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Multicatalytic Stereoselective Synthesis of Highly Substituted Alkenes by Sequential Isomerization/Cross-Coupling Reactions

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ABSTRACT: Starting from readily available alkenyl methyl ethers, the stereoselective preparation of highly substituted alkenes by two complementary multicatalytic sequential isomerization/cross-coupling sequences is described. Both elementary steps of these sequences are challenging processes when considered independently. A cationic iridium catalyst was identified for the stereoselective isomerization of allyl methyl ethers and was found to be compatible with a nickel catalyst for the subsequent cross-coupling of the in situ generated methyl vinyl ethers with various Grignard reagents. The method is compatible with sensitive functional groups and a multitude of olefinic substitution patterns to deliver products with high control of the newly generated C=C bond. A highly enantioselective variant of this [Ir/Ni] sequence has been established using a chiral iridium precatalyst. A complementary [Pd/Ni] catalytic sequence has been optimized for alkenyl methyl ethers with a remote C=C bond. The final alkenes were isolated with a lower level of stereocontrol. Upon proper choice of the Grignard reagent, we demonstrated that C(sp²)-C(sp²) and C(sp²)-C(sp³) bonds can be constructed with both systems delivering products that would be difficult to access by conventional methods.

■ INTRODUCTION

The development of practical, economical and widely applicable catalytic processes which enable a rapid increase in molecular complexity from readily available chemicals lies at the forefront of synthetic chemistry. In this context, the remote functionalization of an organic molecule by alkene migration along a hydrocarbon skeleton has attracted increased attention, leading to the devise of particularly challenging and creative transformations.¹⁻² In such relay reactions, two distant functional groups can be interconverted through a transmitting process, independently of the length of their tether. The successful realization of remote functionalization protocols hinges on several key factors: (i) the triggering event that initiates olefin migration; (ii) the nature of the terminal functional group undergoing refunctionalization which provides a favorable thermodynamic driving-force; (iii) the kinetic ability of the catalyst to sustain olefin migration independently of the length of the hydrocarbon chain.

Over the last decade, our laboratory has focused on the development of stereoselective short- and long-distance isomerizations of allylic and alkenyl alcohols using well-defined [Ir-H] and [Pd-H] catalysts (Figure 1-A).³ Whereas, iridium catalysts were applied to the highly enantio- and diastereoselective isomerization of primary allylic alcohols, palladium-hydrides enabled the long-range isomerization of primary and secondary alkenyl alcohols as well as the deconjugative isomerization of α,β -unsaturated amides, esters and ketones.⁴ These reactions are typically initiated by rate-determining hydro-metallation of the C=C bond and driven by the final interconversion of the elusive enol intermediates into a ther-

modynamically more stable carbonyl group. In a broader context, the propensity of nickel and palladium catalysts to shuttle C=C bonds over a carbon skeleton ('chain-walking' process)⁵ combined with their widespread use in cross-coupling chemistry has led to the development of some of the most successful and elegant remote functionalizations. Protocols where carbon-carbon bond formation triggers isomerization can be distinguished from methods where it participates in the terminal refunctionalization event. For instance, inspired by pioneering observations made by Molpolder and Heck,⁶ Sigman has established a series of highly enantioselective long-range redox-relay reactions initiated by the arylation of a remote alkene (Figure 1-B).⁷ Using a related Pd-catalyzed Heck arylation as initiator and by combining a chain-walking process with a selective cyclopropane ring-opening event, Marek was able to generate stereochemically complex linear carbonyls (Figure 1-B).⁸ The Baudoin group recently devised an impressive regioconvergent strategy for the synthesis of functionalized linear alkanes starting from (mixtures of) branched alkyl bromides.⁹ The strategy relies on the identification of monodentate phosphine ligands able to retard reductive elimination of a transient organopalladium complex with respect to metal migration (Figure 1-C). Following a similar inspiration, Martin elaborated a Ni-catalyzed site-selective carboxylation of remote C(sp³)-H positions with carbon dioxide based on a bromination/isomerization/cross-coupling concatenation starting from mixtures of simple chemical feedstock. Remarkably, a switch in selectivity was achieved by simple adjustment of the reaction conditions (Figure 1-C).¹⁰ Zhu and coworkers disclosed a regioselective benzylic functionalization using a Ni-catalyzed isomerization/arylation sequence.¹¹ The reaction is initiated by

