported by the energies shown (calculated using dispersion-corrected DFT). **c**, Key Ni(I)-catalyzed C=C bond isomerization transition state structures furnishing *E* and *Z* trisubstituted products including calculated enthalpies and (free energies) for each. All structures (G = Me, Ar = Ph) were optimized using unrestricted open-shell, dispersion-corrected DFT [uB3LYP-D3/def2SVP-CPCM(toluene) level of theory] and all enthalpies/energies are reported in kcal/mol. Conv. and *E*:*Z* ratios were determined by ^{1}H NMR analysis of unpurified mixtures; yields are for isolated and purified products. G, functional group; Ar, aryl group; *t*-Am, *tert*-amyl; Tf, trifluoromethanesulfonyl; IPr, 1,3-bis(2,6diisopropylphenyl)imidazol-2-ylidene; RT, room temperature; TS, transition state.

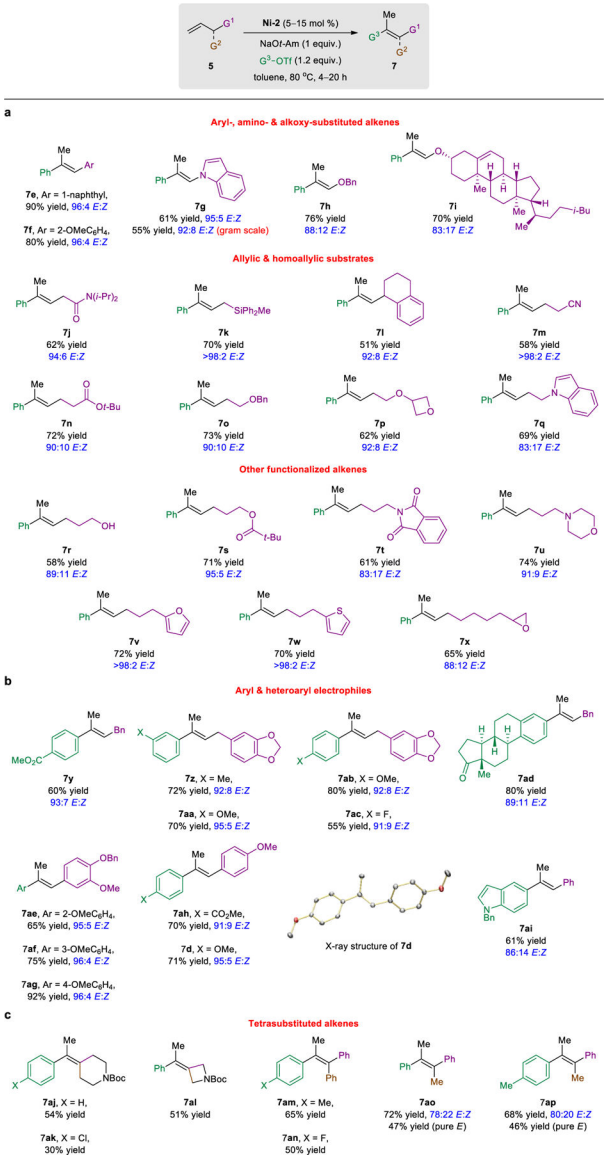


Fig. 3 |. *Trans*-selective synthesis of tri- and tetrasubstituted alkenes.

a, Various classes of functionalized terminal olefin substrates are compatible under the established conditions. **b**, A diverse range of aryl and heteroaryl triflates undergo reaction to deliver the desired products. **c**, The protocol is amenable to the synthesis of sterically encumbered tetrasubstituted C=C bonds. For **7r**, the reaction was conducted with phenyl triflate as the limiting reagent in the presence of alkene substrate (3 equiv.) and tetramethyl-1,3,2-dioxaborolane (3 equiv.). For **7y**, the reaction was conducted in mesitylene as solvent. For **7y** and **7ah**, the reactions were conducted with NaO*t*-Bu as base. For **7ad** and **7ak**, the reactions were conducted at 100 °C. For **7an**, the reaction was conducted at 100 °C for 36 h. For **7ao** and **7ap**, the reactions were conducted at 60 °C. All products were obtained as 91:9 to >98:2 regioisomeric mixtures (**7**:isomers). Regioisomeric ratios and *E*:*Z* ratios were determined by ^{1}H NMR analysis of unpurified mixtures; yields are

