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Research Article

Kinetically Controlled Stereoselective Access to Branched 1,3-Dienes by Ru-Catalyzed Remote Conjugative Isomerization

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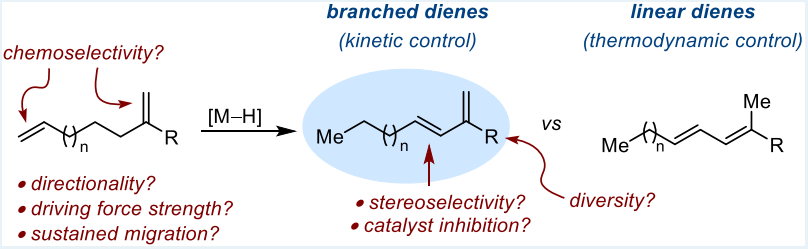

ABSTRACT: A Ru-catalyzed conjugative isomerization of remote alkenes that affords branched 1,3-dienes is described. These kinetic products are obtained in high yields, good levels of regiocontrol, and high stereoselectivity. A broad range of functional groups and heterocycles are compatible with the mild reaction conditions, and isomerization is sustained over long distances. Control experiments support a metal-hydride mechanism consisting of iterative migratory insertions/β-H eliminations, which is initiated preferentially at the terminal olefinic site. Two one-pot multimetallic selective catalytic sequences using [Ru/Cu] and [Ru/Rh] combinations have been developed to illustrate the synthetic potential of the process.

KEYWORDS: *ruthenium catalysis, isomerization, 1,3-dienes, remote functionalization, stereocontrol, kinetic control*

In addition to being a highly prevalent structural element in numerous natural products and biologically active molecules, conjugated dienes serve as pivotal building blocks in the synthesis of a broad range of compounds, ranging from fine chemicals to functional polymers (Figure 1A).[1−3] Because the inherent reactivity of dienes is influenced by the nature, the number, and the relative position of their substituents, they also constitute a particularly modular and versatile platform for the discovery and development of catalytic synthetic methods that streamline access to more complex polyfunctional small molecules. More specifically, beyond any reactivity consideration, transition-metal-catalyzed functionalization of dienes is typically faced with the difficulty of exerting excellent chemo-, regio-, diastereo-, and enantiocontrol.[4]

To date, the *stereoselective* synthesis of substituted 1,3-dienes still represents a considerable challenge.[5] Conjugated dienes are most commonly prepared by conventional non-atom economical olefinations of carbonyl precursors or by stereoretentive cross-coupling reactions using stereochemically well-defined starting materials.[6] Approaches based on C−H activation, photoredox catalysis, and metathesis have also been described.[7] Notably, the stereoselective preparation of substituted dienes has been achieved by rearrangements, transpositions, or isomerizations of allenes and alkynes, albeit with a narrow substrate scope.[8] Examples of conjugated dienes obtained by alkene isomerization are scarce (Figure 1B).[9] This is surprising because such redox economic strategies could offer increased flexibility and generality, in particular, for the preparation of less accessible substitution patterns. In 2000, an isolated example of Ru-catalyzed deconjugative isomerization of an α,β-unsaturated ester producing a linear diene with a reduced level of stereocontrol was disclosed by Mori and co-workers.[10] Inspired by precedents from Negishi, the Marek group reported a one-pot isomerization/elimination sequence, which delivers geometrically pure linear or branched dienes starting from alkenyl methyl vinyl ethers. In this system, long-range isomerization of the remote alkene is mediated by a stoichiometric amount of a zirconocene derivative and is followed by simple hydrolysis.[11] Diver developed a [Ru−H]-catalyzed stereoconvergent positional isomerization of branched dienes resulting from an ene−yne metathesis into the thermodynamically more stable linear isomers.[12] The reaction can be conducted in a single vessel starting from simple alkynes and alkenes and by triggering decomposition of the alkylidene metathesis catalyst into an isomerization catalyst using vinyloxytrimethylsilane.[13]

We have recently initiated a program aimed at developing remote functionalization strategies based on alkene isomerization.[14−16] As part of these investigations, we wondered

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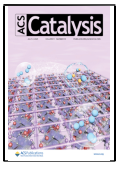

