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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

Dattatraya H. Dethe* and Nagabhushana C B

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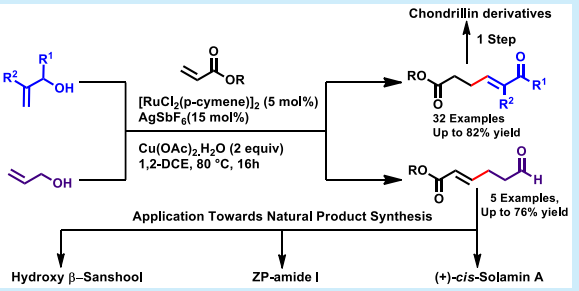
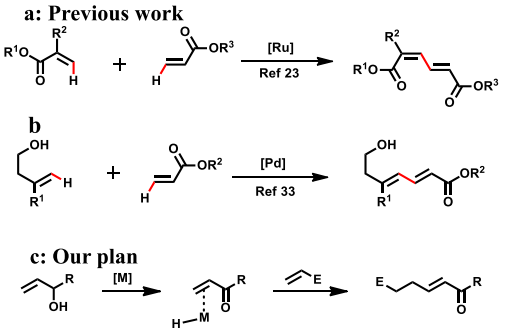
ABSTRACT: Ru-catalyzed oxidative coupling of allyl alcohols and activated olefins has been developed by C(allyl)−H activation of allyl alcohols providing efficient and direct access to synthetically useful α,β-unsaturated enone intermediates. Synthetic utility of this method was demonstrated by its application 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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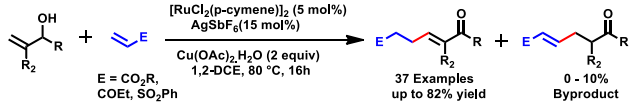
(Scheme 1c). In this context, herein, we report the highly atom-/step-economical ruthenium-catalyzed sp^2 C−H activation of allyl alcohols followed by a cross-coupling reaction with activated olefins (Scheme 2).

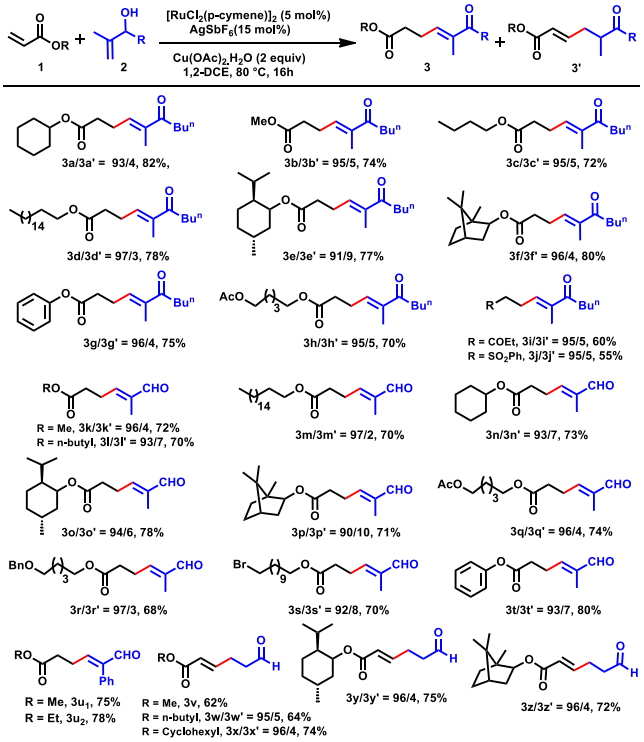
Scheme 2. This Method



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.