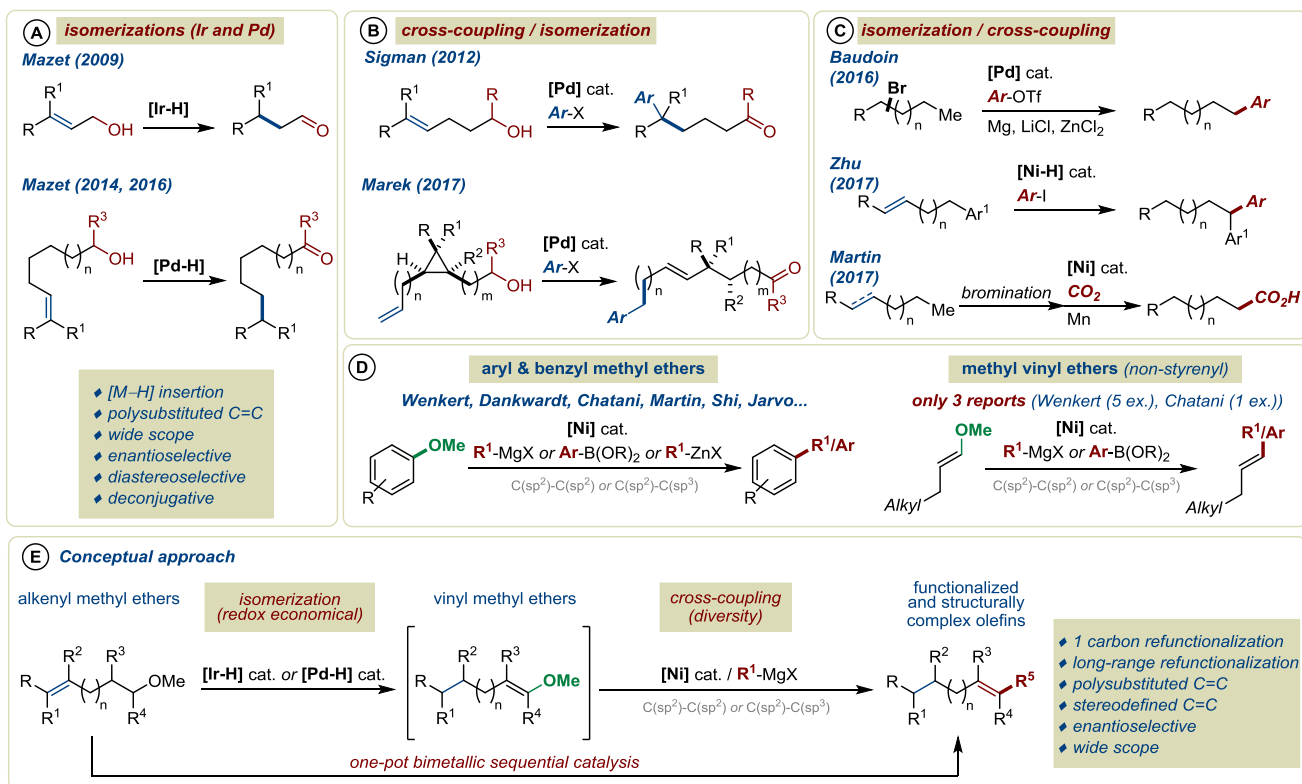


Figure 1. (A) Ir- and Pd-catalyzed isomerization of alkenyl alcohols. (B) Remote refunctionalization reactions triggered by a cross-coupling reaction. (C) Remote refunctionalizations terminated by a cross-coupling reaction. (D) Ni-catalyzed cross-coupling reactions using C-OMe electrophiles. (E) Proposed isomerization/cross-coupling sequence starting from alkenyl methyl ethers and affording stereodefined polysubstituted alkenes.

the hydrometallation of a remote (terminal or 1,2-disubstituted) olefin and is driven by the formation of a thermodynamically more stable benzyl-nickel intermediate prior to product formation (Figure 1-C).

To further extend the current portfolio of long-range refunctionalization reactions, we wondered whether we could merge a [M-H]-catalyzed (long-range) isomerization of alkenyl methyl ethers with a Ni-catalyzed cross-coupling by C-O bond activation of the transiently generated methyl vinyl ethers to stereoselectively generate structurally sophisticated polysubstituted olefins (Figure 1-E).¹² Conceptually, this approach integrates the features of an underdeveloped and potentially stereoselective redox-economical isomerization with the modularity and diversity of a challenging cross-coupling process for C(sp²)-C(sp²) and C(sp²)-C(sp³) bond formation. Moreover, as it bypasses preformation of electrophilic coupling partners that are notoriously difficult to synthesize and isolate, it bears the potential to substantially impact synthetic efficiency. The successful realization of our objective requires addressing the specific challenges associated with each individual step as well as the difficulties inherent to the development of a sequential one-pot multicatalytic process employing two distinct transition metal catalysts.¹³

