List of publications

1. Dethe**,** D. H.; **Nagabhushana, C. B.** Ruthenium-Catalyzed Direct Dehydrogenative Cross-Coupling of Allyl Alcohols and Acrylates: Application to Total Synthesis of Hydroxy β-Sanshool, ZP-Amide I, and Chondrillin. *Org. Lett.* **2020,** *22***,** 1618-1623.

2. Dethe**,** D. H.; **Nagabhushana, C. B.;** Bhat, A. A. Cp*Co(III)-Catalyzed Ketone-Directed *ortho*-C–H Activation for the Synthesis of Indene Derivatives. *J. Org. Chem.* **2020**, *85*, 7565-7575.

3. Dethe**,** D. H.; **Nagabhushana, C. B.;** Das, S.; Nirpal, A. K. Ruthenium-catalyzed formal sp^3 C–H activation of allylsilanes/esters with olefins: efficient access to functionalized 1,3-dienes. *Chem. Sci.*, **2021,** *12***,** 4367-4372.

4. Dethe**,** D. H.; **Nagabhushana, C. B.;** Uike, A. Ruthenium-Catalyzed Oxidative Cross-Coupling Reaction of Activated Olefins with Vinyl Boronates for the Synthesis of (*E*,*E*)-1,3-Dienes. *J. Org. Chem.* **2021,** *86***,** 3444-3455.

5. Dethe**,** D. H.; **Nagabhushana, C. B.;** Kumar, V. Weakly Coordinating, Hydroxyl Directed Ruthenium Catalyzed C–H Alkylation of Ubiquitous Benzyl Alcohols with Maleimides. *Org. Lett.* **2021**, *23*, 6267-6271.

6. Dethe**,** D. H.; **Nagabhushana, C. B.;** Balu, D. D. Carboxylic Acid Promoted, Redox-Neutral Ru-Catalyzed C−H Allylation of Aromatic Ketones. *Eur. J. Org. Chem.* **2021**, 4611-4615.

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Ruthenium-catalyzed formal sp^3 C–H activation of allylsilanes/esters with olefins: efficient access to functionalized 1,3-dienes†

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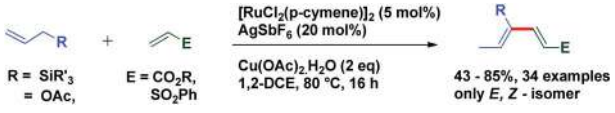
Ru-catalysed oxidative coupling of allylsilanes and allyl esters with activated olefins has been developed *via* isomerization followed by C(allyl)–H activation providing efficient access to stereodefined 1,3-dienes in excellent yields. Mild reaction conditions, less expensive catalysts, and excellent regio- and diastereoselectivity ensure universality of the reaction. In addition, the unique power of this reaction was illustrated by performing the Diels–Alder reaction, and enantioselective synthesis of highly functionalized cyclohexenone and piperidine and finally synthetic utility was further demonstrated by the efficient synthesis of norpyrenophorin, an antifungal agent.

1,3-Dienes not only are widespread structural motifs in biologically pertinent molecules but also feature as a foundation for a broad range of chemical transformations.[1–14] Indeed, these conjugated dienes serve as substrates in many fundamental synthetic methodologies such as cycloaddition, metathesis, ene reactions, oxidoreduction, or reductive aldolization. It is well-understood that the geometry of olefins often influences the stereochemical outcome and the reactivity of reactions involving 1,3-dienes.[15] Hence, a plethora of synthetic methods have been developed for the stereoselective construction of substituted 1,3-dienes.[16–24] The past decade has witnessed a huge advancement in the field of metal-catalyzed C–H activation/functionalization.[25–27] Although, a significant amount of work in the field of C(alkyl)–H and C(aryl)–H activation has been reported; C(alkenyl)–H activation has not been explored conspicuously, probably due to the complications caused by competitive reactivity of the alkene moiety, which can make chemoselectivity a significant challenge. Over the past few years, several different palladium-based protocols have been developed for C(alkenyl)–H functionalization, but the reactions are generally limited to employing conjugated alkenes, such as styrenes,[28–31] acrylates/acrylamides,[32–36] enamides,[37] and enol esters/ethers.[38,39] To date, only a few reports have appeared in the literature for expanding this reactivity towards non-conjugated olefins, which can be exemplified by camphene dimerization,[40] and carboxylate-directed C(alkenyl)–H alkenylation of 1,4-cyclohexadienes.[41] In 2009, Trost *et al.* reported a ruthenium-catalyzed stereoselective alkene–alkyne coupling method for the synthesis of 1,3-dienes.[42] The same group also reported alkene–alkyne coupling for the stereoselective synthesis of trisubstituted ene carbamates.[43] A palladium catalyzed chelation control method for the synthesis of dienes *via* alkenyl sp^2 C–H bond functionalization was described by Loh *et al.*[44] Recently, Engle and coworkers reported an elegant approach for synthesis of highly substituted 1,3-dienes from two different alkenes using an 8-aminoquinoline directed, palladium(II)-mediated C(alkenyl)–H activation strategy.[45] Allyl and vinyl silanes are known as indispensable nucleophiles in synthetic chemistry.[46] Alder ene reactions of allyl silanes with alkynes are reported for the synthesis of 1,4-dienes.[47] Innumerable methods are known for the preparation of both allyl and vinyl silanes[48–52] but limitations are associated with many of the current protocols, which impedes the synthesis of unsaturated organosilanes in an efficient manner. Silicon-functionalized building blocks are used as coupling partners in the Hiyama reaction[53] and are easily converted into iodo-functionalized derivatives (precursor for the Suzuki cross-coupling reaction), but there is little attention given for the synthesis of functionalized vinyl silanes. Herein, we report a general approach for the stereoselective synthesis of trisubstituted 1,3-dienes by the Ru-catalyzed C(sp^3)–H functionalization reaction of allylsilanes (Scheme 1).



Scheme 1 Highly stereoselective construction of 1,3-dienes.