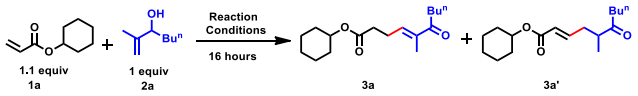
With the optimized conditions in hand, we began to explore the scope of the reaction. As shown in Table 2, a variety of

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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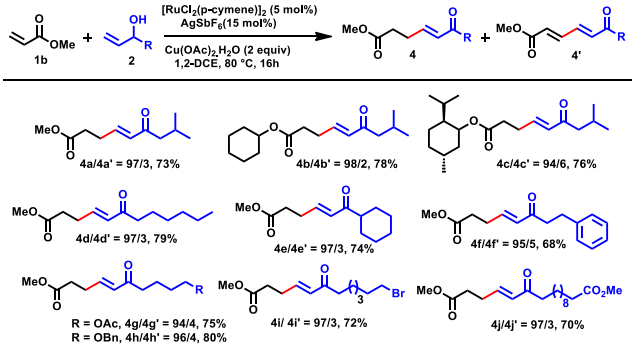
Org. Lett. XXXX, XXX, XXX−XXX

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.

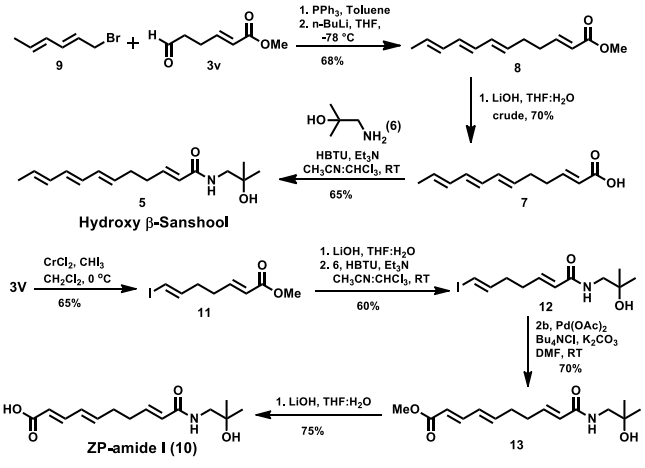
Table 3. Scope of Allyl Alcohols[a]



[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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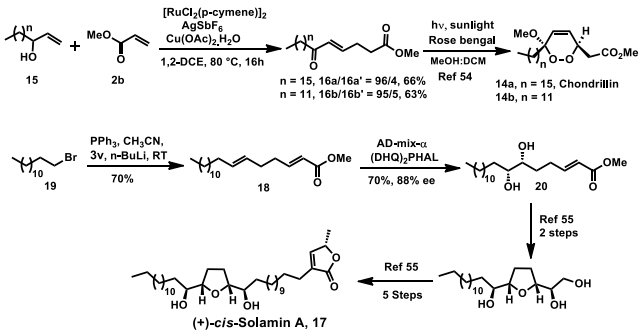
yield. Compound **11** could be utilized for many coupling reactions and other functional group transformations, since it appears as a part the natural product like Lactimidomycin.[51,52] LiOH mediated hydrolysis followed by coupling with hydroxy amine **6** using HBTU and Et_3N afforded corresponding 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

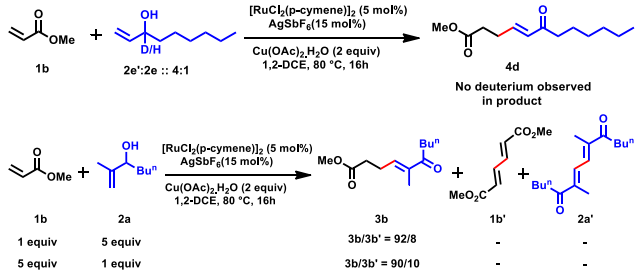
Scheme 4. Formal Synthesis of Chondrillin and (+)-*cis*-Solamin A



