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Iridium-Catalyzed Enantioselective Vinylogous and Bisvinylogous Allenylic Substitution

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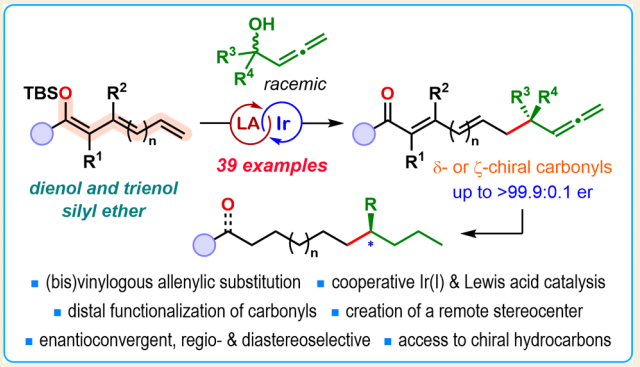
ABSTRACT: Compared to the widely explored enol silanes, the applicability of their extended variants especially as bisvinylogous nucleophiles in enantioselective catalysis has been sparse. Herein, we describe the first enantioselective vinylogous and bisvinylogous allenylic substitution using silyl dienol and trienol ethers, respectively, as a nucleophile. With racemic allenylic alcohols as the electrophile, these enantioconvergent reactions are cooperatively catalyzed by an Ir(I)/(phosphoramidite,olefin) complex and Lewis acidic La(OTf)$_3$ and display remarkable regio- and diastereoselectivity in most cases. The ability of such extended silyl enol ethers in distant functionalization and creation of remote stereocenters is evident from the resulting γ- and ϵ-allenylic unsaturated ketones, bearing δ- and ζ-stereocenters, respectively, which are obtained in moderate to high yields with good to excellent enantioselectivity. The synthetic utility of these unsaturated carbonyls bearing an allene moiety is demonstrated with several transformations, including controlled reductions and stereoselective olefinations, which lead to products with desired degrees of unsaturation.



KEYWORDS: *allenylic substitution, enantioselectivity, iridium catalysis, vinylogous, bisvinylogous, silyl enol ether*

1. INTRODUCTION

Introduction of a functional group in an organic compound at a position distant from an existing functional group, commonly known as remote functionalization (Scheme 1A), has remained a coveted strategy in organic synthesis.[1−5] 1,5-Hydrogen atom transfer (HAT, eq 1)[6−11] and ring opening of (strained) cycloalkanols (eq 2)[12−16] represent rare strategies for remote functionalization in a saturated alkyl chain, with the possibility of generating a stereocenter far away from the parent functional group (termed remote stereocenter) (Scheme 1A). Although not functionalizing at a distant position per se, the Pd-catalyzed redox-relay oxidative Heck arylation of alkenyl alcohols emerged as an effective strategy for synthesizing acyclic compounds containing a stereocenter remote from an aldehyde or ketone group through olefin chain-walking (eq 3).[17−19]

Propagation of electronic properties of a functional group through a conjugated π-system, known as the principle of vinylogy,[20] is another powerful strategy for enantioselective remote functionalization reactions, especially in unsaturated carbonyl compounds (Scheme 1A, eq 4).[21−23] Regardless of its popularity, this strategy is not devoid of challenges. Apart from the attenuation of reactivity with increasing distance from the parent functional group,[24] flexibility of the intervening fragment, particularly in acyclic systems, makes the control of the newly formed stereocenter challenging. This aspect is especially pertinent for reactions where the enantiocontrol is dictated through the activation of the vinylogous component by the chiral catalyst (e.g., dienamine, trienamine, or vinylogous iminium catalysis).[25,26] In contrast, with the use of preformed vinylogous and bisvinylogous nucleophiles, such as extended silyl enol ethers in combination with a suitable catalyst-activated electrophile, this problem can be averted.