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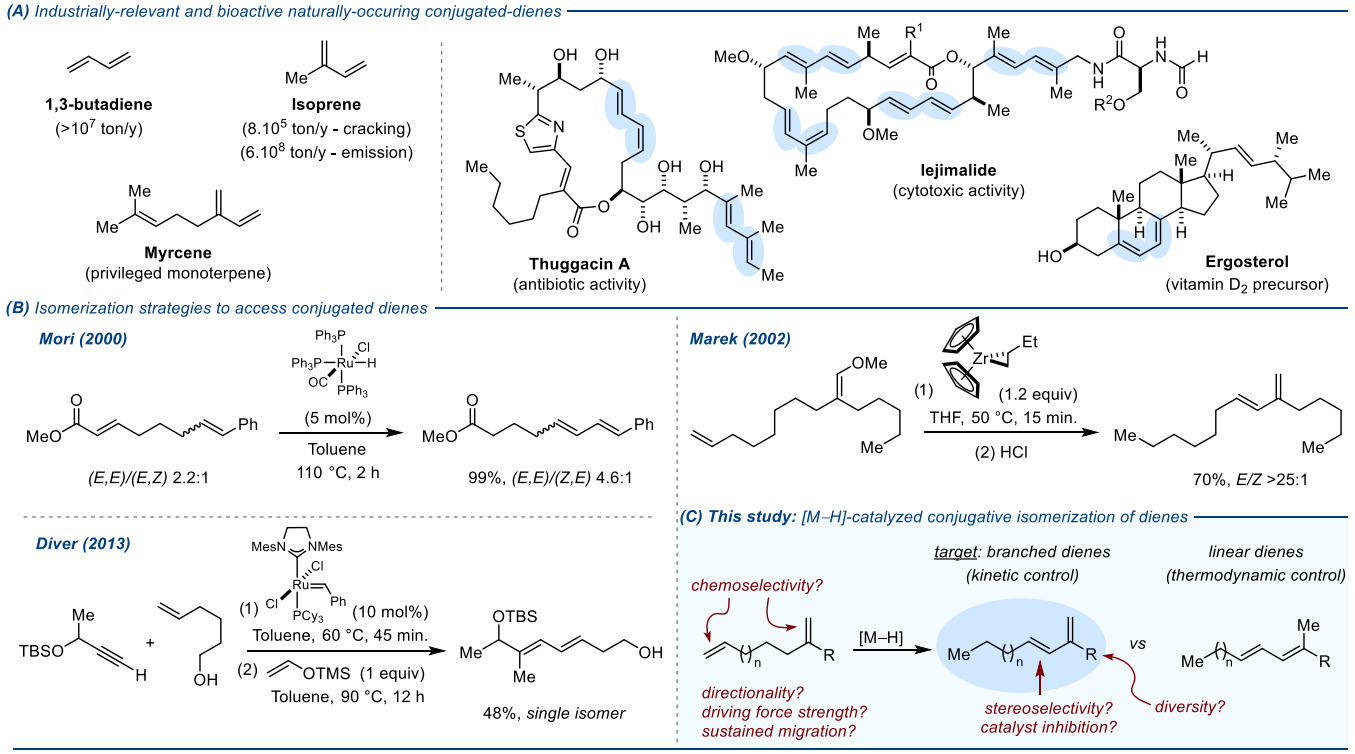

Figure 1. (A) Industrially relevant and bioactive naturally occurring conjugated dienes highlighting the diversity of substitution patterns. (B) Precedents in metal-catalyzed and metal-mediated isomerization strategies to access conjugated dienes. (C) Challenges associated with the development of a [M-H]-catalyzed conjugative isomerization to access branched dienes.

whether branched 1,3-dienes could be stereoselectively accessed by bringing in conjugation two distant carbon−carbon double bonds using well-defined transition metal hydride catalysts (Figure 1C). To achieve this goal, we anticipated that it was necessary to identify a system able to (i) distinguish between two minimally differentiated olefins, (ii) sustain migration over several methylene units, (iii) operate under mild conditions to favor formation of the branched dienes rather than the thermodynamically more stable linear isomers, (iv) induce stereocontrol, and (v) display broad functional group tolerance. Moreover, in addition to potential directionality issues upon migration of the C═C bond(s), it was unclear whether a remote alkene would constitute a sufficiently strong driving force to the overall process. Indeed, examples of long-range isomerization where the end group does not possess a heteroatom are less common.[10,15g,17] Finally, we also hypothesized that, if generated preferentially, branched dienes may act as a catalyst inhibitor by forming a stable chelate with a transition-metal complex or engage in parasitic cycloaddition reactions.