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,

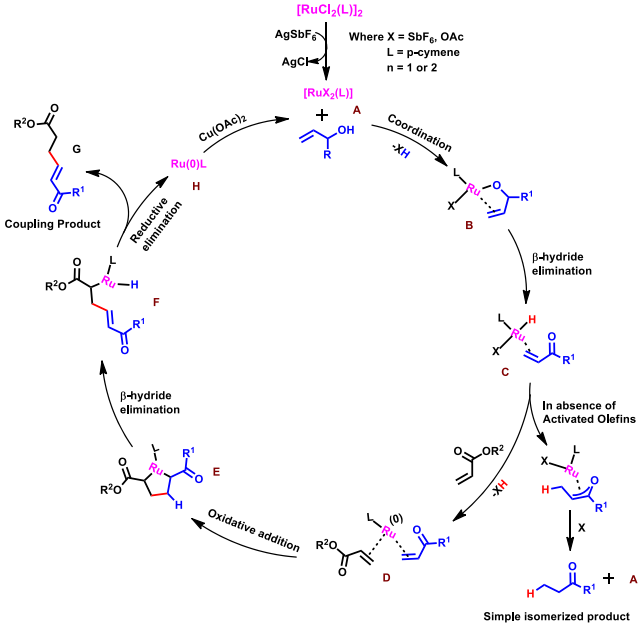
Scheme 5. Mechanistic Studies



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)

■ AUTHOR INFORMATION

Corresponding Author

Dattatraya H. Dethe − *Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India;* orcid.org/0000-0003-2734-210X; Email: ddethe@iitk.ac.in

Author

Nagabhushana C B − *Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00200

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Cattelan, L.; Noe, M.; Selva, M.; Demitri, N.; Perosa, A. Methyltriphenylphosphonium Methylcarbonate, an All-In-One Wittig Vinylation Reagent. *ChemSusChem* **2015**, *8*, 3963−3966.

(2) Greenwald, R.; Chaykovsky, M.; Corey, E. J. The Wittig Reaction using Methylsulfinyl Carbanion-Dimethyl Sulfoxide 1. *J. Org. Chem.* **1963**, *28*, 1128−1129.

(3) Maryanoff, B. E.; Reitz, A. B. The Wittig Olefination Reaction and Modifications Involving Phosphoryl-Stabilized Carbanions. Stereochemistry, Mechanism, and Selected Synthetic Aspects. *Chem. Rev.* **1989**, *89*, 863−927.

(4) Moritz, R.; Wagner, M.; Schollmeyer, D.; Baumgarten, M.; Mullen, K. Hydrophobic Encapsulated Phosphonium Salts—Synthesis of Weakly Coordinating Cations and their Application in Wittig Reactions. *Chem. - Eur. J.* **2015**, *21*, 9119−9125.

(5) Palacios, F.; Alonso, C. D.; Aparicio, G.; Rubiales, J.; Delos Santos, M. The Aza-Wittig Reaction: An Efficient Tool for the Construction of Carbon-Nitrogen Double Bonds. *Tetrahedron* **2007**, *63*, 523−575.

(6) Zhou, R. C.; Wang, H.; Song, Z. He Wittig Olefination between Phosphine, Aldehyde, and Allylic Carbonate: A General Method for Stereoselective Synthesis of Trisubstituted 1,3-Dienes with Highly Variable Substituents. *Org. Lett.* **2010**, *12*, 976−979.

(7) Chinchilla, R.; Najera, C. The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **2007**, *107*, 874−922.

(8) Dieck, H. A.; Heck, R. F. Palladium-Catalyzed Conjugated Diene Synthesis from Vinylic Halides and Olefinic Compounds. *J. Org. Chem.* **1975**, *40*, 1083−1090.

(9) Kotha, S. L.; Lahiri, K.; Kashinath, D. Recent Applications of the Suzuki—Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron* **2002**, *58*, 9633−9695.

(10) Liu, C.; Zhang, H.; Shi, W.; Lei, A. Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions. *Chem. Rev.* **2011**, *111*, 1780−1824.

(11) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.

(12) Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles. *J. Organomet. Chem.* **1999**, *576*, 147−168.

(13) Xiao, Q.; Wang, B.; Tian, L.; Yang, Y.; Ma, J.; Zhang, Y.; Chen, S.; Wang, J. Palladium-Catalyzed Three-Component Reaction of Allenes, Aryl Iodides, and Diazo Compounds: Approach to 1,3-Dienes. *Angew. Chem., Int. Ed.* **2013**, *52*, 9305−9308.

