

Biomimetic Total Syntheses of Flinderoles B and C

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S Supporting Information

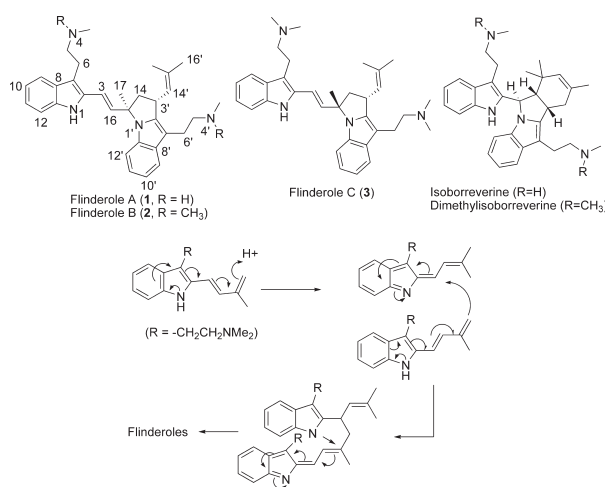
ABSTRACT: A simple and efficient biomimetic synthesis of pyrrolo[1,2-*a*]indoles using a highly stereo- and regioselective [3 + 2] reaction cascade was developed and then further applied in the first total synthesis of flinderoles B and C, which proceeded in 17.2% yield over the longest linear sequence of 11 steps.

Malaria chemotherapy is under continuous threat from the evolution and rise of multidrug resistance of *Plasmodium falciparum*.¹ To counter the threat of resistance, structurally and functionally novel antimalarial compounds with new mechanisms of action are needed. In 2009, flinderoles A–C (**1–3**, respectively; Scheme 1) were isolated through an initial antimalarial natural product extract screening program.² All of the flinderoles have shown impressive selective antimalarial activity against the *P. falciparum* parasite,² with flinderole C being most active (IC_{50} = 150 nM), and flinderoles thus present new molecular scaffolds for antimalarial drug discovery. Flinderoles have a new skeleton that is rearranged relative to the known borreverine class of tryptamine isoprene-derived compounds borreverine, isoborreverine, and dimethylisoborreverine.³ The dimeric structure of the flinderoles lends itself to a symmetrical retrosynthetic dissection through the center of the molecule. This dissection reveals monomeric tryptamine diene as a possible precursor—a scenario that might not be so dissimilar to their biosynthetic pathway (Scheme 1).

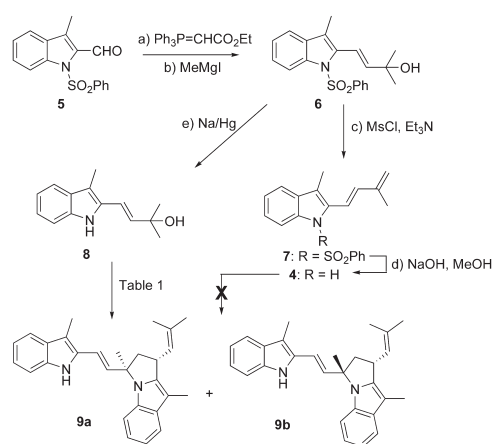
Our explorations to test this overall hypothesis began with the preparation of diene **4** from the known indole aldehyde **5**⁴ (Scheme 2) on a multigram scale. Treatment of indole aldehyde **5** with $Ph_3P=CHCO_2Et$ followed by reaction of the resultant ester with MeMgBr generated the tertiary alcohol **6**. Mesylation of alcohol **6** and subsequent elimination yielded diene **7**, which gave the required diene **4** upon desulfonation using methanolic NaOH. To our surprise, diene **4** was found to polymerize with different Lewis acids under various reaction conditions employed, resulting in intractable mixtures. This could be explained by reasoning that the actual site of protonation in **4** is at C3 of the indole nucleus to produce a conjugated enamine, which could undergo cationic polymerization. At this juncture, it was reasoned that if diene **4** were generated in situ in sufficiently low concentration, it might undergo dimerization by a formal intermolecular [3 + 2] cycloaddition,^{5,6} leading to the flinderole framework. On the basis of this hypothesis, the available alcohol **6** was desulfonated to obtain alcohol **8**. Various Lewis acids were screened for the proposed dimerization of **8**, and results are summarized in Table 1.