Vinyl methyl ethers are particularly reactive molecules and methods for their stereoselective preparation are scarce. Base-assisted or metal-catalyzed isomerizations approaches are restricted to a 1-carbon migration of allyl

methyl ethers.¹⁴ They display limited scope and are often moderately stereoselective. In 1978, Baudry and Ephritikhine reported the Ir-catalyzed isomerization of a handful of linear and cyclic primary allyl ethers into (*E*)-configured methyl vinyl ethers.¹⁴⁰ Later, Miyaura elaborated on this study and developed related systems for the preparation of a limited set of alkoxy-allylboronates and silyl enol ethers¹⁵ While our studies were in progress, Nishimura and coworkers disclosed an iridium-catalyzed hydroarylation of alkenyl ethers based on an isomerization/asymmetric C-H activation sequence affording secondary alkyl ethers with high levels of enantioselectivity.¹⁶ As is often the case in metal-catalyzed isomerization reactions initiated by hydrometallation, in all these reports, we note that more reactive terminal or 1,2-disubstituted olefins are common substrates. *Importantly, tri- or tetrasubstituted olefinic substrates are much less employed owing to their reduced ability to coordinate to transition metal catalysts and therefore to react.*^{3c,i,1,4,12}

Recent years have witnessed a renewed interest in the use of C-O electrophiles as alternative to aryl halides in metal-catalyzed cross-coupling reactions.^{17,18} Since the seminal report of Wenkert,^{18a,b} the superiority of Ni catalysts over Pd catalysts has been clearly established. Despite their much reduced reactivity compared to other C-O electrophiles, aryl, benzyl and styrenyl methyl ethers have attracted great attention (Figure 1-D). This is motivated by their synthetic availability, the inertness of the waste generated and their compatibility with a variety of

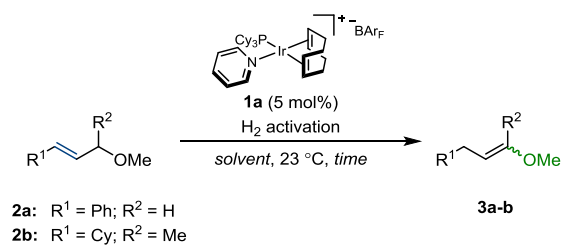
nucleophiles. Specifically, organoboron, organozinc and Grignard reagents have been established as excellent coupling partners in Suzuki-Miyaura, Negishi and Kumada-Tamao-Corriu type cross-couplings respectively, leading to the development of a number of efficient catalytic technologies.¹⁸ In sharp contrast, a survey of the recent and ever-growing literature on this topic reveals that alkyl vinyl ethers have been found to be competent coupling partners only on very rare occasions.^{18a-b,h} Mechanistically this may be explained by the lack of beneficial π interactions of the metal center with the neighboring aromatic system.¹⁹

In this article, we report the development of two highly efficient one-pot multicatalytic processes which streamline access to a wide variety of structurally complex polysubstituted alkenes with high levels of olefin stereoselectivity. These sequential reactions combine either one-carbon (Ir) or long-range (Pd) catalytic isomerizations of allyl or alkenyl methyl ethers with a subsequent and equally challenging Ni-catalyzed cross-coupling between the *in situ* generated methyl vinyl ethers and various Grignard reagents. By capitalizing on the compatibility of mechanistically distinct metal-catalyzed transformations as well as on the complementarity of the two isomerization reactions, this approach bypasses isolation of sensitive reaction intermediates while increasing catalytic efficiency and molecular complexity. The unusual reactivity observed for highly substituted prochiral olefinic substrates enabled the development of an enantioselective variant of the [Ir/Ni] catalytic sequence.

RESULTS AND DISCUSSION

Reaction development (I): Ir-catalyzed isomerization of allyl methyl ethers. We commenced our study by evaluating the Pfaltz modified version of Crabtree's catalyst (**1a**) in the isomerization of two representative allyl methyl ethers **2a-b** (Table 1).²⁰ This iridium catalyst was selected for its ability to isomerize a broad range of primary allylic alcohols under mild reaction conditions once activated with molecular hydrogen.^{3c,b,21} While no reaction occurred with **2a** after 0.5 h in toluene, 66% conversion into 3-methoxyallyl-benzene **3a** was attained within 2 h with a satisfactory *E/Z* ratio (10:1). A prolonged reaction time led to decomposition of the product (Entry 1-3). Rapid isomerization into **3a** was achieved in THF (0.5 h, 70% conv., 18:1 *E/Z*). Prolonging the reaction time did not improve significantly conversion and was accompanied by noticeable erosion in stereoselectivity (Entry 4-6). These results are in line with observation made by Miyaura and coworkers in the isomerization of allyl silyl ethers.¹⁵ Remarkably, reducing the catalyst loading to 2.5 mol% enabled to achieve a similar productivity while maintaining a high level of stereoselectivity (Entry 7). Similar results were obtained in 2-methyl-tetrahydrofuran (2-MeTHF), a solvent derived from biomass (Entry 8-10). Gratifyingly, isomerization of (*E*)-(3-methoxybut-1-en-1-yl)cyclohexane **2b** was achieved under similar conditions affording **3b** quantitatively with excellent stereocontrol (*E/Z* >20:1; Entry 12). This result is more surprising as only primary