(14) Clavier, H.; Grela, K.; Kirschning, A.; Mauduit, M.; Nolan, S. P. Sustainable Concepts in Olefin Metathesis. *Angew. Chem., Int. Ed.* **2007**, *46*, 6786−6801.

(15) Connon, S. J.; Blechert, S. Recent Developments in Olefin Cross-Metathesis. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

(16) Ferrie, L. D.; Amans; Reymond, S.; Bellosta, V.; Capdevielle, P.; Cossy, J. Chemoselective Cross-Metathesis Reaction between Electron-Deficient 1,3-Dienes and Olefins. *J. Organomet. Chem.* **2006**, *691*, 5456−5465.

(17) Grubbs, R. H. Olefin-Metathesis Catalysts for the Preparation of Molecules and Materials. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760−3765.

(18) Hoffman, T. J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. Synthesis of Vinyl-Functionalized Oxazoles by Olefin Cross-Metathesis. *J. Org. Chem.* **2008**, *73*, 2400−2403.

(19) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. An Olefin Metathesis Route for the Preparation of (1→6)-Linked *C*-Disaccharide Glycals. A Convergent and Flexible Approach to *C*-Saccharide Synthesis. *J. Org. Chem.* **2000**, *65*, 6061−6068.

(20) Boultadakis-Arapinis, M.; Hopkinson, M. N.; Glorius, F. Using Rh(III)-Catalyzed C−H Activation as a Tool for the Selective Functionalization of Ketone-Containing Molecules. *Org. Lett.* **2014**, *16*, 1630−1633.

(21) Feng, C.; Feng, D.; Loh, T.-P. Rhodium(III)-Catalyzed Olefinic C-H Alkynylation of Enamides at Room Temperature. *Chem. Commun.* **2014**, *50*, 9865−9868.

(22) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. Oxidative Cross-Coupling of Acrylates with Vinyl Carboxylates Catalyzed by a $Pd(OAc)_2$/HPMoV/O_2 System. *Org. Lett.* **2004**, *6*, 4623−4625.

(23) Hu, X. H.; Zhang, J.; Yang, X. F.; Xu, Y. H.; Loh, T. P. Stereo- and Chemoselective Cross-Coupling between Two Electron-Deficient Acrylates. An Efficient Route to (*Z*,*E*)-Muconate Derivatives. *J. Am. Chem. Soc.* **2015**, *137*, 3169−3172.

(24) Shang, X.; Liu, Z.-Q. Transition Metal-Catalyzed C(vinyl)-C(vinyl) Bond Formation via Double C(vinyl)-H Bond Activation. *Chem. Soc. Rev.* **2013**, *42*, 3253−3260.

(25) Shibata, Y.; Hirano, M.; Tanaka, K. Rhodium-Catalyzed Regio- and Stereoselective Codimerization of Alkenes and Electron-Deficient Internal Alkynes Leading to 1,3-Dienes. *Org. Lett.* **2008**, *10*, 2829−2831.

(26) Tsujita, H.; Ura, Y.; Matsuki, S.; Wada, K.; Mitsudo, T. A.; Kondo, T. Regio- and Stereoselective Synthesis of Enamides and Dienamides by Ruthenium-Catalyzed Co-Oligomerization of *N*-Vinylamides with Alkenes or Alkynes. *Angew. Chem., Int. Ed.* **2007**, *46*, 5160−5163.

(27) Wen, Z.-K.; Xu, Y.-H.; Loh, T. P. Palladium(II)-Catalyzed Cross-Coupling of Simple Alkenes with Acrylates: a Direct Approach to 1,3-Dienes through C-H Activation. *Chem. Sci.* **2013**, *4*, 4520.

(28) Xu, Y.-H.; Lu, J.; Loh, T. P. Direct Cross-Coupling Reaction of Simple Alkenes with Acrylates Catalyzed by Palladium Catalyst. *J. Am. Chem. Soc.* **2009**, *131*, 1372−1373.