The reaction of alcohol **8** with TMSOTf furnished a complex mixture of products, and the dimers **9a** and **9b** were obtained in

Scheme 1. Structures of Flinderoles A–C and the Proposed Biosynthetic Pathway



Scheme 2. Exploration of the Biosynthetic Pathway^a



^a Conditions: (a) $Ph_3P=CHCO_2Et$ (1.5 equiv), CH_2Cl_2 , RT, 6 h, 95%; (b) MeI (7.0 equiv), Mg turnings (6.0 equiv), I_2 (cat.), Et_2O , 0 °C to RT, 2 h, 81%; (c) MsCl (3.0 equiv), Et_3N (6.0 equiv), THF, 0 °C to reflux, 2 h, 82%; (d) NaOH (5.0 equiv), MeOH, 70 °C, 3 h, 75%; (e) Na/Hg (4.0 equiv), Na_2HPO_4 (4.0 equiv), MeOH, RT, 1 h, 91%.

Received: December 29, 2010

Published: February 11, 2011

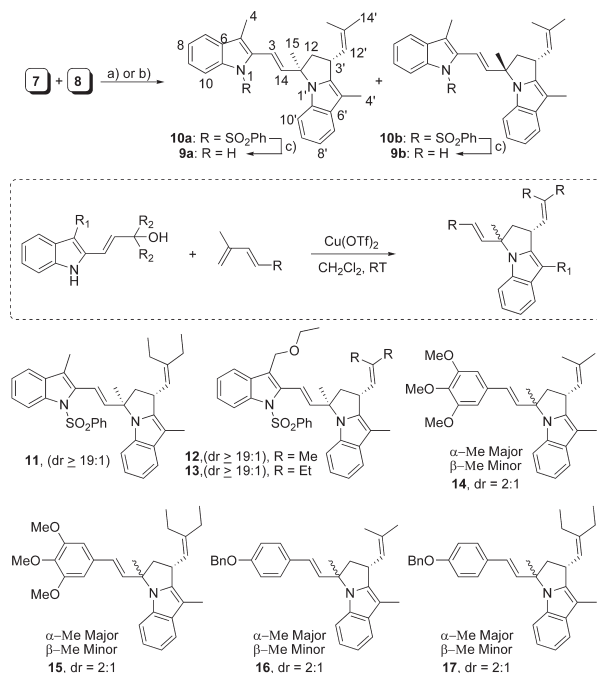
Table 1. Invention and Optimization of the Dimerization Reaction of Alcohol 8^a

entry	Lewis acid	yield (%) ^b	dr (9a:9b) ^c
1	TMSOTf	10	1:1
2	Yb(OTf) ₃	25	1:1
3	Sc(OTf) ₃	25	1:1
4	BF ₃ ·OEt ₂	38	3:2
5	Cu(OTf) ₂	46	2:1
6	TFA	35	3:2
7	Tf ₂ O	0	N.A.

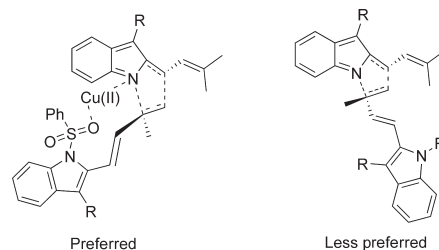
^a All reactions were carried out on a 0.25 mmol scale in CH₂Cl₂ as the solvent (0 °C to RT). ^b Isolated yield. ^c Determined by ¹H NMR analysis of the crude reaction mixture.