To address these challenges, we began our investigations by evaluating a series of established isomerization precatalysts ($\mathbf{C_1}$−$\mathbf{C_8}$; 5 mol %) using vinylarene **1a** as a model substrate (Table 1). The reactions were monitored over 24 h by ^{1}H NMR in CD_2Cl_2, a noncoordinating solvent to avoid competing binding with the substrate and with a temperature never exceeding 60 °C. Group IX catalytic systems $\mathbf{C_1}$−$\mathbf{C_2}$ and our homemade Pd complex ($\mathbf{C_3}$) led essentially to the 1-carbon isomerization product **2a** with poor stereocontrol, while only traces of **3a** and **4a** were detected (entries 1−4).[15] With the protocol developed by Nelson and modified by Marek ($[Ir(cod)Cl]_2/PCy_3/NaBAr_F$; $\mathbf{C_4}$) or with Grotjahn's catalyst $\mathbf{C_5}$, the targeted branched diene **3a** was generated preferentially with a high level of stereoselectivity (Entries 5−6).[18,19] Nonetheless, the substantial amount of **2a** and **4a** and the similar polarity of all three isomeric products prevented efficient purification. The marked differences between the structurally closely related hydrido-ruthenium complexes $\mathbf{C_6}$−$\mathbf{C_8}$ is particularly noteworthy because each of them displayed distinct regioselectivity (entries 7−9). While, chlorohydridotris-(triphenylphosphine) ruthenium $\mathbf{C_6}$ produced exclusively **4a**, in turn, $\mathbf{C_7}$ generated **2a** as the major regioisomer. By contrast, $\mathbf{C_8}$ afforded branched diene **3a** preferentially with excellent stereoselectivity (E/Z > 20:1).[17a] The effect of the added ligand was explored next and revealed that the addition of 5 mol % PPh_3 had a beneficial impact on product distribution without deterioration of the stereoselectivity (entries 10−15). Additional control experiments confirmed that at higher temperatures, the thermodynamically more stable linear diene **4a** could be formed exclusively, albeit with a poor level of stereocontrol (entries 16−18).[20,21]

Gratifyingly, with the optimized conditions disclosed in entry 14 (Table 1), purification was greatly facilitated and branched diene **3a** was isolated in pure form in a 70% yield (E/Z > 20:1). Similar performances were obtained when this experiment was conducted on a gram scale. Therefore, the scope of selective isomerization was explored using this protocol (Figure 2). Variation of the electronic properties of the vinylarene end group was well tolerated. Electron-rich, electron-neutral, and electron-deficient aromatic rings led to consistently appreciable catalytic performances, be it in terms of reactivity, regio-, or stereoselectivity (**3a**−**k**). Substituents could be indifferently installed in *para*, *meta*, and *ortho* positions, the latter providing the highest regioisomeric ratio and consequently the highest yield (**3j,k**). In addition to alkyl ether, aryl ether, silyl ether, bromide, and chloride, which were found to be compatible with the reaction conditions, heteroaromatics such as a pyridine (**3l**),

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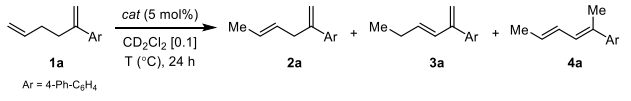
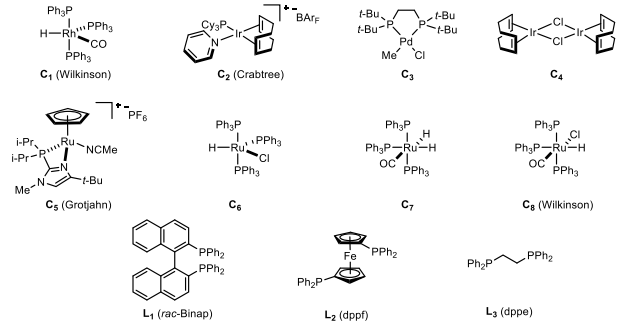
Table 1. Catalyst Survey[a]