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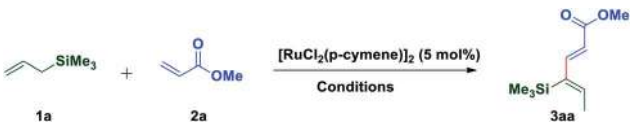
In 1993, Trost and coworkers reported an elegant method for highly chemoselective ruthenium-catalyzed redox isomerization of allyl alcohols without affecting the primary and secondary alcohols and isolated double bonds.[54,55] Inspired by the potential of ruthenium for such isomerization of double bonds in allyl alcohols, we sought to identify a ruthenium-based catalytic system that can promote isomerization of olefins in allylsilanes followed by *in situ* oxidative coupling with an activated olefin to form substituted 1,3-dienes. We initiated our studies by choosing trimethylallylsilane **1a** and acrylate **2a** by using a commercially available $[RuCl_2(p\text{-cymene})]_2$ catalyst in the presence of $AgSbF_6$ as an additive and co-oxidant $Cu(OAc)_2$ in 1,2-DCE at 100 °C. Interestingly, it resulted into direct formation of (2*E*,4*Z*)-1,3-diene **3aa** as a single isomer in 55% yield. It is likely that this reaction occurs by C(allyl)–H activation of the π-allyl ruthenium complex followed by oxidative coupling with the acrylate and leaving the silyl group intact (Table 1). π-Allyl ruthenium complex formation may be highly favorable due to the α-silyl effect which stabilizes the carbanion forming *in situ* in the reaction.[56] Next, the regioselective C–H insertion of vinyl silanes could be controlled by stabilization of the carbon–metal (C–M) bond in the α-position to silicon. This stability arises due to the overlapping of the filled carbon–metal orbital with the d orbitals on silicon or the antibonding orbitals of the methyl–silicon (Me–Si) bond.[57] The stereochemistry of the diene was established by **1D** and **2D** spectroscopic analysis of the compound **3aa**. To quantify the C–H activation mediated coupling efficiency, an extensive optimization study was conducted (allylsilanes followed by *in situ* oxidative coupling with an activated olefin to form substituted 1,3-dienes). The change of solvents from 1,2-DCE to t-AmOH, DMF, dioxane, THF or MeCN did not give any satisfactory result, rather a very sluggish reaction rate or decomposition of starting materials was observed in each case (entry 2–6).

The increase of temperature from 100 °C to 120 °C resulted in the formation of diene in lower yield (entry 7). To our delight, it was found that a substantial enhancement in the yield (82%) was observed when the reaction was performed at 80 °C (entry 8). In particular, this was found to be the best reaction condition since further lowering of the temperature led to noteworthy attenuation of the reaction rate and yield (entry 9). Interestingly, the reaction was not efficient, when $AgSbF_6$ was replaced with other additives, such as Ag_2CO_3 and AgOAc. It was also observed that, co-oxidant $Cu(OAc)_2$ is necessary for the success of this reaction (entry 12).

With these optimized conditions in hand, various allyl sources and acrylates have been tested (Table 2). It was found that a variety of acrylates **2** bearing alkyl and sterically crowded cyclic substituents successfully underwent the coupling reaction with allyl silane **1a** to afford corresponding silyl substituted (2*E*,4*Z*)-1,3-dienes in good yields (**3aa–3af**). Similarly, dimethyl benzylallylsilane **1b** reacted smoothly with acrylates such as methyl, isobutyl and *n*-butyl to generate desired dienes **3ba**, **3bb** and **3bc** in 83%, 85% and 82% yield respectively. Interestingly, sterically crowded, *tert*-butyldimethyl allylsilane **1c** showed its

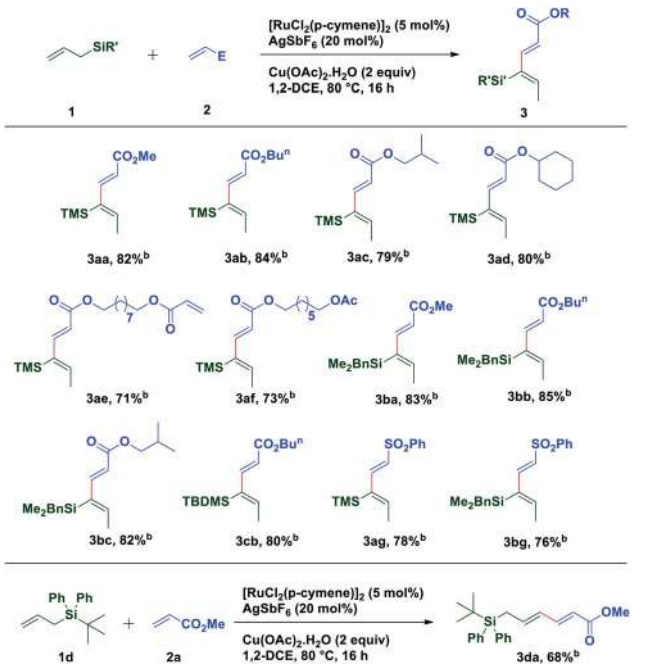
Table 1 Optimization of reaction conditions[a]



Entry	Additive (20 mol%)	Oxidant (2 equiv.)	Solvent	Yield[b] (%)
1	$AgSbF_6$	$Cu(OAc)_2$	DCE	55
2	$AgSbF_6$	$Cu(OAc)_2$	t-AmOH	10
3	$AgSbF_6$	$Cu(OAc)_2$	DMF	0
4	$AgSbF_6$	$Cu(OAc)_2$	Dioxane	8
5	$AgSbF_6$	$Cu(OAc)_2$	THF	21
6	$AgSbF_6$	$Cu(OAc)_2$	MeCN	0
7[c]	$AgSbF_6$	$Cu(OAc)_2$	DCE	35
8[d]	$AgSbF_6$	$Cu(OAc)_2$	DCE	82
9[e]	$AgSbF_6$	$Cu(OAc)_2$	DCE	45
10[d]	Ag_2CO_3	$Cu(OAc)_2$	DCE	0
11[d]	AgOAc	$Cu(OAc)_2$	DCE	20
12[d]	$AgSbF_6$	—	DCE	0

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), additive (20 mol%) and oxidant (2 equiv.) at 100 °C in a specific solvent (2.0 mL), under argon, for 16 h. [b] Isolated yields are of product **3aa**. [c] The reaction was performed at 120 °C. [d] The reaction was performed at 80 °C. [e] The reaction was performed at 60 °C. t-AmOH – tertiary amyl alcohol, DMF – *N*,*N*-dimethylformamide, DCE – 1,2-dichloroethane.

Table 2 Substrate scope for oxidative coupling of allylsilanes with acrylates and vinyl sulfones[a]



[a] Reaction conditions: **1** (0.24 mmol), **2** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv.) at 80 °C in 1,2-dichloroethane (2.0 mL), under argon, 16 h. [b] Isolated yields are of product **3**. TMS – trimethylsilyl, TBDMS – tertiarybutyldimethyl silyl.

reactivity towards the coupling reaction with *n*-butyl acrylate to provide required diene **3cb** in 80% yield. It is worth mentioning that allylsilanes **1a** and **1b** also exhibited their coupling reactivity with phenyl vinyl sulfone and successfully generated corresponding 1,3-dienes **3ag** and **3bg** in 78% and 76% yield respectively. When *tert*-butyldiphenylallylsilane **1d** was subjected to the coupling reaction with methyl acrylate **2a**, end–end coupling product **3da** was isolated in 68% yield. This may be attributed to the steric crowding offered by bulky groups on silicon which prevents allyl to vinyl isomerization.