poor yield as 1:1 mixture of diastereomers (Table 1, entry 1). Similarly, Yb(OTf)₃ and Sc(OTf)₃ gave the desired adducts **9a** and **9b** in low yield (entries 2 and 3). BF₃·OEt₂ was found to be a useful catalyst for effecting this transformation in a much cleaner manner, generating the products **9a** and **9b** in moderate yield and diastereoselectivity (entry 4). Even though Tf₂O did not give any desired product, trifluoroacetic acid (TFA) did furnish the required products **9a** and **9b** in comparable yield (Table 1, entries 6 and 7). More interestingly Cu(OTf)₂ generated the flinderole frameworks **9a** and **9b** in much improved yield and diastereoselectivity (Table 1, entry 5). It is worth mentioning that no [4 + 2] cycloaddition product was observed even in trace amounts under these conditions. The dimers **9a** and **9b** could be separated by careful column chromatography, and their structures were established by spectroscopic analysis (¹H and ¹³C NMR, IR, HRMS) through comparison with flinderole spectral data.² Their relative stereochemistry was determined by rotational Overhauser effect spectroscopy (ROESY). Weak ROESY correlations between H3' and H14 and between 3H15 and H12' indicated that the C17 methyl group and the isobutene group must be on the same side of the five-membered ring in the major isomer **9a**.⁷

Scheme 3 describes the scope of this dimerization reaction. It was envisaged that the dimerization reaction would be more facile if the intermediate generated in situ from alcohol **8** were reacted with an olefin such as **7** bearing a sulfonyl group. It was anticipated that since the olefin would be preformed and the intermediate trapped immediately, the formation of polymerization products would be significantly reduced. Gratifyingly, when tertiary alcohol **8** and diene **7** were mixed together and treated with Cu(OTf)₂, the dimers **10a** and **10b** were indeed obtained in excellent yield and diastereoselectivity (≥ 19:1). When BF₃·OEt₂ was used as the catalyst, the diastereomeric ratio decreased to 2:1. The relative stereochemistry of **10a** and **10b** was determined by ROESY and nuclear Overhauser effect spectroscopy (NOESY) experiments. Although the reason for the excellent diastereoselectivity is not very clear at this moment, it was observed that excellent diastereoselectivity was obtained only when the –SO₂Ph group was present and Cu(OTf)₂ was used as catalyst; thus, the diastereoselectivity could be rationalized in terms of a transition-state structure in which copper is coordinated to the –SO₂Ph group of one indole unit and the nitrogen of the other unit. The approach of the olefin is endo, similar to the Diels–Alder reaction (Figure 1).⁸ This transition-state structure reduces the unfavorable steric interaction present when the olefin approaches in exo mode. Removal of the benzenesulfonyl

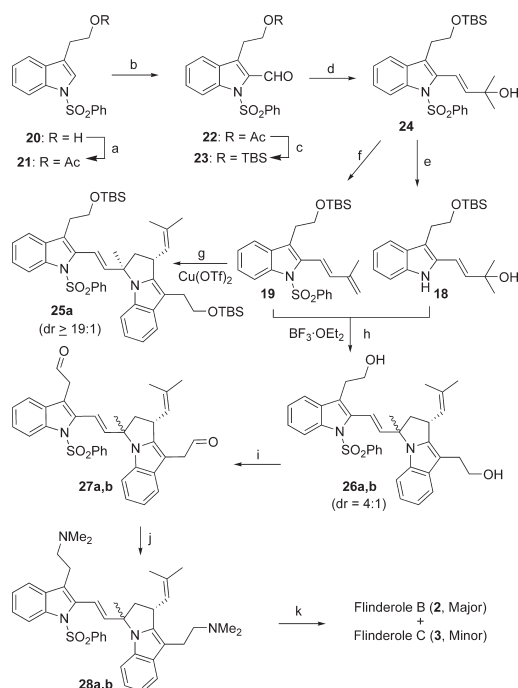
Scheme 3. Intermolecular Cascade Reaction^a

^a Conditions: (a) Cu(OTf)₂ (0.2 equiv), CH₂Cl₂, RT, 30 min, 95%; (b) BF₃·OEt₂ (0.2 equiv), CH₂Cl₂, RT, 20 min, 92%; (c) Na/Hg (4.0 equiv), Na₂HPO₄ (4.0 equiv), MeOH, RT, 1 h, 94%.