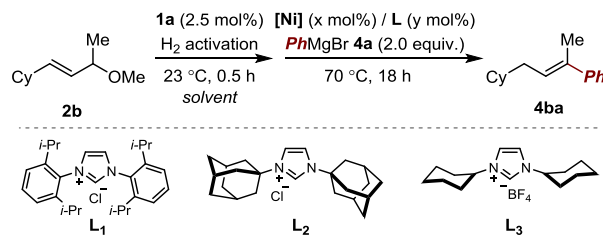
Table 1. Reaction optimization^a



entry	substrate	solvent	t (h)	conv. (%) ^b	<i>E/Z</i> ^b
1	2a	toluene	0.5	<5	<i>nd</i> ^c
2	2a	toluene	2	66	10:1
3	2a	toluene	18	<i>dec.</i> ^d	<i>nd</i> ^c
4	2a	THF	0.5	70	18:1
5	2a	THF	3	79	2.2:1
6	2a	THF	18	80	2.2:1
7	2a	THF	18	69 ^e	>20:1
8	2a	2-MeTHF	0.5	63	8.3:1
9	2a	2-MeTHF	18	80	2:1
10	2a	2-MeTHF	18	74 ^e	14:1
11	2b	THF	0.5	>99 ^e	8.8:1
12	2b	2-MeTHF	0.5	>99 ^e	>20:1

^a Reaction conditions: **2a-b** (0.05-0.1 mmol), [0.1]. The precatalyst is activated by H₂ for 1 min. followed by degassing of the solution prior to substrate addition. ^b Determined by ¹H NMR of the crude mixture using an internal standard. ^c Not determined. ^d Decomposition. ^e Using 2.5 mol% of **1a**.

Table 2. Reaction optimization^a



Entry	[Ni] (x)	L (y)	solvent	yield (%) ^b	<i>E/Z</i> ^b
1	[Ni(cod) ₂] (5)	PCy ₃ (20)	THF	<i>dec.</i> ^c	-
2	[Ni(cod) ₂] (5)	PCy ₃ (20)	2-MeTHF	47 ^d	>20:1
3	[(Ph ₃ P) ₂ NiCl ₂] (5)		2-MeTHF	20	>20:1
4	[Ni(cod) ₂] (5)	dcpe (5) ^e	2-MeTHF	<i>nr</i> ^f	-
5 ^g	[Ni(OAc) ₂] (5)	L ₁ (10)	2-MeTHF	37	>20:1
6 ^g	[Ni(OAc) ₂] (5)	L ₂ (10)	2-MeTHF	31	>20:1
7 ^g	[Ni(OAc) ₂] (5)	L ₃ (10)	2-MeTHF	56	>20:1

^a Reaction conditions: **2a-b** (0.1-0.25 mmol), [0.1]. The precatalyst is activated by H₂ for 1 min. followed by degassing of the solution prior to substrate addition. ^b Determined by ¹H NMR of the crude mixture using an internal standard. ^c Decomposition. ^d After purification by column chromatography. ^e dcpe = 1,2-bis(dicyclohexylphosphino)ethane. ^f No cross-coupling product observed although **3b** was generated quantitatively. ^g Using 1.3 equiv. of PhMgBr **4a**.