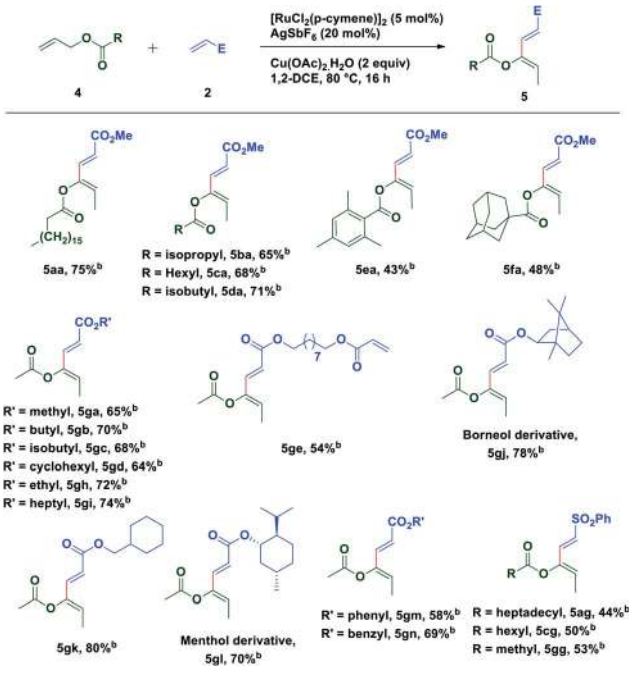
To extend the substrate scope of the reaction, we next examined the scope of allylesters by employing **2a** as the coupling partner. First, we carried out the coupling reaction between allyl ester derivative **4a** and methyl acrylate **2a** under standard conditions. To our delight, a single isomer of acetate substituted (2*E*,4*Z*)-1,3-diene **5aa** was isolated with a good yield (75%) (Table 3). This result may be extremely unusual due to the weak thermodynamic driving force for the double bond migration of allyl esters and tendency of many metal catalysts to insert themselves into the C(allyl)–O bond to form a stable carboxylate complex.[58] Even for unsubstituted allyl esters very few reports of double bond migrations exist.[59–62] It is worth mentioning that unlike the Tsuji–Trost reaction,[63–65] the C(allyl)–O bond doesn't break to form the π-allyl palladium complex as an electrophile, instead it forms a nucleophilic π-allylruthenium complex (umpolung reactivity) keeping the acetate group intact, which further reacts with an electrophile. The stereochemistry of the diene was established by **1D** and **2D** spectroscopic analysis of the compound **5ga** and also by comparison of spectroscopic data with those of an authentic compound.[66] Next we turned our attention to expand the scope of the coupling reaction between various acrylates and allyl esters. It was found that a variety of allyl esters bearing alkyl substituents on the carbonyl carbon could provide moderate to good yields of the corresponding stereodefined (2*E*,4*Z*)-1,3,4-trisubstituted 1,3-dienes successfully. As can be seen from Table 2, alkyl substituents (**4b–4d**) had little influence on the yields (65–75%). Gratifyingly, we noticed that the presence of a bulky substituent in **4** also showed its viability towards the coupling reaction, albeit with modest yields (**5ea** & **5fa**). Also, various acrylate derivatives reacted smoothly to generate the 1,3-dienes in excellent yield. A simple allyl acetate **4g** reacted with a series of different acrylates **2** to afford the desired products in good yields.

Several acrylates such as methyl-, ethyl-, *n*-butyl-, isobutyl-, *n*-heptyl-, cyclohexylmethyl-, benzyl-, *etc.* were tested and good to very good yields of the products were obtained. Also, gram scale synthesis of **5gh** (1.35 g) by the reaction of acetate **4g** with **2h** gave identical results in terms of yield (69%) and diastereoselectivity, indicating the robustness and practicality of this method. Markedly, a C2-symmetric diacrylate (**2e**) also reacted with allyl acetate to form a mono-coupled product **5ge**, though in a somewhat lower yield. In contrast to the allyl esters, the coupling was not affected by the steric bulk of the acrylate substituents as depicted in Table 3. Even the borneol derivative **2j** and menthol derivative **2l**, which can offer considerable steric hindrance, were found to be equally effective in the formation of **5gj** and **5gl** in very good yields. A somewhat reduced yield of the product **5gm** was observed while using phenyl acrylate (**2m**) perhaps due to competitive reactive sites. Interestingly, the versatility of this methodology was not restricted only to acrylates, since phenyl vinyl sulfone was also found to be equally efficient for oxidative C–H functionalization with different allyl esters and a successful C–C coupling reaction was observed in each case with moderate yield and excellent diastereoselectivity.

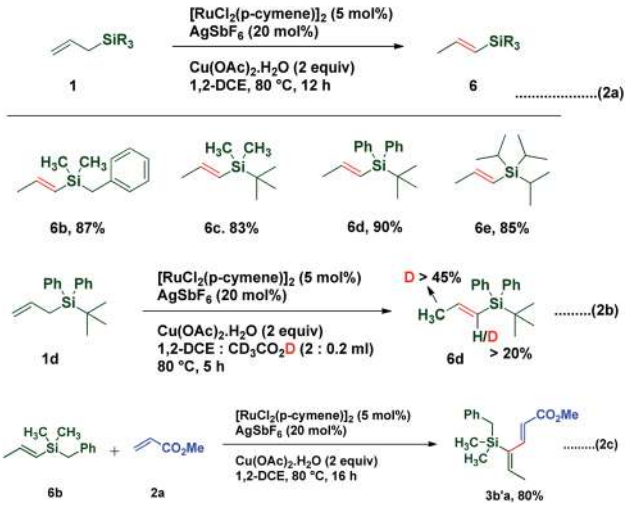
Interestingly treatment of allylsilanes under standard reaction conditions in the absence of an acrylate coupling partner led to isomerization of various allylsilanes to afford corresponding vinylsilanes **6b–6e** in excellent yields (Scheme 2a). When allylsilane **1d** was subjected to isomerization in the presence of CD_3CO_2D, a significant amount of deuterium scrambling at the α-position (>20%) as well as at the methyl group (>45%) was observed in corresponding vinylsilane, indicating that the isomerization step is reversible and the rate determining step (Scheme 2b). It is also observed that when vinylsilane **6b** was made to react with methyl acrylate **2a** under standard conditions, it successfully underwent highly regioselective C–H activation and afforded coupling product **3b′a** in 80% yield (Scheme 2c). This result confirms that the coupling reaction proceeds *via* vinyl silane intermediate **6**.