**Figure 1. Proposed stereochemical model for the [3 + 2] cycloaddition.**

protection could be readily accomplished using sodium amalgam, furnishing the dimers **9a** and **9b**, whose ¹H and ¹³C NMR data were identical to those of the samples generated earlier. In order to expand the scope of the reaction, several diverse examples were carried out, as illustrated in Scheme 3. The reaction was found to work with equal efficiency when the tertiary alcohol had ethyl rather than methyl substitution (cf. adduct **11**). Similarly, having an ethoxymethyl substituent at C3 of the indole did not affect the yield or selectivity (cf. adducts **12** and **13**). It is noteworthy that not only indole derivatives but also even simple 1-phenyl-3-methylbutadiene derivatives reacted to give the corresponding highly substituted pyrrolo[1,2-*a*]indole derivatives in good yield, albeit with only modest selectivity.⁹ These results encouraged us to proceed further to a biomimetic total synthesis of flinderoles.¹⁰

To access flinderoles B and C, indole tertiary alcohol **18** and indole diene **19** were identified as appropriate precursors for the key [3 + 2] cycloaddition reaction. The synthesis began with

Scheme 4. Total Synthesis of Flinderoles B (2) and C (3)^a

^a Conditions: (a) Ac_2O (5.0 equiv), DMAP (0.2 equiv), pyridine (5.0 equiv), CH_2Cl_2 , RT, 6 h, 91%; (b) dichloromethyl methyl ether (5.0 equiv), stannic chloride (5.0 equiv), CH_2Cl_2 , -78 to -10 °C, 1 h, 80%; (c) (i) LiOH (5.0 equiv), H_2O , THF, RT, 3 h; (ii) TBSCl (1.3 equiv), imidazole (1.5 equiv), CH_2Cl_2 , 0 °C to RT, 6 h, 81% (over two steps); (d) (i) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ (1.5 equiv), CH_2Cl_2 , RT, 6 h, 91%; (ii) MeI (10 equiv), Mg turnings (9 equiv), I_2 (cat.), Et_2O , 0 °C to RT, 2 h, 89%; (e) Na/Hg (4.0 equiv), Na_2HPO_4 (4.0 equiv), MeOH , RT, 1 h, 97%; (f) MsCl (3.0 equiv), Et_3N (6.0 equiv), THF, 0 °C to reflux, 2 h, 81%. (g) $\text{Cu}(\text{OTf})_2$ (0.2 equiv), CH_2Cl_2 , RT, 30 min, 62%; (h) $\text{BF}_3\cdot\text{OEt}_2$ (4.0 equiv), CH_2Cl_2 , RT, 30 min, 78%; (i) IBX (6.0 equiv), EtOAc , reflux, 1 h, 84%; (j) NHMe_2 (4.0 equiv), NaCNBH_3 (4.0 equiv), AcOH (cat.), MeOH , RT, 12 h, 91%; (k) Na/Hg (4.0 equiv), Na_2HPO_4 (4.0 equiv), MeOH , RT, 1 h, 2 (62%), 3 (15%).

known protected tryptophol **20**.¹¹ The primary hydroxyl group of **20** was acylated using acetic anhydride to furnish acetate **21**. Formylation of **21** using dichloromethyl methyl ether and stannic chloride gave acetate **22**. The acetyl protection in indole derivative **22** was changed to TBS protection following hydrolysis of acetate and reaction of the resultant alcohol with TBSCl to obtain TBS ether **23**. Wittig olefination of aldehyde **23** with $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ generated the unsaturated ester in 91% yield, which upon treatment with methylmagnesium iodide gave tertiary alcohol **24** in excellent yield. Dehydration of the hydroxyl group of **24** was achieved via its mesylate followed by elimination to furnish the requisite olefin **19**. On the other hand, deprotection of the phenylsulfonyl group in **24** using sodium amalgam gave the other coupling partner, alcohol **18** (Scheme 4). With gram quantities of tertiary alcohol **18** and diene **19** in hand, the stage was set for the key dimerization reaction for the synthesis of the flinderole skeleton.