(29) Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. Palladium-Catalyzed Cross-Coupling of Internal Alkenes with Terminal Alkenes to Functionalized 1,3-Butadienes Using C-H Bond Activation: Efficient Synthesis of Bicyclic Pyridones. *Angew. Chem., Int. Ed.* **2010**, *49*, 5792−5797.

(30) Zhang, J.; Loh, T.-P. Ruthenium- and Rhodium-Catalyzed Cross-Coupling Reaction of Acrylamides with Alkenes: Efficient

Access to (Z,E)-Dienamides. *Chem. Commun.* **2012**, *48*, 11232−11234.
(31) Zhang, Y.; Cui, Z.; Li, Z.; Liu, Z.-Q. Pd-Catalyzed Olefination of Perfluoroarenes with Allyl Esters. *Org. Lett.* **2012**, *14*, 1838−1841.
(32) Delcamp, J. H.; Gormisky, P. E.; White, M. C. Oxidative Heck Vinylation for the Synthesis of Complex Dienes and Polyenes. *J. Am. Chem. Soc.* **2013**, *135*, 8460−8463.
(33) Liang, Q. J.; Yang, C.; Meng, F. F.; Jiang, B.; Xu, Y. H.; Loh, T. P. Chelation versus Non-Chelation Control in the Stereoselective Alkenyl sp^2 C-H Bond Functionalization Reaction. *Angew. Chem., Int. Ed.* **2017**, *56*, 5091−5095.
(34) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalyzed C−H Bond Activation and Functionalization. *Chem. Rev.* **2012**, *112*, 5879−5918.
(35) Trost, B. M.; Indolese, A. Ruthenium-Catalyzed Addition of Alkenes to Acetylenes. *J. Am. Chem. Soc.* **1993**, *115*, 4361.
(36) Trost, B. M.; Indolese, A. F.; Muller, T. J. J.; Treptow, B. A Ru Catalyzed Addition of Alkenes to Alkynes. *J. Am. Chem. Soc.* **1995**, *117*, 615.
(37) Trost, B. M.; Toste, F. D. A New Ru Catalyst for Alkene-Alkyne Coupling. *Tetrahedron Lett.* **1999**, *40*, 7739.
(38) Trost, B. M.; Toste, F. D. Ruthenium-Catalyzed Cycloisomerizations of 1,6- and 1,7-Enynes. *J. Am. Chem. Soc.* **2000**, *122*, 714.
(39) Trost, B. M.; Kulawiec, R. J. Chemoselectivity in the Ruthenium-Catalyzed Redox Isomerization of Allyl Alcohols. *J. Am. Chem. Soc.* **1993**, *115*, 2027.
(40) Trost, B. M.; Livingston, R. C. Two-Metal Catalyst System for Redox Isomerization of Propargyl Alcohols to Enals and Enones. *J. Am. Chem. Soc.* **1995**, *117*, 9586−9587.
(41) Fang, X.; Zhang, M.; Jackstell, R.; Beller, M. Selective Palladium-Catalyzed Hydroformylation of Alkynes to α,β-Unsaturated Aldehydes. *Angew. Chem., Int. Ed.* **2013**, *52*, 4645−4649.
(42) An, Q.; Shen, J.; Butt, N. A.; Liu, D.; Liu, Y.; Zhang, W. Asymmetric Domino Double Michael Addition of Nitro-olefins and Aldehyde Esters with trans-Perhydroindolic Acid as an Organocatalyst. *Synthesis* **2013**, *12*, 1612−1623.
(43) Altendorfer, M.; Raja, A.; Sasse, F.; Irschik, H.; Menche, D. Modular Synthesis of Polyene Side Chain Analogues of the Potent Macrolide Antibiotic Etnangien by a Flexible Coupling Strategy Based on Hetero-bis-Metallated Alkenes. *Org. Biomol. Chem.* **2013**, *11*, 2116−39.
(44) Sharma, G. V. M.; Rajagopal, D.; Rao, E. S. A Practical Synthesis of (2E,6E,8E)-N-(2-Methylpropyl)-2,6,8-hexadecatrien-10 ynamide. *Synth. Commun.* **1989**, *19*, 3181−3189.