It is delightful to mention that diene **3aa** successfully underwent the Diels–Alder reaction with *N*-phenyl maleimide **7** in toluene at 80 °C, to afford single isomer **8** in 70% yield

Table 3 Substrate scope for oxidative coupling of various allyl esters with different acrylates and vinyl sulfones[a]



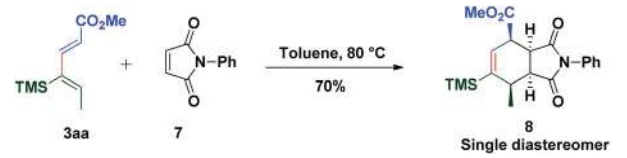
[a] Reaction conditions: **4** (0.24 mmol), **2** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv.) at 80 °C in 1,2-dichloroethane (2.0 mL), under argon, 16 h. [b] Isolated yields are of product **5**.



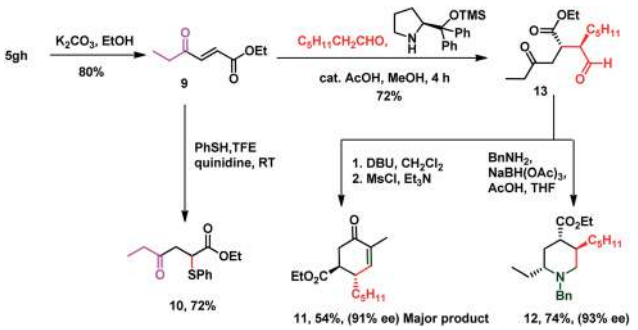
Scheme 2 Isomerization of allylsilanes and deuterium study.

which ensures the pragmatism of the method (Scheme 3). The unique power of this ruthenium-catalyzed C–H functionalization strategy is illustrated by the late-stage diversification of the diene **5gh**, to a very reactive Michael acceptor **9** (conventional route for preparation of **9** requires *in situ* oxidation of α-hydroxyketones using 10 equiv. MnO_2 followed by the Wittig reaction, which generates a superstoichiometric amount of phosphine waste)[67,68] *via* selective hydrolysis of the acetate group, which is useful in the synthesis of ester-thiol **10**,[69] cyclohexenone **11** and polysubstituted piperidine **12** (ref. 70) (Scheme 4). Thus the Micheal acceptor **9** on reaction with thiophenol generated compound **10** in excellent yield and high regioselectivity. On the other hand compound **9** on reaction with heptanal in the presence of Hayashi–Jørgensen's catalyst afforded the Michael adduct **13** in 72% yield and excellent diastereoselectivity. Keto-aldehyde **13** was converted to highly substituted cyclohexenone **11** and piperidine **12**.

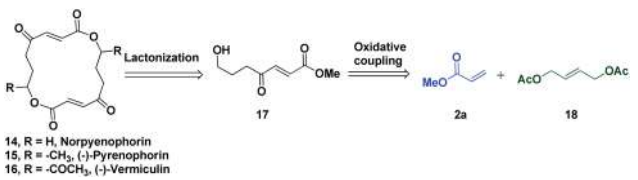
The potential of this Ru-catalysed reaction was further demonstrated by norpyrenophorin synthesis.[71–74] Norpyrenophorin **14** is a synthetic 16-membered lactone which has essentially the same physiological activity as the natural fungicide pyrenophorin **15** and the antibiotic vermiculin **16**.[73] A brief retrosynthetic analysis revealed that the dimeric macrocycle **14** could be dissected into monomer **17** which could be easily accessed from oxidative coupling of **2a** with **18** using the C–H activation reaction (Scheme 5). Ruthenium catalysed oxidative coupling of symmetric allylester **18** with **2a** generated the key intermediate **19** in 32% yield. Selective hydrolysis of acetyl



Scheme 3 Application to the Diels–Alder reaction.

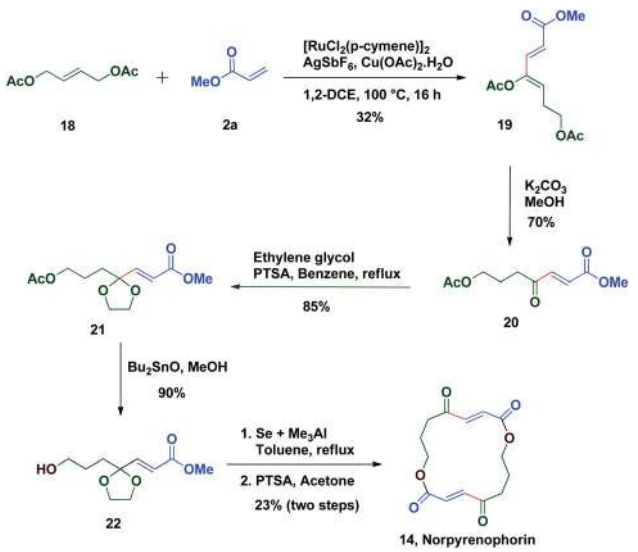


Scheme 4 Application to the organocatalytic Michael addition reaction.

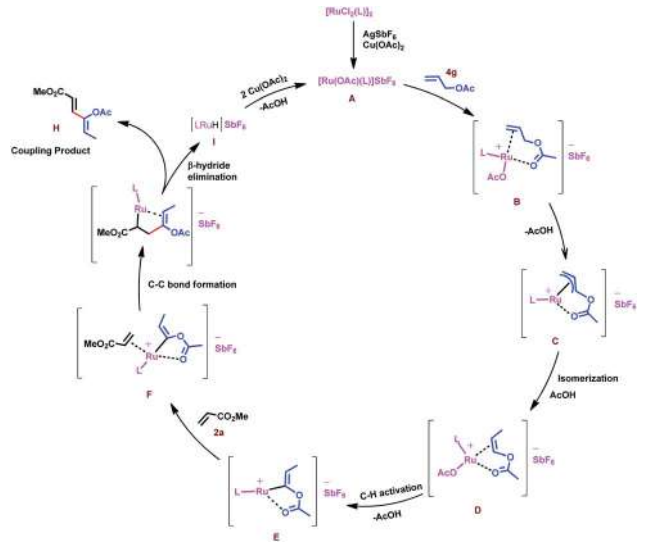


Scheme 5 Retrosynthetic analysis of norpyrenophorin.

enolate **19** was accomplished by the treatment with K_2CO_3 in methanol to provide **20** in 70% yield. In accordance with some previously reported studies, the active ketone functionality of **20** was protected as ketal by treatment with ethylene glycol in refluxing benzene to afford substrate **21**. Selective hydrolysis of acetate was achieved using Bu_2SnO to generate alcohol **22** and finally, aluminium–selenium adduct mediated[72] ring closing lactonization followed by deketalization ensured the completion of synthesis of **14** in 23% yield (two steps) (Scheme 6). A similar type of dimerization reaction could be envisioned to synthesize the natural products pyrenophorin **15** and vermiculin **16**.