To begin with, an equimolar mixture of tertiary alcohol **18** and diene **19** were treated with a catalytic amount of copper(II) triflate, which gratifyingly afforded the adduct **25a** in 62% yield

with excellent diastereoselectivity. Surprisingly, treatment of a mixture of **18** and **19** with excess $\text{BF}_3\cdot\text{OEt}_2$ not only gave the expected dimerization product but also deprotected both TBDMS groups, directly generating diols **26a** and **26b** in excellent overall yield, albeit with moderate diastereoselectivity (4:1). In line with the earlier observation, the major compound was found to be isomer **26a**, in which the methyl and isobutylene groups are *cis* to each other. The mixture of diols **26a** and **26b** was not separated at this stage, given the fact that both isomers would finally lead to the natural products, which could be separated in the last step. All of our attempts to convert **26a** and **26b** to the corresponding diamines via their mesylates or triflates failed to give the desired products. Finally, oxidation of the mixture of **26a** and **26b** using IBX followed by reductive amination of the resultant bisaldehydes **27a** and **27b** gave a mixture of amines **28a** and **28b** in 91% yield. Deprotection of the indole nitrogens of **28a** and **28b** followed by purification by preparative TLC delivered flinderoles B (**2**) and C (**3**), which were then treated individually with 0.005 M TFA in acetonitrile to get the corresponding TFA salts. The TFA salts of synthetic flinderoles B and C thus obtained possessed physical properties (IR, mass, ^1H and ^{13}C NMR data) identical to those reported in the literature.²

In summary, a highly stereo- and regioselective formal [3 + 2] cycloaddition reaction between a tertiary alcohol and an olefin has been developed for use in the synthesis of pyrrolo[1,2-*a*]indoles. The potential of this methodology has been amply demonstrated in the first total synthesis of the isomeric flinderoles B and C, which involves 11 steps in the longest linear sequence and gave an overall yield of 17.2%. The strategy is fairly general and is amenable to the synthesis of other natural products of this class as well as their analogues.

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

This paper is dedicated to Prof. A. Srikrishna. We thank Dr. C. V. Ramana and Dr. S. J. Gharpure for their valuable suggestions. We thank Dr. P. R. Rajmohan and team for recording NMR spectra. R.D.E. and A.R. thank CSIR, New Delhi, for the award of research fellowship. Financial support from NCL, Pune (Project MLP017726) and DST, New Delhi (Project GAP291026) is gratefully acknowledged.

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Ruthenium-catalyzed formal sp^3 C–H activation of allylsilanes/esters with olefins: efficient access to functionalized 1,3-dienes†Dattatraya H. Dethe,^{ID}* Nagabhushana C. Beeralingappa, Saikat Das‡ and Appasaheb K. Nirpal‡

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.

Received 15th December 2020

Accepted 1st February 2021

DOI: 10.1039/d0sc06845d

rsc.li/chemical-science

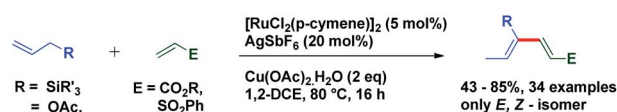
1,3-Dienes not only are widespread structural motifs in biologically pertinent molecules but also feature as a foundation for a broad range of chemical transformations.^{1–14} Indeed, these conjugated dienes serve as substrates in many fundamental synthetic methodologies such as cycloaddition, metathesis, 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 reaction⁵³ 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).