entry	catalyst	T (°C)	conv. (%)[b]	2a : 3a : 4a[b]	E/Z (3a)[b]
1	C_1	23	93	>20 : 2 : 1	nd[c]
2	C_1	60	79	>20 : 1 : 2.2	nd[c]
3	C_2[d]	23	33	1.9 : 1 : 1.3	>20:1
4	C_3[e]	60	73	3.8 : - : 1	nd[c]
5	C_4/PCy_3[f,g]	50	39	4 : 4.8 : 1	19:1
6	C_5	60	97	4.6 : 13.8 : 1	>20:1
7	C_6	60	90	- : - : 1	nd[c]
8	C_7	60	98	11.6 : 7 : 1	5:1[c]
9	C_8	60	98	1 : 11.7 : 3.5	>20:1
10	C_8/L_1[h]	60	99	1.8 : 9.6 : 1	17:1
11	C_8/L_2[h]	60	98	3 : 1 : -	3.3:1[c]
12	C_8/L_3[h]	60	16	15 : 1 : -	nd[c]
13	C_8/PCy_3[h]	60	99	1 : 1.1 : -	9:1
14	C_8/PPh_3[h]	60	99	1.7 : 11.5 : 1	>20:1
15	C_8/PPh_3[i,j]	60	99	2.4 : 16.4 : 1	>20:1
16	C_8/PPh_3[h,k]	60	97	1 : 1.7 : -	11:1
17	C_8/PPh_3[h,k]	90	99	- : 1 : 9	>20:1[c]
18	C_8/PPh_3[h,k]	110	99	- : 1 : >20	nd[c]



[a]Reactions conducted in a J-Young NMR tube: **1a** (0.05 mmol). [b]Determined by ^{1}H NMR using an internal standard. [c]Major regioisomer was obtained as a mixture of stereoisomers (see the Supporting Information (SI)). [d]H_2 activation. [e]5 mol % $NaBAr_F$. [f]30 mol %. [g]12.5 mol % $NaBAr_F$. [h]5 mol %. [i]10 mol %. [j]30 h. [k]In toluene-d_8.

a benzothiophene (**3m**), and a pyrazole (**3n**) were also tolerated. A more congested 2,3,4-substituted conjugated diene could be prepared using this method (**3o**). Quite notably, alkyl containing substrates were also isomerized successfully to the kinetic product, thus highlighting the possibility to access diversely substituted 1,3-dienes with this strategy. A sterically demanding 1-adamantyl substituent (**3p**), a cyclohexyl (**3q**), and a phenethyl moiety (**3r**) gave satisfactory results. Of note, the similar physicochemical properties of the regioisomeric cyclohexyl products prevented efficient purification, further highlighting the necessity to achieve excellent selectivity. Starting from a perillic acid derivative, [3]-dendralene **3s**, which possess a potentially labile allylic stereocenter, was also prepared by this approach.[22] Even though the stereoselectivity was lower in this case (E/Z = 5:1), this example illustrates the exquisite chemoselectivity of the [Ru−H] catalyst because four distinct alkenes are present in the substrate/product. Remarkably, a benzylic stereocenter in the α-position to the 1,1-disusbtituted alkene was not enantiomerized as demonstrated with the enantiospecific isomerization of **1t** into **3t**. Finally, with proper adjustment of the reaction time, long-range conjugative isomerization was achieved without noticeable reduction of the catalytic performances with up to five methylene units between each olefinic moiety (**3u**−**w**).

The limits of our protocol were further explored by subjecting a substrate terminated by a stereodefined vinyl ether (E)-**5a** to the optimized reaction conditions (Figure 3A). Gratifyingly, the corresponding conjugated dienyl ether (E,E)-**6a** was isolated in 65% with excellent stereocontrol (EE > 20:1). We also found that an α,β-unsaturated ester (**7a**) could be deconjugated to produce preferentially a conjugated branched 1,3-diene (**8a**, E/Z > 20:1, 53% yield) (Figure 3B).