for isolated and purified products. G, functional group; Ar, aryl group; *t*-Am, *tert*-amyl; Tf, trifluoromethanesulfonyl; Boc, *tert*-butoxycarbonyl; Bn, benzyl.

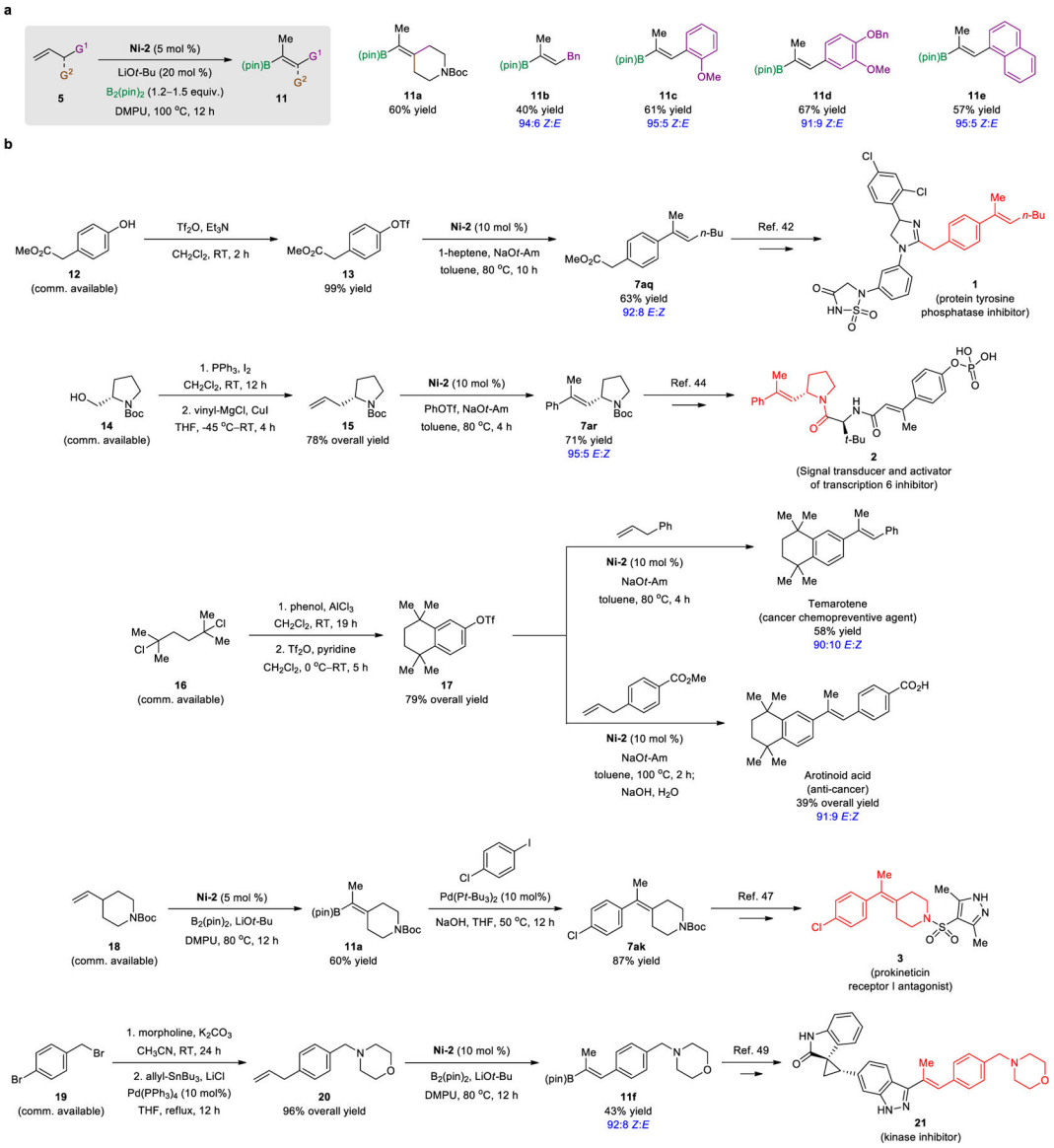


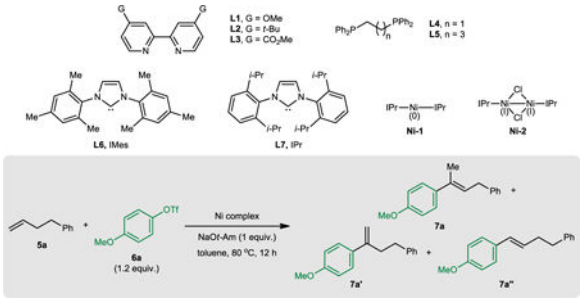
Fig. 4 |. Access to boron-containing olefins and application to synthesis of biologically active compounds.

a, By switching the electrophilic reaction partner to a diboryl reagent, the functionalization/isomerization approach can be extended to highly substituted alkenyl boronates. **b,** Expedient transformation of readily accessible monosubstituted alkenes to more valuable tri- and tetrasubstituted products enables concise preparation of a number of medicinally important compounds. For **11a**, the reaction was conducted with 1 equiv. of LiO*t*-Bu. For **11b**, the reaction was conducted with 2 equiv. of LiO*t*-Bu at 80 °C. All products were obtained as 91:9 to >98:2 regioisomeric mixtures (**7**:isomers or **11**:isomers). Regioisomeric ratios and *E*:*Z* ratios were determined by ^{1}H NMR analysis of unpurified mixtures; yields are for isolated and purified products. G, functional group; *t*Am, *tert*-amyl; Tf, trifluoromethanesulfonyl; pin, pinacolato; Boc, *tert*-butoxycarbonyl; Bn, benzyl;