Scheme 6 Synthesis of norpyrenophorin.



Scheme 7 Plausible reaction mechanism.

Based on the above result and previous report, a plausible mechanism for this oxidative coupling reaction is depicted in Scheme 7. The catalytic cycle is initiated by substrate **4g** coordination to *in situ* generated reactive cationic ruthenium complex **[Ru(OAc)L]$^+$ A**, followed by weakly coordinating ester group directed C–H activation of allyl ester to give a π-allyl ruthenium intermediate **C**, which again would undergo isomerization to produce intermediate **D**. In the case of allyl silanes, an α-silyl effect might play an important role for the isomerisation of allylsilanes to vinylsilanes *via* the silylated allyl anion.[56] Regioselective C–H activation of *in situ* generated vinyl acetate would give intermediate **E**. Induction of stability to the carbon–metal bond by the silyl group favours regioselective C–H insertion in the case of vinyl silanes.[57] Coordination followed by 1,4-addition of vinyl ruthenium species to the activated olefins (acrylate, **2a**) would generate intermediate **G**, which would further undergo β-hydride elimination to provide a single isomer of 1,3-diene **H** and intermediate **I** could undergo reductive elimination followed by reoxidation of *in situ* forming Ru(0) species in the presence of $Cu(OAc)_2$ to regenerate the reactive ruthenium(II) complex **A** for the next catalytic cycle.

Conclusions

In summary, we have developed a ruthenium catalyzed efficient and straightforward method for the synthesis of highly stereodefined 1,3-dienes. Synthetic utility of this reaction towards the Diels–Alder reaction and diverse functional group transformations has been demonstrated. Finally, the scope of this reaction was further explored by the synthesis of norpyrenophorin in five steps.

Author contributions

D. H. D. directed the project and wrote the manuscript. N. C. B. conducted most of the synthetic experiments and wrote the manuscript. S. D. and A. K. N. synthesized some of the silyl and acetate substituted dienes.

Conflicts of interest

The authors declare no competing financial interest.

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Ruthenium-Catalyzed Direct Dehydrogenative Cross-Coupling of Allyl Alcohols and Acrylates: Application to Total Synthesis of Hydroxy β-Sanshool, ZP-Amide I, and Chondrillin

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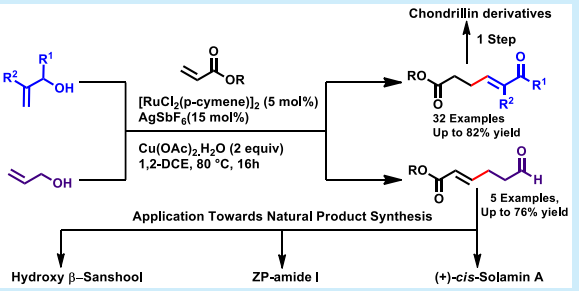
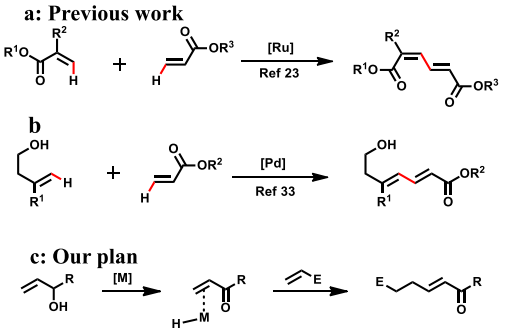
ABSTRACT: Ru-catalyzed oxidative coupling of allyl alcohols and activated olefins has been developed by C(allyl)−H activation of allyl alcohols providing efficient and direct access to synthetically useful α,β-unsaturated enone intermediates. Synthetic utility of this method was demonstrated by its application to synthesis of bioactive natural products such as Hydroxy-β-sanshool, ZP-amide I, Chondrillin, Plakorin, and (+)-*cis*-Solamin A.



Carbon−carbon bond forming reactions are the backbone of organic synthesis. These reactions give access to an important class of compounds such as alkanes, alkenes, and alkynes. Thus, development of novel approaches for the carbon−carbon bond formation is a continuous process in organic synthesis. So, several synthetic approaches for accessing alkenes have been reported such as Wittig reaction,[1−6] olefin metathesis,[7−13] metal-catalyzed cross-coupling reactions, and many more.[14−19] However, many of these methods suffer from poor atom economy and use of toxic reagents. Thus, it is highly desirable to develop cheap, selective, and highly atom-economical reactions to access alkenes. Therefore, to overcome aforementioned limitations for synthesis of alkenes, recently developed approaches rely on transition-metal-catalyzed alkenyl C−H bond coupling reactions, as these reactions are performed in a catalytic, atom- and step-economic manner.[20−31] Most importantly, the Loh group reported an elegant method for the stereoselective synthesis of muconate derivatives via ruthenium-catalyzed sp^2 C−H activation (Scheme 1a).[23] White and co-workers developed a Pd(II)/sulfoxide-catalyzed oxidative Heck vinylation reaction for the synthesis of complex dienes and polyenes.[32] A palladium-catalyzed stereoselective alkenyl sp^2 C−H bond functionalization reaction was developed by Loh and co-workers (Scheme 1b).[33] In the past decade, several approaches where a ruthenium(II)-catalyzed directing group facilitated C−H bond activation/functionalization of aromatic compounds have been reported;[34] however, C−H bond activation/functionalization of an alkene/alkane are less explored. In the past three decades, Trost et al. have done pioneering work in this field and extensively studied the ruthenium-catalyzed alkynes−alkenes coupling reaction which is an atom-economic

Scheme 1



strategy for carbon−carbon bond formation.[35−38] Surprisingly, ruthenium-catalyzed alkene−alkene coupling reactions are underdeveloped. Trost and co-workers disclosed an inventive method for highly chemoselective redox isomerization of allyl alcohols using a ruthenium catalyst without affecting the primary and secondary alcohols and isolated double bonds.[39,40] Encouraged by the potentiality of ruthenium for such isomerization of olefins in allyl alcohols, we sought to develop a new method that can promote isomerization of olefin in allyl alcohols as well as *in situ* formed enone can be oxidatively coupled to an another activated olefin leading to a new approach for the carbon−carbon bond forming process

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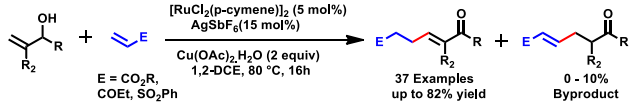
(Scheme 1c). In this context, herein, we report the highly atom-/step-economical ruthenium-catalyzed sp^2 C−H activation of allyl alcohols followed by a cross-coupling reaction with activated olefins (Scheme 2).