To gain insights into the origin of the regio- and chemoselectivity, preliminary mechanistic experiments were conducted. The Ru-catalyzed remote isomerization of a geminally dideuterated substrate at C1 (**1b**-d_2) was particularly instructive (Figure 4A). While a substantial decrease of the deuterium content at C1 was noted, D incorporation was measured at C3, C4, C5, and C6. These observations are consistent with a metal-hydride mechanism in which: (i) migratory insertion across C1═C2 is reversible and produces catalytically competent [Ru−D] species, (ii) the terminal olefin is isomerized via iterative migratory insertion/β-H elimination sequences, and (iii) incorporation at C3 occurs after formation of the branched 1,3-diene **3b**. This last conclusion is further supported by the results of the experiment disclosed in Figure 4B. Indeed, when a pure sample of **3a** was resubjected to the optimized reaction conditions and monitored by ^{1}H NMR spectroscopy, gradual formation of linear diene **4a** was accompanied by the appearance of deconjugated diene **2a**. This suggests that **2a** is a likely precursor to **4a**, the latter being produced by [Ru−H] insertion across C1═C2 and subsequent β-H3 elimination. Finally, exposing **3a** to the catalytic combination C_8/PPh_3 in refluxing toluene led to the exclusive formation of a complex stereoisomeric mixture of the thermodynamically more stable regioisomer **4a** (Figure 4C). We found that the stereochemical purity of a 2:1 E/Z mixture of **3f** could be improved to >20:1 within 8 h by subjecting it to our optimized reaction conditions (Figure 4D). This prompted us to apply this protocol to diene **3x** (E/Z 6:1), prepared independently by a Ru-catalyzed ene−yne metathesis. Perfect stereocorrection was achieved within 10 h without traces of other regioisomeric products. This result complements those obtained by Diver.[12] We anticipate this approach may be systematized because intermolecular ene−yne metathesis generally produces stereoisomeric mixtures (typical E/Z ratio ranges from ∼1:1 to ∼5:1).[23] Importantly, we noted that while developing Ru-catalyzed addition of aldehydes to dienes, Ryu and co-workers observed the quantitative formation of a π-allyl ruthenium complex within ∼15 min when C_8 was reacted with 1.0 equiv of isoprene in $CDCl_3$ at 90 °C.[20,24,25] When a similar experiment was conducted using equimolar amounts of C_8, PPh_3 and **3a** at 60 °C, we could not detect formation of analogous π-allyl intermediates as no apparent reaction occurred based on ^{1}H and ^{31}P NMR spectroscopy (see the SI for details). Overall, the results presented in Figure 4 put into further perspective the perfect enantiospecific nature of the