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc06845d

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

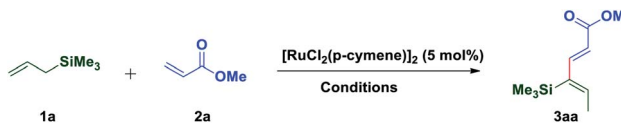
In 1993, Trost and coworkers reported an elegant method for highly chemoselective ruthenium-catalyzed redox isomerization of allyl alcohols without affecting the primary and secondary alcohols and isolated double bonds.^{54,55} Inspired by the potential of ruthenium for such isomerization of double bonds 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 $[\text{RuCl}_2(p\text{-cymene})]_2$ catalyst in the presence of AgSbF_6 as an additive and co-oxidant $\text{Cu}(\text{OAc})_2$ 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 $\text{Cu}(\text{OAc})_2$ is necessary for the success of this reaction (entry 12).

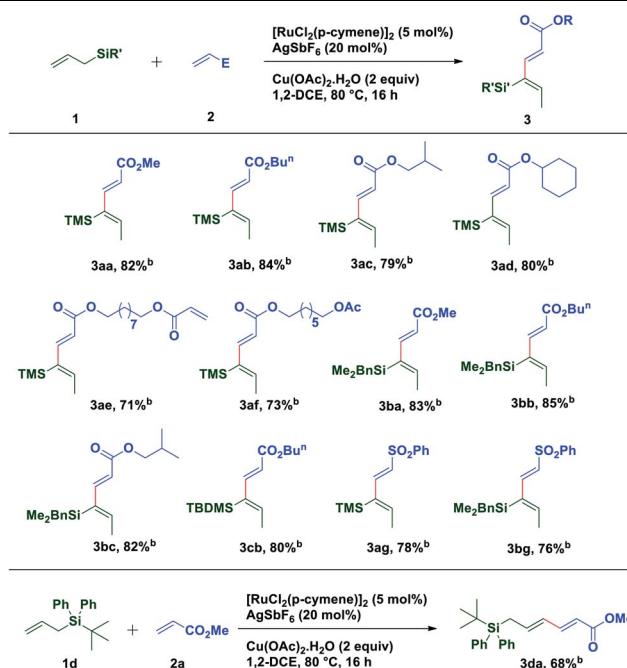
With these optimized conditions in hand, various allyl sources and acrylates have been tested (Table 2). It was found that a variety of acrylates **2** bearing alkyl and sterically crowded cyclic substituents successfully underwent the coupling reaction with allyl silane **1a** to afford corresponding 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	$\text{Cu}(\text{OAc})_2$	DCE	55
2	AgSbF_6	$\text{Cu}(\text{OAc})_2$	<i>t</i> -AmOH	10
3	AgSbF_6	$\text{Cu}(\text{OAc})_2$	DMF	0
4	AgSbF_6	$\text{Cu}(\text{OAc})_2$	Dioxane	8
5	AgSbF_6	$\text{Cu}(\text{OAc})_2$	THF	21
6	AgSbF_6	$\text{Cu}(\text{OAc})_2$	MeCN	0
7 ^c	AgSbF_6	$\text{Cu}(\text{OAc})_2$	DCE	35
8 ^d	AgSbF_6	$\text{Cu}(\text{OAc})_2$	DCE	82
9 ^e	AgSbF_6	$\text{Cu}(\text{OAc})_2$	DCE	45
10 ^d	Ag_2CO_3	$\text{Cu}(\text{OAc})_2$	DCE	0
11 ^d	AgOAc	$\text{Cu}(\text{OAc})_2$	DCE	20
12 ^d	AgSbF_6	—	DCE	0

^a Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (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), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (5 mol%), AgSbF_6 (20 mol%) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (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