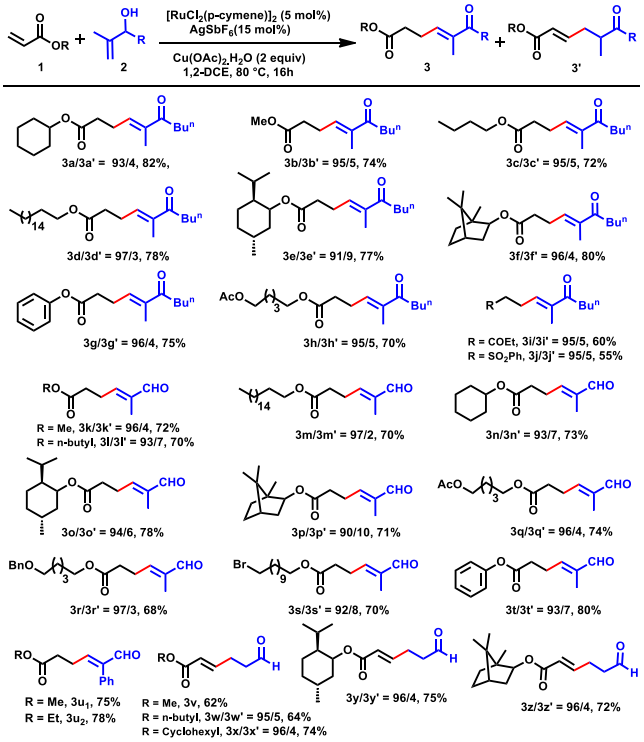
Scheme 2. This Method



In this direction, we initiated our studies by choosing the C−H activation reaction between substituted ally alcohol (**1a**) and cyclohexyl acrylate (**2a**) as the model reaction (Table 1). First, we investigated a variety of transition metal catalysts in the presence of additive $AgSbF_6$, $Cu(OAc)_2$ in 1,2-dichloroethane (DCE) at 60 °C (entries 1−4) for 16 h. The results indicated that the reaction did not take place when $[Cp^*RhCl_2]_2$ (**C1**), $Cp^*Co(CO)I_2$ (**C2**), or $[Cp Ru(CH_3CN)_3]PF_6$ (**C3**) were used as catalysts. In contrast, the reaction afforded product **3a** and **3a′** in 45% yield with good regio- (80/20) and stereoselectivity when $[RuCl_2(p\text{-cymene})]_2$ (**C4**) was employed as the catalyst. Subsequently, several solvents were screened (entries 5−8). To our delight, the catalytic system afforded the desired product **3a**/**3a′** with excellent improvement in the regioselectivity (96/4) in good yield (82%) when the reaction was conducted at 80 °C (entry 9). It was found that no reaction occurred in the absence of $Cu(OAc)_2{\cdot}H_2O$, and also replacement of $Cu(OAc)_2{\cdot}H_2O$ with AgOAc and KOAc generated a trace amount of product **3a**. It confirms that the catalytic cycle involves a redox pathway. The catalytic reaction was screened with various additive sources such as Ag_2CO_3, AgOAc, and NH_4PF_6 (entrries 13−15). These additives did not provide any satisfactory result; rather, a very sluggish reaction rate or decomposition of starting materials was observed in each case. It was found that the reaction conditions for entry 9 to be the best, since further lowering of the temperature led to noteworthy attenuation of the reaction rate and yield.

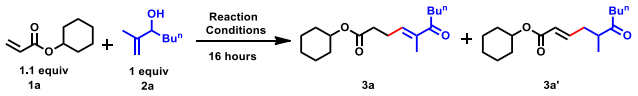
With the optimized conditions in hand, we began to explore the scope of the reaction. As shown in Table 2, a variety of

Table 2. Scope of Acrylates[a]



[a]Reaction conditions: **1** (0.20 mmol), **2** (0.22 mmol), [Ru(p-cymene)Cl_2]$_2$ (5 mol %), additive (15 mol %) and oxidant (2 equiv) at 80 °C in a 1,2-dichloroethane (3.0 mL) for 16 h. Isolated yields are of product **3**/**3′**. 1.5 equiv., of allyl alcohol 2c was used.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst **5** (mol %)	additive **15** (mol %)	oxidant **2** (equiv)	solvent	yield (%)[f]	**3a**/**3a′** (%)
1	**C1**	$AgSbF_6$	$Cu(OAc)_2$	DCE	0	–
2[b]	**C4**	$AgSbF_6$	$Cu(OAc)_2$	DCE	45%	80/20
3	**C2**	$AgSbF_6$	$Cu(OAc)_2$	DCE	0	–
4	**C3**	–	–	DCE	0	–
5[c]	**C4**	$AgSbF_6$	$Cu(OAc)_2$	DCM	10/25	75/25
6	**C4**	$AgSbF_6$	$Cu(OAc)_2$	THF	0	0
7	**C4**	$AgSbF_6$	$Cu(OAc)_2$	dioxane	18	88/12
8	**C4**	$AgSbF_6$	$Cu(OAc)_2$	TFE	trace	–
9[d]	**C4**	$AgSbF_6$	$Cu(OAc)_{22}$	DCE	82	96/4
10[e]	**C4**	$AgSbF_6$	–	DCE	0	0
11	**C4**	$AgSbF_6$	KOAc	DCE	trace	–
12	**C4**	$AgSbF_6$	NaOAc	DCE	trace	–
13	**C4**	Ag_2CO_3	$Cu(OAc)_2$	DCE	0	–
14	**C4**	AgOAc	$Cu(OAc)_2$	DCE	0	–
15	**C4**	NH_4PF_6	$Cu(OAc)_2$	DCE	0	–

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), [Ru(p-cymene)Cl_2]$_2$ (5 mol %), additive (15 mol %), and oxidant (2 equiv) in a specific solvent (3.0 mL) for 16 h. [b]Reaction conducted at 60 °C for 10 h. [c]Reaction conducted using DCM at 60/80 °C. [d]Reaction conducted at 80 °C for 16 h. [e]The reaction was performed without $Cu(OAc)_2{\cdot}H_2O$. [f]Isolated yields are of product **3a**/**3a′** w.r.t. acrylate **1a**. TFE = Trifluoroethanol.