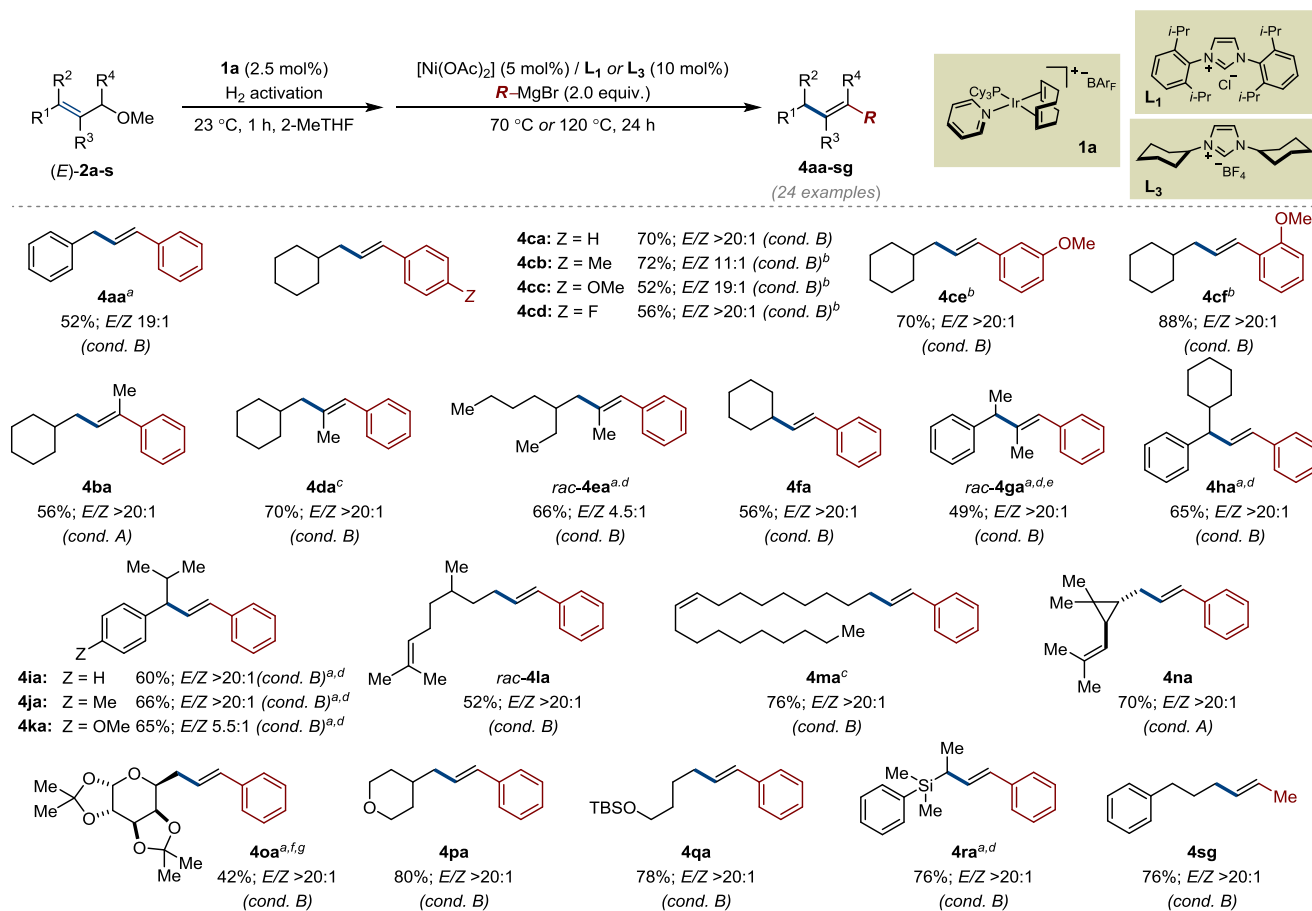


Figure 2. Scope of the [Ir/Ni]-catalyzed isomerization/cross-coupling sequence with variations both on the nucleophilic and electrophilic component of the reaction (0.25 mmol, [0.1]). Conditions A: **L**₃, 70 °C. Conditions B: **L**₁, 120 °C. ^a Isomerization: 18 h. ^b 3 equiv. of RMgBr. ^c 2 h. ^d 5 mol% **1a**. ^e 95% purity. ^f 10 mol% Ni(OAc)₂, 20 mol% **L**₁. ^g 10 mol% **1a**.

allylic alcohols were isomerized effectively with **1a**.^{3c,g}

Reaction development (II): Sequential [Ir/Ni]-catalyzed isomerization/cross-coupling of allyl methyl ethers using Grignard reagents. Having identified suitable reaction conditions for the isomerization of two model allyl methyl ethers, we next set out to assess whether this system could be combined with a Ni-catalyzed cross-coupling reaction following a one-pot/sequential approach (Table 2). To this end, preliminary investigations were conducted under relatively mild conditions using **2b**, phenylmagnesium bromide **4a** as nucleophilic coupling partner and the ubiquitous PCy₃/[Ni(cod)₂] combination for activation of C–O electrophiles. Only decomposition of the starting materials was observed in THF (Entry 1). In contrast, complete consumption of **2b** was obtained in 2-MeTHF and (*E*)-**4ba** was the only detectable product by ¹H NMR analysis of the crude reaction mixture after evaporation of all volatile residues (Entry 2). Although the cross-coupling product was isolated in only 47% after purification, this result clearly validates our initial design plan. Variation of the nickel source and/or the phosphine ligand did not lead to significant improvements (Entry 3–4; see SI for additional screening results).²² Subsequently, a small set of *N*-heterocyclic carbene precursors **L**₁–**L**₃ was evaluated using [Ni(OAc)₂] (Entry 5–7). Much to our satisfaction, the cy-

clohexyl-*N*-substituted ligand **L**₃ delivered **4ba** in 56% yield as a single stereoisomer.²³