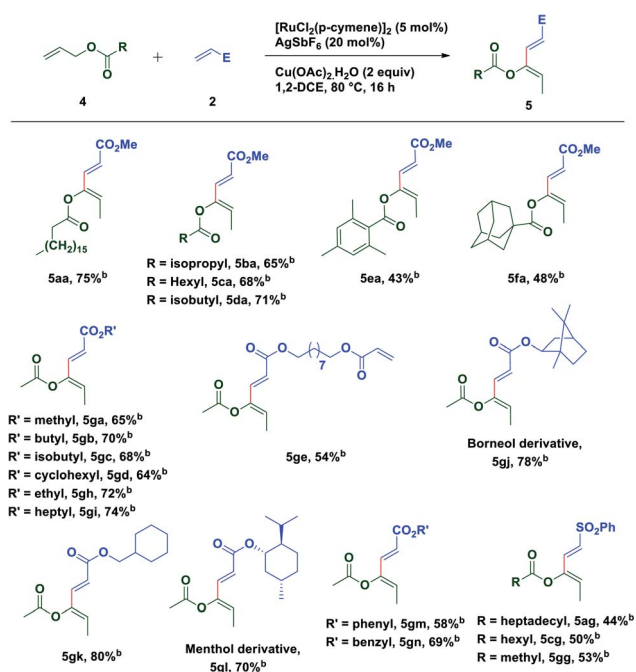
acetate group intact, which further reacts with an electrophile. The stereochemistry of the diene was established by **1D** and **2D** spectroscopic analysis of the compound **5ga** and also by comparison of spectroscopic data with those of an authentic compound.⁶⁶ Next we turned our attention to expand 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.

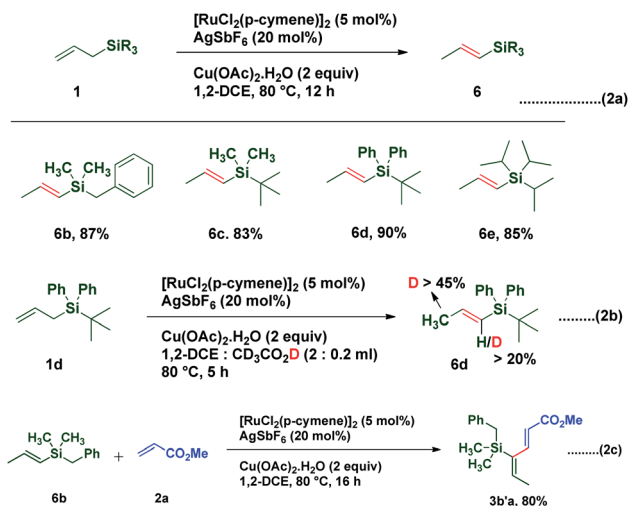
Interestingly treatment of allylsilanes under standard reaction conditions in the absence of an acrylate coupling partner led to isomerization of various allylsilanes to afford corresponding vinylsilanes **6b–6e** in excellent yields (Scheme 2a). When allylsilane **1d** was subjected to isomerization in the presence of CD₃CO₂D, 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



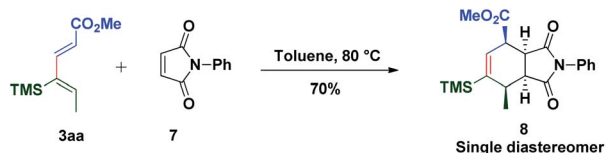
^a Reaction conditions: **4** (0.24 mmol), **2** (0.2 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol%), AgSbF₆ (20 mol%) and Cu(OAc)₂·H₂O (2 equiv.) at 80 °C in 1,2-dichloroethane (2.0 mL), under argon, 16 h. ^b Isolated yields are of product **5**.



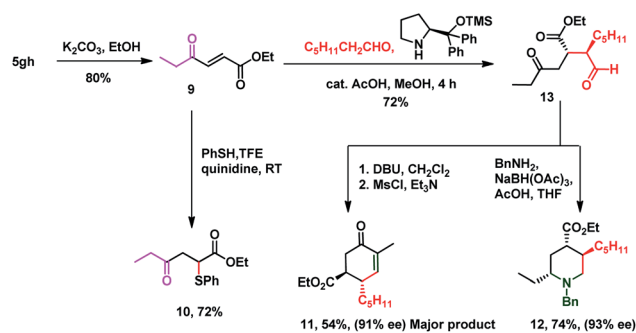
Scheme 2 Isomerization of allylsilanes and deuterium study.