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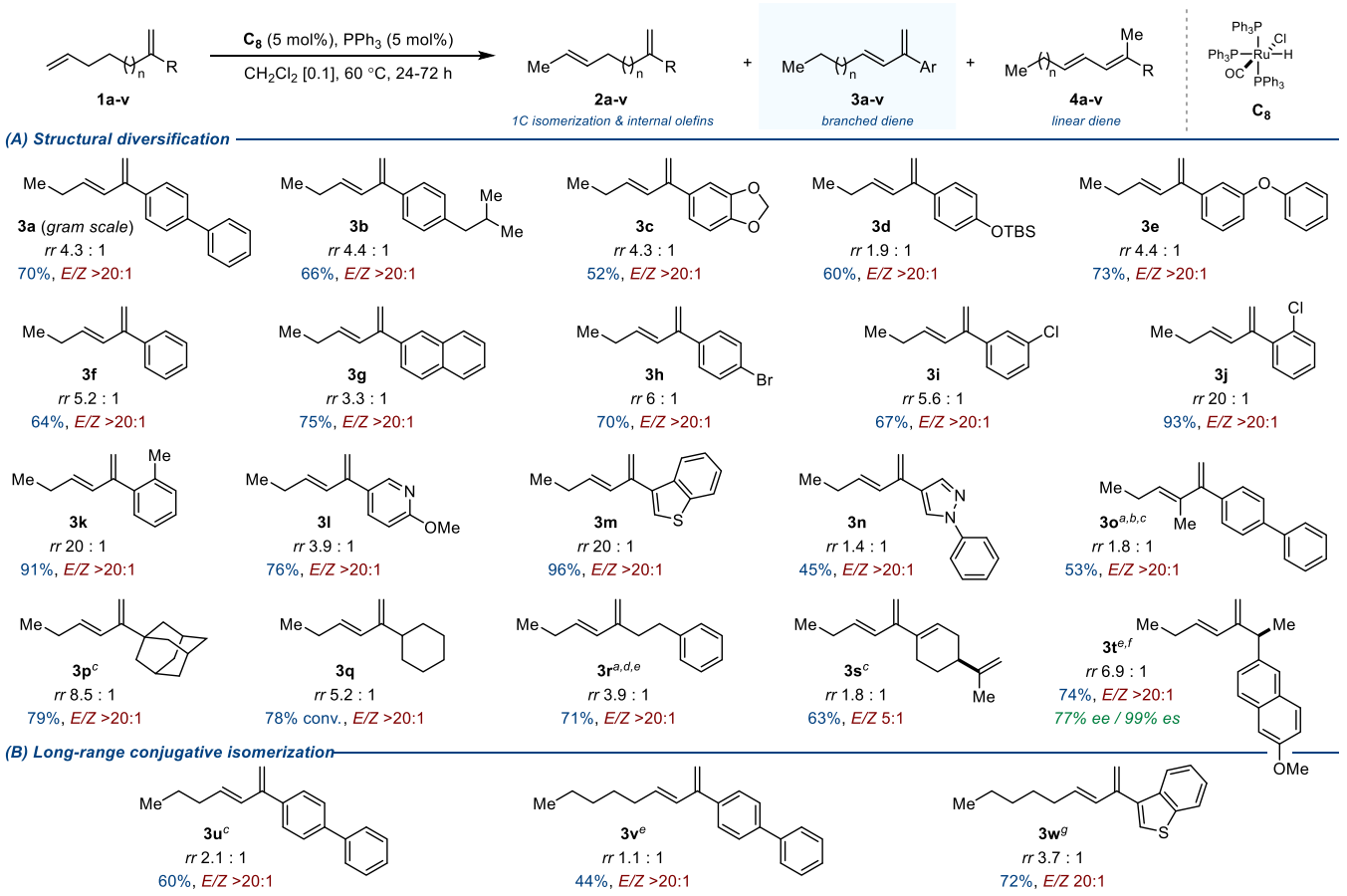

Figure 2. Scope of the Ru-catalyzed conjugative isomerization of dienes (0.3 mmol scale, unless otherwise noted). The yield was reported for the pure major regioisomer, isolated by column chromatography (except **3p** and **3s**). Stereoselectivity (E/Z) was determined by ^{1}H NMR using an internal standard. The regioisomeric ratio (rr) is expressed as the ratio between **3** and all other isomers (**2** + **4**) as determined by ^{1}H NMR using an internal standard. [a]In toluene. [b]90 °C. [c]48 h. [d]80 °C. [e]72 h. [f]Enantiomeric excess was determined by high-performance liquid chromatography (HPLC) using a chiral stationary phase. [g]120 h.

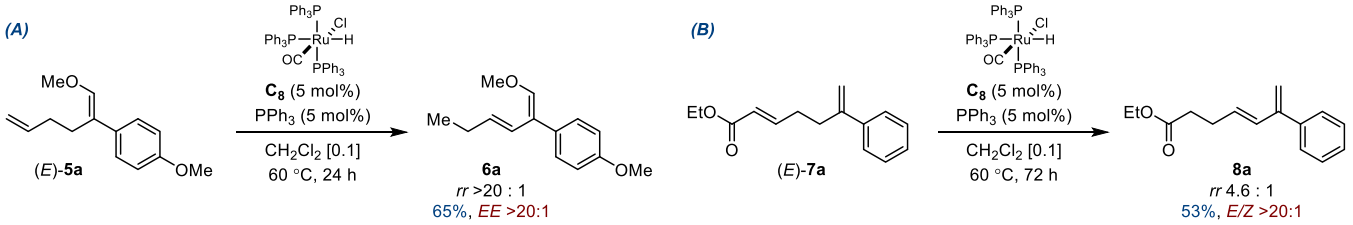

Figure 3. Ru-catalyzed conjugative isomerization of electronically biased substrates. The yield was reported for the major regioisomer after purification. Stereoselectivity (E/Z) was determined by ^{1}H NMR with an internal standard. The regioisomeric ratio (rr) is expressed as the ratio between **6a** or **8a** and all other isomers as determined by ^{1}H NMR using an internal standard.

isomerization of **1t** into **3t** (Figure 2). Retrospectively, the high level of regioselectivity obtained for the sterically more demanding substrates (**1j,k**, **1m**, **1p**, **1w**) may also be ascribed to the limited ability of the Ru−H catalyst to insert across the 1,1-disubstituted alkene moiety.