DMPU, *N,N'*-dimethylpropyleneurea; THF, tetrahydrofuran; comm., commercially; RT, room temperature.

Table 1|

Evaluation of Ni-based complexes for the reaction of 5a and 6a



Entry	Ni complex	Conversion (%)*; yield (%)†	7a:(7a'+7a")‡	*E:Z* ‡
1	$Ni(cod)_2$ (10 mol %), **L1, L2** or **L3** (12 mol %)	<2; NA	NA	NA
2	$Ni(cod)_2$ (10 mol %), **L4, L5** or (±)-BINAP (12 mol %)	<2; NA	NA	NA
3	$Ni(cod)_2$ (10 mol %), $PPhCy_2$ (12 or 24 mol %)	<2; NA	NA	NA
4	$Ni(cod)_2$ (10 mol %), **L6** (12 mol %)	>98; 65	15:85	75:25
5	$Ni(cod)_2$ (10 mol %), **L7** (12 mol %)	>98; 72	69:31	90:10
6	**Ni-1** (10 mol %)	>98; 55	90:10	85:15
7¶	**Ni-2** (5 mol %)	>98; 83	95:5	93:7

Reactions were carried out under a N_2 atmosphere.

*Conversion was based on the disappearance of **5a** and determined by GC analysis.

†Yield of isolated and purified product (*E:Z* and regioisomeric mixtures).

‡Regioisomeric ratios and *E:Z* ratios (**7a**) were determined by ^1H NMR analysis of unpurified mixtures. NA, not applicable.

¶The reaction was conducted for 2 hours.