The generality of the reaction was next examined using a broad range of primary and secondary allyl methyl ethers with diversely substituted olefinic moieties (Figure 2). Although the conditions identified in Table 2 (**L**₃, 70 °C) were applicable to several substrate combinations, a second set of reaction conditions was developed for more difficult cases using **L**₁ and higher temperatures (120 °C). Remarkably, with both protocols, the newly generated olefinic products were quasi-systematically obtained with high to very high levels of stereocontrol (4.5:1 to >20:1) and in moderate to very good yields (42–88%). Electron-rich and electron-deficient aryl Grignard reagents were successfully cross-coupled with in situ generated methyl vinyl ethers derived from allyl methyl ethers lacking a proximal aromatic substituent able to stabilize reactive intermediates by favorable secondary interactions (**4ca–cf**).¹⁹ Substrates with diverse alkene substitution patterns (R¹, R², R³; **4ba–ga**) were also found to be compatible with our strategy and even **2g** which possesses a tetrasubstituted olefinic moiety was reacted to afford the final product **4ga** in 49% yield and a *E/Z* ratio >20:1. Similarly, particularly congested allyl methyl ethers were engaged in a productive and selective one-pot [Ir/Ni]-catalyzed isomerization/cross-coupling sequence (**4ha–4ka**). While allyl me-

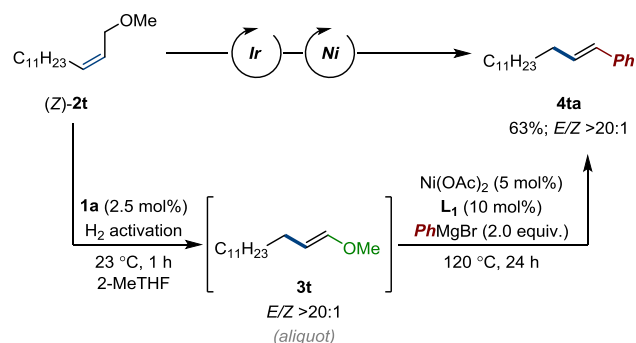


Figure 3. Demonstration of the stereoconvergence of the [Ir/Ni]-catalyzed isomerization/cross-coupling sequence using (Z)-2t.

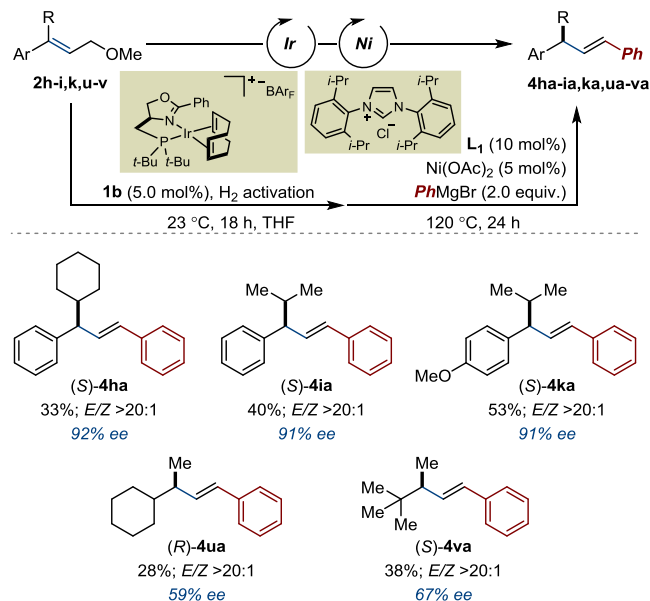


Figure 4. Proof-of-principle for the [Ir/Ni]-catalyzed enantioselective isomerization/cross-coupling sequence. Reactions conducted on a 0.1 mmol scale. Yield after purification by column chromatography.

thyl ethers with additional C=C bonds and/or proximal stereocenters did not undergo parasitic isomerization and/or epimerization (41a-40a), O- and Si-containing substrates were well tolerated (40a-4ra). Finally, methyl magnesium bromide could also be employed as nucleophile in the cross-coupling reaction, highlighting the possibility to also create C(sp²)-C(sp³) bonds with high levels of stereocontrol. Other alkyl Grignard reagents were also successfully cross-coupled. Unfortunately product formation was systematically accompanied by generation of inseparable terminal olefins resulting from protodemetalation as well as products of homocoupling of the Grignard reagents (See SI).²⁴ Submitting (Z)-2t to the same sequence delivered 4ta in 63% yield as a single stereoisomer (E/Z > 20:1). Aliquots taken during the isomerization reaction already showed that 3t was generated in a E/Z ratio > 20:1, indicating the Ir-catalyzed process is stereoconvergent in nature (Figure 3).