The synthetic utility of our approach was established by conducting a series of one-pot processes (Figure 5). We showed that the Ru-catalyzed conjugative isomerization can be combined with [4 + 2] cycloaddition reactions using either an electron-deficient dienophile such as dimethyl acetylenedicarboxylate or nitrosobenzene to afford cycloadducts **9a** and **10y** in 62 and 64% yields, respectively (Figure 5A,B). Noticeably, **10y** was isolated as a single regioisomer.[26] Based on our mechanistic investigations, the cycloadditions were performed at 60 °C to avoid extensive formation of nonconjugated dienes **2** and linear dienes **4**.

In recent years, the development of selective catalytic methods using cyclic or linear dienes has flourished.[4c−f] To date, protocols based on dienes with a 2,4-disubstitution pattern are much less common. Pleasingly, we found that the Ru-catalyzed conjugative isomerization could be effected in THF sequentially with a Cu-catalyzed protoboration of the in situ generated diene, followed by a classical oxidative work-up procedure. Quite remarkably, among the dozen of possible isomeric structures that can be generated theoretically, homoallylic alcohol (*E*)-**11k**, resulting from a formal 1,2-borylation, was obtained preferentially in a 74% yield (Figure 5C).[4f,27] The Dong group recently reported a highly

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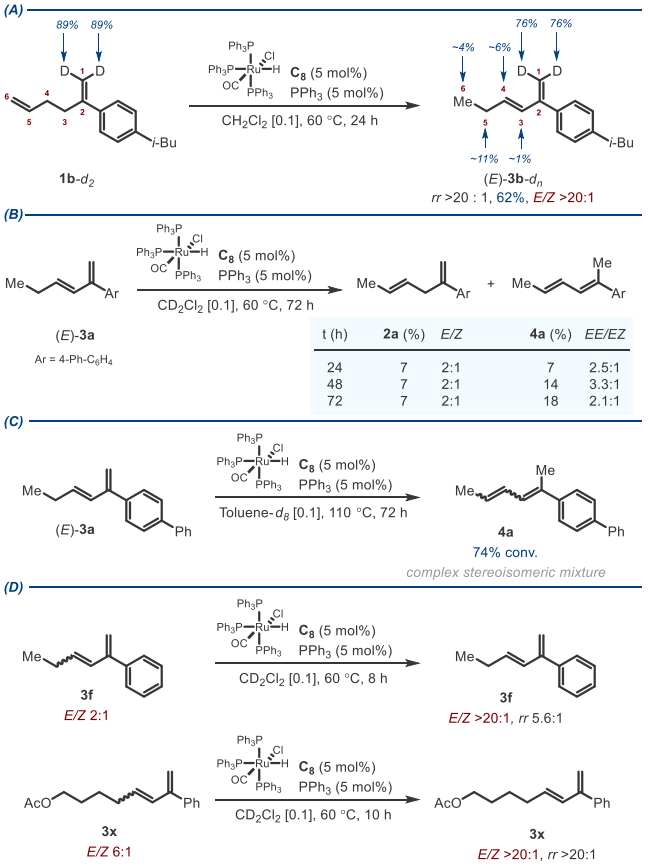

Figure 4. Preliminary mechanistic investigations. (A) Labeling experiments. (B) Postcatalytic isomerization of **3a**. (C) Isomerization of **3a** under thermodynamic reaction conditions. (D) Stereocorrective isomerizations.