(45) Marqués-López, E. M.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Christmann, M. Enantioselective Rauhut-Currier-Type Cyclizations via Dienamine Activation: Scope and Mechanism. *Synthesis* **2013**, *45*, 1016−1028.
(46) Chruma, J. J.; Cullen, D. J.; Bowman, L.; Toy, P. H. Polyunsaturated Fatty acid Amides from the *Zanthoxylum* genus − from Culinary Curiosities to Probes for Chemical Biology. *Nat. Prod. Rep.* **2018**, *35*, 54−74.
(47) Bader, M.; Stark, T. D.; Dawid, C.; Losch, S.; Hofmann, T. All-*trans*-Configuration in *Zanthoxylum* Alkylamides Swaps the Tingling with a Numbing Sensation and Diminishes Salivation. *J. Agric. Food Chem.* **2014**, *62*, 2479−2488.
(48) Chen, J.; Zhang, T.; Zhang, Q.; Liu, Y.; Li, L.; Si, J. G.; Zou, Z.; Hua, H. Isobutylhydroxyamides from Sichuan Pepper and Their Protective Activity on PC12 Cells Damaged by Corticosterone. *J. Agric. Food Chem.* **2018**, *66*, 3408−3416.
(49) Xu, J.; Caro-Diaz, E. J. E.; Diaz, C.; Trzoss, L.; Theodorakis, E. A. Nature-Inspired Total Synthesis of (−)-Fusarisetin A. *J. Am. Chem. Soc.* **2012**, *134*, 5072−5075.
(50) Xu, Q.-Q.; Zhao, Q.; Shan, G. S.; Yang, X. C.; Shi, Q. Y.; Lei, X. Synthesis of Δ^3-2-Hydroxybakuchiol Analogues and Their Growth Inhibitory Activity against Rat UMR106 Cells. *Tetrahedron* **2013**, *69*, 10739−10746.
(51) Li, W.; Georg, G. I. A Concise Formal Total Synthesis of Lactimidomycin. *Chem. Commun.* **2015**, *51*, 8634−8636.
(52) Larsen, B. J.; Lachacz, Z. S. E.; Khomutnyk, Y.; Soellner, M. B.; Nagorny, P. Synthesis and Biological Evaluation of Lactimidomycin and Its Analogues. *Chem. - Eur. J.* **2015**, *21*, 19159−19167.
(53) Jeffery, T. Highly Stereospecific Palladium-Catalysed Vinylation of Vinylic Halides under Solid-Liquid Phase Transfer Conditions. *Tetrahedron Lett.* **1985**, *26*, 2667.
(54) Snider, B. B.; Shi, Z. Total synthesis of (+)-Chondrillin.; (+)-Plakorin.; and Related Peroxy Ketals. Development of a General Route to 3,6-dihydro-1,2-dioxin-3-ols. *J. Am. Chem. Soc.* **1992**, *114*, 1790−1800.
(55) Donohoe, T. J.; Butterworth, S. Oxidative Cyclization of Diols Derived from 1,5-Dienes: Formation of Enantiopure *cis*-Tetrahydrofurans by Using Catalytic Osmium Tetroxide; Formal Synthesis of (+)-*cis*-Solamin. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766−4768.
(56) Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. Total Synthesis and Preliminary Biological Evaluation of *cis*-Solamin Isomers. *J. Org. Chem.* **2004**, *69*, 3368−3374.
(57) Kovalev, I. P.; Kolmogorov, Y. N.; Strelenko, Y. A.; Ignatenko, A. V.; Vinogradov, M. G.; Nikishin, G. I. Head-to-Head" Dimerization and Dehydrodimerization of Vinyl Ketones Catalyzed by Modified Rhodium (I) Complexes. *J. Organomet. Chem.* **1991**, *420*, 125−133.

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Org. Lett. XXXX, XXX, XXX−XXX