The one-pot isomerization/cross-coupling sequence was next conducted with five prochiral allyl methyl ethers (2h-i, k, u-v) and chiral catalyst 1b was used instead of 1a

(Figure 4).^{3c,8} In line with previous observations made for the iridium-catalyzed isomerization of primary allylic alcohols, the reactivity of the chiral catalyst was lower than that of 1a and THF was found to be the optimal solvent in this system. Ligand L1 was best suited for the nickel-catalyzed cross-coupling reaction. The products were therefore isolated in moderate yield but with particularly high levels of stereo- and enantiocontrol for aryl containing substrates (E/Z > 20:1; 91-92% ee). For alkyl containing substrates, lower levels of enantiocontrol were obtained while maintaining a high level of stereocontrol (E/Z > 20:1; 59-67% ee). These results are in contrast with the consistently high levels of enantioselectivity obtained across a broad range of substrates in the related Ir-catalyzed isomerization of allylic alcohols and point to subtle mechanistic differences.^{3b}

Reaction development (III): Sequential [Pd/Ni]-catalyzed long-range isomerization/cross-coupling of alkenyl methyl ethers. Because attempts to isomerize homoallylic methyl ethers or more remote alkenyl methyl ethers with iridium catalyst 1a were not met with success, we decided to evaluate the compatibility between some of the palladium catalysts developed in our group for long-range isomerizations with the nickel-catalyzed cross-coupling of methyl vinyl ethers potentially generated in situ.^{3b-1,4,25}

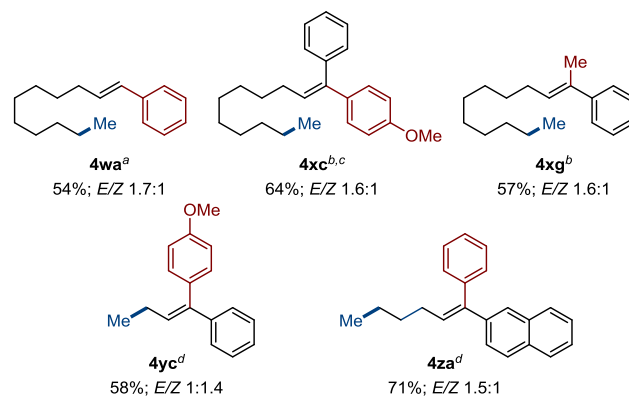
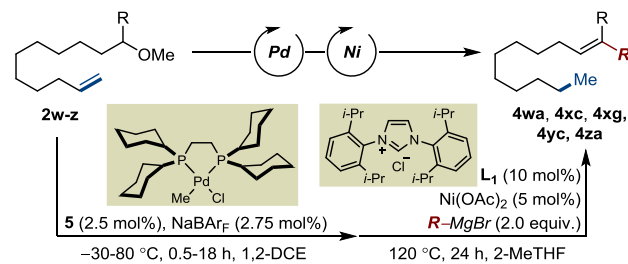


Figure 5. [Pd/Ni]-catalyzed long-range isomerization/cross-coupling sequence starting from alkenyl methyl ethers (0.25 mmol). The major isomer is displayed. ^a Isomerization conducted at -30 °C. ^b Isomerization conducted at 80 °C. ^c Contains 15% of internal olefins derived from 2x. ^d Isomerization conducted at 50 °C

For this sequence to be operative, we found that two different solvents had to be used for each individual reaction (1,2-dichloroethane then 2-MeTHF) (Figure 5). In the case of 2w and 2x, ¹H NMR monitoring of the isomerization reaction indicated that generation of the targeted

methyl vinyl ether was not quantitative and was systematically accompanied by the formation of ca. 20% of several internal olefins. This is in contrast with the long-range isomerization of alkenyl alcohols and deconjugative isomerization of α,β -unsaturated carbonyls for which the refunctionalization into a ketone or an aldehyde seems to constitute a stronger driving force as these reactions are often quantitative.^{2b,3} Interestingly, the isomerization of **2w** could be conducted at $-30\text{ }^{\circ}\text{C}$ and followed - after solvent exchange - by the nickel-catalyzed cross-coupling using phenyl magnesium bromide to yield **4wa** (54%; $E/Z = 1.7:1$). The secondary alkenyl methyl ethers **2x-z** were less reactive and required a temperature of $50\text{--}80\text{ }^{\circ}\text{C}$ for the isomerization to proceed but were nonetheless successfully cross-coupled with aryl magnesium bromide **3a** or **3c** and methyl magnesium bromide **3g** (**4xc**: 64%; **4xg**: 57%; **4yc**: 58%; **4za**: 71%).

A noticeable difference between the [Ir/Ni] and [Pd/Ni] sequences is the much reduced levels of stereocontrol measured with the latter. In order to better understand the origin of this dichotomy several experiments were conducted using a 1.5:1 E/Z stereoisomeric mixture of methyl vinyl ether **3f** (itself prepared by an independent Wittig olefination reaction. See Supporting Information) (Figure 6).