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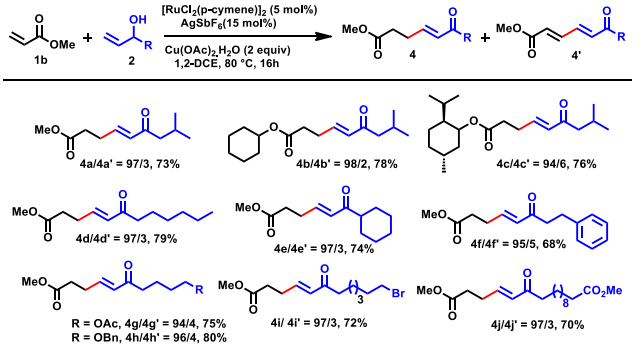
acrylates and allyl alcohols bearing different functionality reacted well, providing the corresponding coupling products in moderate to good yields with excellent stereoselectivity. For example, acrylates with distinct alkyl substituents such as cyclohexyl, methyl, butyl, and heptadecyl underwent a coupling reaction with α-methyl substituted secondary allyl alcohol **2a** successfully generating corresponding coupling products in good yields (**3a**−**3d**). Gratifyingly, it was found that acrylates containing bulky and chiral substituents such as menthol and borneol derivative did not effect the reaction in terms of yield and reactivity, affording corresponding products (**3e** and **3f**) in 77% and 80% yield, respectively. It is noteworthy to mention that phenyl acrylate can provide side products due to competitive reactive sites, but generated product **3g** without having any impact on yield (75%). Interestingly, the versatility of this methodology was not restricted only to the acrylates, since activated olefins such as ethyl vinyl ketone and phenyl vinyl sulfone were found to be equally effective for C−H functionalization with allyl alcohol **2a** and corresponding C−C coupling reaction was observed in each case with moderate yield (**3i**, 60% and **3j**, 55%) and excellent stereoselectivity. We further extended the scope of the reaction by choosing β-substituted allyl alcohol **2b** as a coupling source, since it was a primary alcohol. The corresponding aldehyde product was observed after reacting with various acrylates (**3k**−**3u**). The trans stereochemistry of the double bond was further confirmed by comparison with literature reported data of $\mathbf{3u}_2$.[41] It is surprising that, when we used allyl alcohol **2c** as a coupling partner with methyl acrylate **1b**, coupled product **3v** was observed with double bond migration toward the ester side (instead of toward aldehyde) which was confirmed by NMR analysis with the reported data.[42,43] It is necessary to highlight that, to date, there is no report of synthesis of crucial intermediate **3v** in a single step obtained under catalytic conditions. The traditional reported synthesis requires a five-step longest linear sequence to prepare **3v** using a protection−deprotection strategy.[44,45] To further evaluate the efficiency and potential of this coupling reaction, a scale-up experiment was performed. Gram-scale synthesis of **3v** by the reaction of allyl alcohol **2c** (1.17g) with methyl acrylate (1.5 g) **1b** gave identical results in terms of yield (1.47g, 60%) and stereoselectivity, indicating the robustness and practicality of this method. To check the reproducibility of this product, we carried out the coupling reaction with various acrylates such as butyl, cyclohexyl, menthol, and borneol which successfully generated similar products (**3w**−**3z**) with moderate to good yields, highlighting the broad scope of both coupling partners.

It was delightful and interesting to observe that secondary allyl alcohols (**2d**−**2k**) without having any β-substitution smoothly underwent reaction to afford coupling products (**4a**−**4j**). Various substituents and functional groups on the alkyl chain of the secondary allyl alcohol such as phenyl, bromo, benzyl, acetate, and CO_2Me were well tolerated (Table 3).

The past decade has witnessed a significant enhancement in academic and industrial interest for pungent *Zanthoxylum*-derived alkylamides, due to the universal interest for both culinary and medicinal applications. Sanshools are the main alkylamide natural products found in the pericarp of the fruit, Szechuan pepper (*Zanthoxylum piperitum*).[46] It is observed that the olefin geometry of these natural products can dramatically alter both the degree and specific nature of the observed biological activities; thus, it is important to have diastereomerically pure compounds for all biological studies.

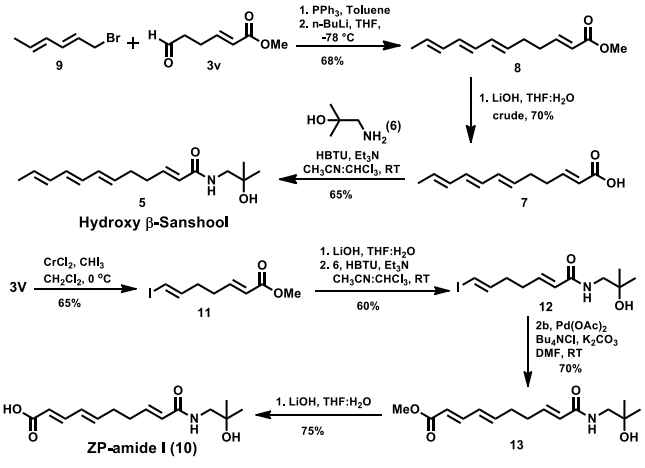
Table 3. Scope of Allyl Alcohols[a]



[a]Reaction conditions: **1b** (0.2 mmol), **2** (0.22 mmol), [Ru(p-cymene)Cl_2]$_2$ (5 mol %), additive (15 mol %), and oxidant (2 equiv) at 80 °C in a 1,2-dichloroethane (3.0 mL) for 16 h. Isolated yields are of product **4**/**4′**.

Herein, we demonstrate the application of our reaction by the shortest synthesis of two natural products, Hydroxy β-Sanshool and ZP-Amide I, in a highly diastereoselective manner. Several synthetic reports have been developed for the synthesis of pungent polyunsaturated fatty acid amides.[46−48] A brief retrosynthetic analysis revealed that the unsaturated alkylamide **5** could be dissected into commercially available amine **6** and corresponding acid **7**, which could be easily achieved from methyl ester **8**. Intermediate **8** could be obtained by a Wittig reaction between sorbyl bromide **9** and ester-aldehyde **3v**. Initially, a Wittig salt of sorbyl bromide[49] was subjected to base treatment using *n*-butyl lithium at −78 °C followed by reaction with aldehyde **3v** which provided unsaturated alkyl ester **8** in 68% yield with an approximate 3:1 *E*/*Z* stereoselectivity. Ester **8** was then converted into corresponding acid **7** in 70% yield using LiOH. Finally, coupling of **7** with commercially available hydroxy amine **6** using HBTU and Et_3N afforded hydroxy-β-sanshool **5** in 65% yield with a 31% overall yield, making it efficient and the shortest synthesis to date (Scheme 3).[47,48] Also demonstrated was the first total synthesis of the other natural product called ZP-amide I[48] **10**, a isobutylhydroxyamide isolated from Sichuan peppers. Aldehyde **3v** was subjected to Takai olefination[50] using $CrCl_2$ and iodoform, providing corresponding vinyl iodide derivative **11** with 65%