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 Michael 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**.

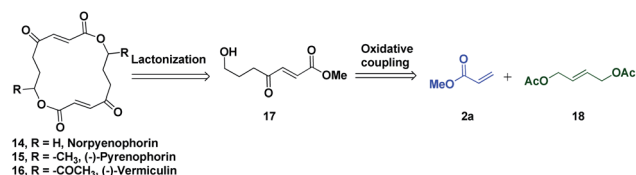
The potential of this Ru-catalysed reaction was further demonstrated by norpyrenophorin synthesis.^{71–74} Norpyrenophorin **14** is a synthetic 16-membered lactone which has essentially the same physiological activity as the natural fungicide pyrenophorin **15** and the antibiotic vermiculin **16**.⁷³ 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.

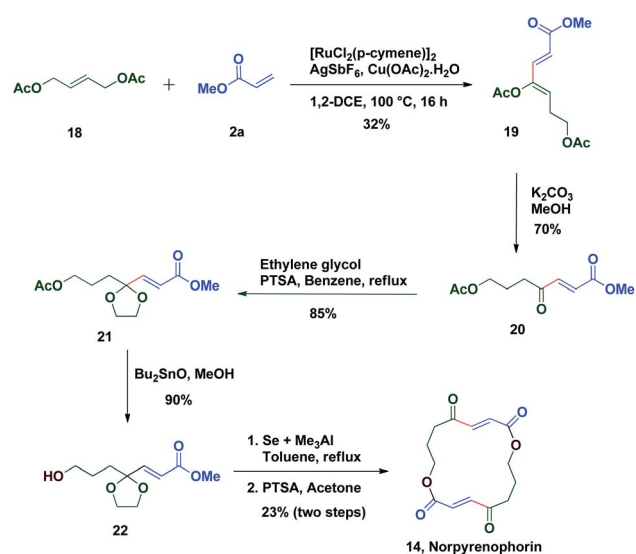


Scheme 4 Application to the organocatalytic Michael addition reaction.

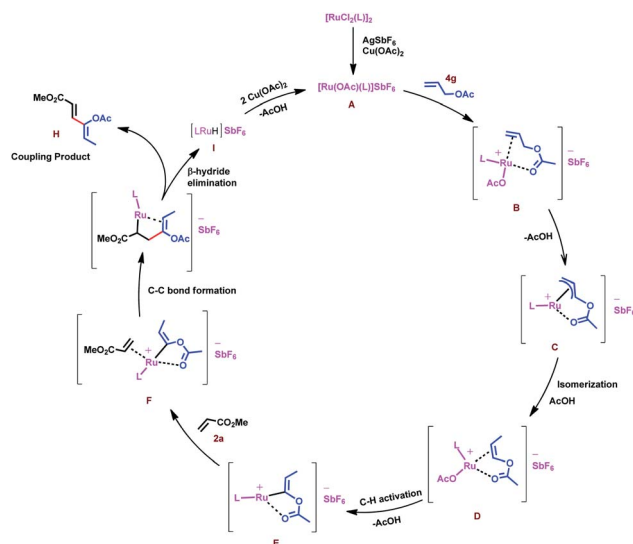


Scheme 5 Retrosynthetic analysis of norpyrenophorin.

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 mediated⁷² 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 $[\text{Ru}(\text{OAc})\text{L}]^+$ **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 $\text{Cu}(\text{OAc})_2$ 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 stereo-defined 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 norbornene 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.

Acknowledgements

N. C. B. thanks UGC, New Delhi, for the award of a research fellowship and A. K. N. thanks IIT Kanpur for the fellowship. Financial support from CSIR Project No. 02(0274)/16/EMR-II is gratefully acknowledged.

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