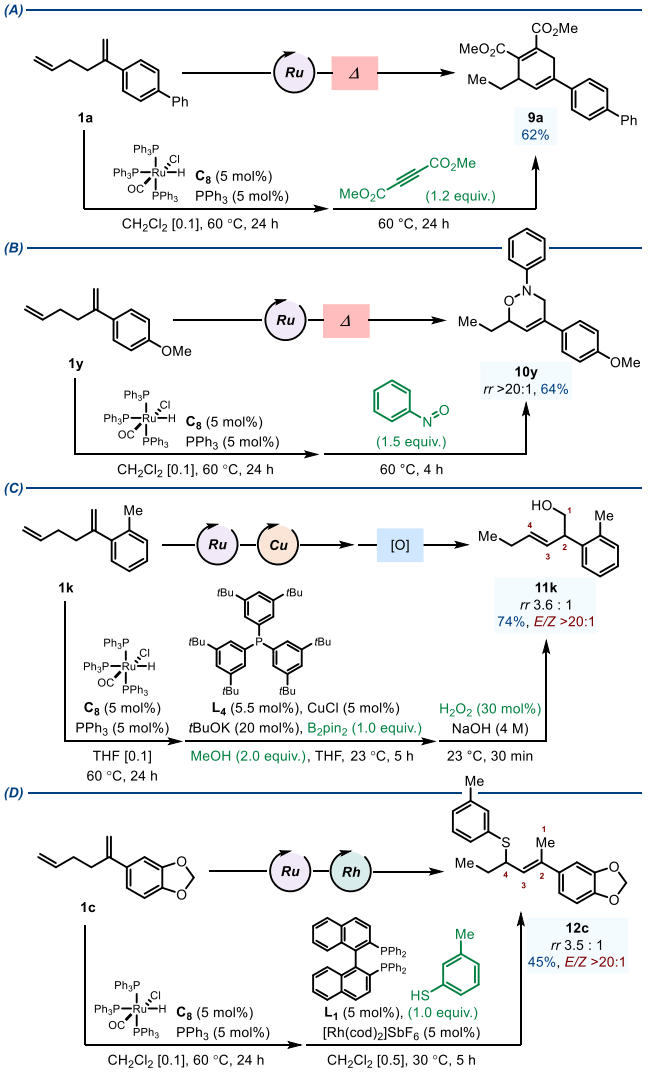

Figure 5. One-pot catalytic processes. (A) and (B) Ru-catalyzed conjugative isomerization/[4 + 2] cycloadditions. (C) Ru-catalyzed conjugative isomerization/Cu-catalyzed protoboration followed by alkali oxidation. (D) Ru-catalyzed conjugative isomerization/Rh-catalyzed hydrothiolation.

regioselective Rh-catalyzed Markovnikov 1,2-hydrothiolation of 2-substituted 1,3-dienes.[28] To explore the compatibility of this system with our conjugative isomerization protocol, **1c** was engaged in a multimetallic [Ru/Rh] catalytic sequence (Figure 5D). Unexpectedly, allyl aryl sulfide (*E*)-**12c** was produced in majority with a high level of stereocontrol. Upon inspection of the crude reaction mixture, the expected 1,2-addition product was detected in a minor amount along with traces of other regioisomers. Beyond considerations of catalyst affinity in multimetallic reactions,[15g] this result further underscores the impact of the diene substitution pattern on the outcome of established selective catalytic methods.

In summary, using a commercially available ruthenium hydride complex, we have developed an operationally simple protocol that affords branched 1,3-dienes by conjugative isomerization of two remote alkenes. These kinetic products are obtained preferentially over the thermodynamically more stable linear isomers by conducting the reaction at temperatures not exceeding 60 °C and in the presence of a catalytic amount of triphenylphosphine. A variety of functional groups and heterocycles are well tolerated and isomerization can be sustained over several methylene units. Preliminary investigations point to a metal-hydride mechanism consisting of repeated migratory insertions/β-H eliminations, while sterically demanding substrates limit the contribution of competing pathways by increasing chemoselective insertion across the terminal olefin. Two one-pot sequential multimetallic selective catalytic sequences using [Ru/Cu] and [Ru/Rh] couples have been developed. They are intended to serve as blueprints for the discovery of related enantioselective processes. Work is currently underway in our laboratories to tackle these challenges.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02144.

Experimental procedures and characterization of all new compounds (PDF)
(ZIP)

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Notes

The authors declare no competing financial interest.

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