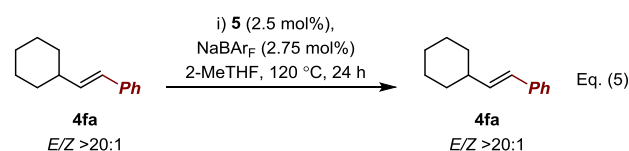
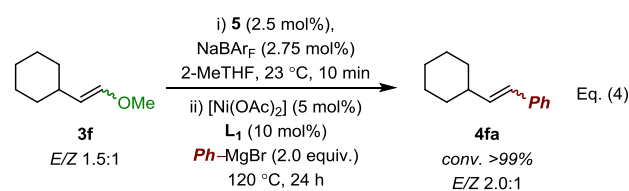
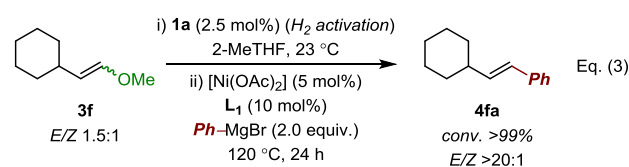
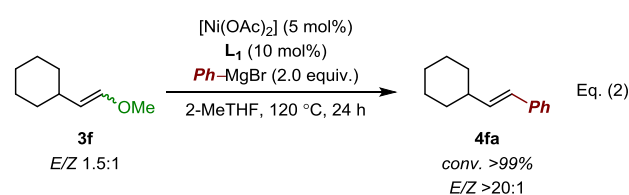
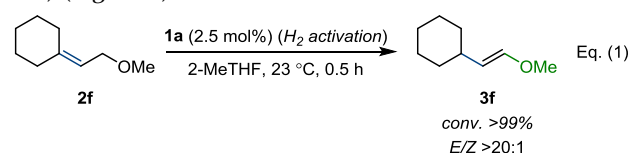


Figure 6. Evaluation of potential interactions between the transition metal catalysts used in the [Ir/Ni] and [Pd/Ni] catalytic sequences.

Subjecting **3f** to the prototypical Ni-catalyzed cross-coupling reaction conditions using $[\text{Ni}(\text{OAc})_2]$, **L1** and

phenyl magnesium bromide afforded **4fa** quantitatively in a $>20:1$ E/Z ratio (Eq. (2)). A similar result was obtained when this reaction was conducted in presence of iridium complex **1a** previously activated by molecular hydrogen (Eq. (3)). When the cross-coupling reaction between **3f** ($E/Z = 1.5:1$) and PhMgBr was conducted in presence of the activated palladium complex **5**, **4fa** was generated in a 2:1 ratio (Eq. (4)). Collectively, these data indicate that in the case of the [Ir/Ni] sequence, if the isomerization is not perfectly stereoselective, the nickel catalyst exerts a corrective effect that increases the E/Z ratio of the final olefinic product. In contrast, in the [Pd/Ni] catalytic sequence such corrective effect is marginal. Because no isomerization of (*E*)-**4fa** was detected when using **5** alone (Eq. (5)), we propose that interactions between both transition metals are likely to be responsible for this phenomenon rather than competing post-reaction isomerizations.

In conclusion, we have developed two complementary one-pot multicatalytic sequences that provide access to polysubstituted olefins. Both elementary steps of these sequences are challenging processes when considered independently. The first sequence consists in a combination of an iridium-catalyzed isomerization of allyl methyl ethers followed by a nickel catalyzed-cross coupling of the in situ generated methyl vinyl ethers with Grignard reagents which delivers the products with high degree of olefin stereocontrol. The method is compatible with a variety of functional groups and a multitude of olefinic substitution patterns to afford products with high control of the newly generated C=C bond and in practical yields. Upon proper choice of the Grignard reagent, we demonstrated that $\text{C}(sp^2)\text{-C}(sp^2)$ and $\text{C}(sp^2)\text{-C}(sp^3)$ bonds can be efficiently constructed. A highly enantioselective variant of the [Ir/Ni] catalytic sequence has been designed for a selected number of aryl-containing prochiral allyl methyl ethers. A complementary [Pd/Ni] catalytic sequence was optimized where the use of palladium catalysts enabled isomerization of the remote C=C bond in several alkenyl methyl ethers, delivering the final alkenes with a lower level of stereocontrol. A corrective effect induced by the nickel catalyst on the olefin geometry was observed during the cross-coupling event in some [Ir/Ni] sequences. This effect is only negligible using the [Pd/Ni] system - presumably due to detrimental interactions between both transition metals.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization of all new compounds and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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(22) Attempts to perform these reactions in tandem rather
than in sequence did not lead to product formation.

(23) Variations of the stoichiometry in Grignard reagent did
not lead to significant improvement.

(24) Vinyl, propenyl and alkynyl Grignard reagents were not
engaged successfully in the sequences described herein.

(25) While we were finalizing this study, a related Pd-
catalyzed isomerization of silylated alkenyl alcohols was report-
ed. See reference 2i.

TOC