Scheme 3. Total Synthesis of Hydroxy β-Sanshool and ZP-amide I



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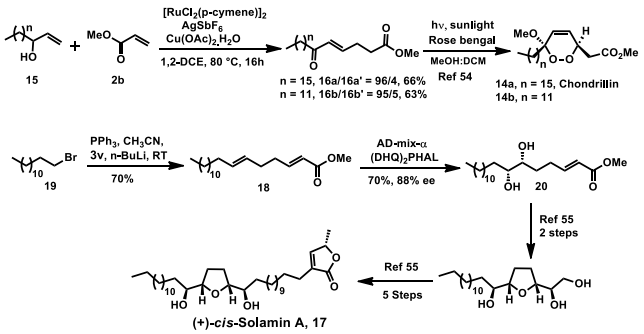
yield. Compound **11** could be utilized for many coupling reactions and other functional group transformations, since it appears as a part the natural product like Lactimidomycin.[51,52] LiOH mediated hydrolysis followed by coupling with hydroxy amine **6** using HBTU and Et_3N afforded corresponding amide **12** in 60% yield. Amide **12**, on Heck reaction[53] with methyl acrylate **1b** using palladium acetate, generated ester-amide **13** in 70% yield. Finally, hydrolysis of the ester group of **13** using LiOH provided natural product ZP-amide I **10** in 75% yield with a 21% overall yield (Scheme 3). The synthetic utility of our method was further demonstrated by synthesizing the key penultimate precursor for antitumor Chondrillin **14a** and Plakorin **14b** in one step (Scheme 4).[54] Ru-catalyzed coupling

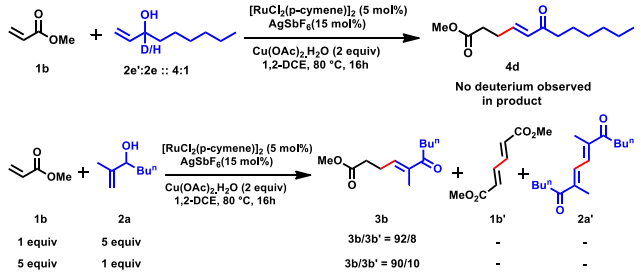
Scheme 4. Formal Synthesis of Chondrillin and (+)-*cis*-Solamin A



of secondary allyl alcohol **15** and methyl acrylate **1b** provided enone-ester intermediate **16a** and **16b**, respectively, in 66% and 63% yield with excellent regioselectivity. (Snider et al. reported the synthesis of **16a**/**b** in six steps starting from phenol by MOM protection, *n*-BuLi mediated alkylation, deprotection, and then Wessely oxidation using lead tetraaceate followed by photolysis in methanol and base hydrolysis.)[54] Snider et al. reported that intermediates **16a** and **16b** were converted to Chondrillin **14a** and Plakorin **14b** under photochemical condition using rose bengal and oxygen.[54] So, this constitutes the shortest synthesis of Chondrillin and Plakorin. Next, the efficacy of this method for the synthesis of fascinating natural product, (+)-*cis*-solamin A **17** (known for cytotoxicity and hemolytic properties), is depicted in Scheme 4.[55,56] We have achieved the synthesis of crucial intermediate **18** in two steps via Wittig reaction using aldehyde **3v** and tridecyl bromide **19** in 70% yield. Regioselective asymmetric dihydroxylation of **18** using AD-mix-α provided diol **20** with 88% ee in 70% yield. Diol **20** is converted to *cis*-Solamin A in seven steps by Donohoe et al.[55]

To understand the mechanistic pathway of the current coupling reaction, we carried out a deuterium experiment (Scheme 5). Deuterated allyl alcohol **2e′** on treatment with methyl acrylate **1b** under standard reaction conditions generated the coupling compound which has no deuterium, and its ^{1}H NMR was exactly matched with product **4d**, which shows that after isomerization the α-proton of the allyl alcohol is no longer involved in the catalytic system. Also to check whether another regioisomer was formed due to either alkene isomerism or incomplete cross-coupling reactions, we conducted two coupling reactions by utilizing 1:5 and 5:1 molar ratios of acrylate and allyl alcohol. It was observed that the cross-coupling product was formed exclusively without significant change in the regioisomeric ratios in both cases,

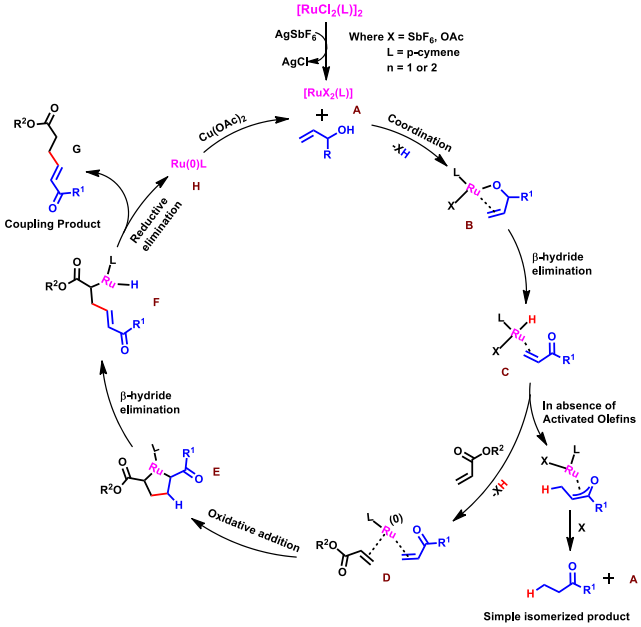
Scheme 5. Mechanistic Studies



which confirms that the other regioisomer formation was due to alkene isomerism.

Based on the above result and literature support, a plausible reaction mechanism for the ruthenium-catalyzed coupling reaction is depicted in Scheme 6.[39,40,57] The catalytic cycle is

Scheme 6. Plausible Reaction Mechanism



initiated by hydroxy group coordination to *in situ* generated reactive cationic ruthenium complex RuX_2L (**A**), followed by β-hydride elimination which would produce a ruthenium hydride species (**C**). In the presence of activated olefins, the intermediate (**C**) could undergo reductive elimination followed by oxidative addition of both the olefins leading to the formation of a five-membered ruthenacycle (**E**). β-Hydride elimination followed by reductive elimination would generate the product (**G**) along with a Ru(0) species. The resulting [Ru(0)] (**H**) may be reoxidized in the presence of $Cu(OAc)_2$, to regenerate the ruthenium(II) cationic reactive complex **A** for the next catalytic cycle.

In summary, we have developed a novel C−C bond forming reaction by ruthenium-catalyzed hydroxy directed sp^2 C−H activation of allyl alcohols followed by oxidative coupling with activated olefins. The developed reaction requires mild reaction conditions, shows a broad substrate scope, and functional group tolerance.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00200.

Details of the experimental procedure and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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