Iridium-catalyzed enantioselective allenylic substitution, pioneered by Carreira and co-workers in 2018,[27] is a class of transformations that offers reliable and predictable stereocontrol on the electrophilic site at the bond-formation step, irrespective of the nature of the nucleophile (Scheme 1B).[28−31] Using allenylic alcohol or the corresponding carbonate as the electrophile under the cooperative catalysis of an Ir(I)/(phosphoramidite,olefin) complex and a Lewis acid, the proposed η^2-Ir(I)-bound allenylic carbocation intermediate **A** has been shown to exhibit outstanding face-selectivity toward nucleophilic attack.[27] Despite this mechanistic premise, very few nucleophiles have so far been explored in this

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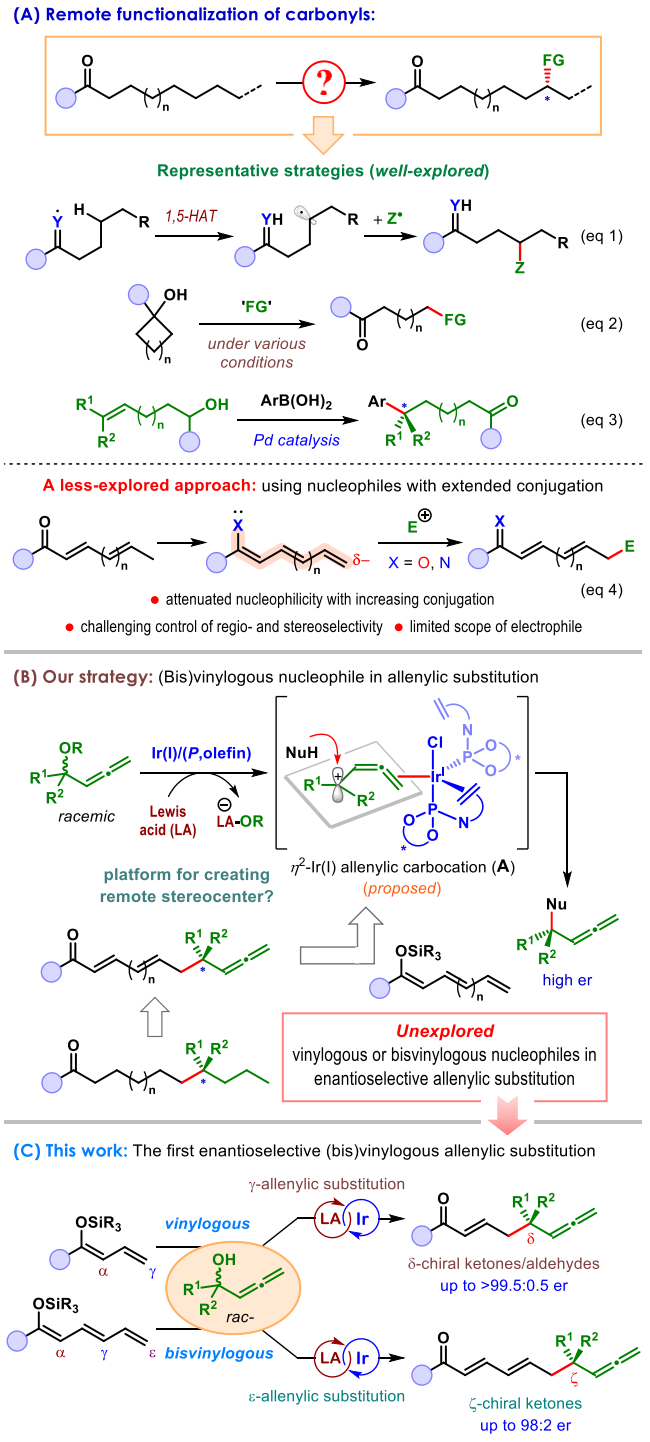
Scheme 1. Remote Functionalization of Carbonyls: Strategies and This Work



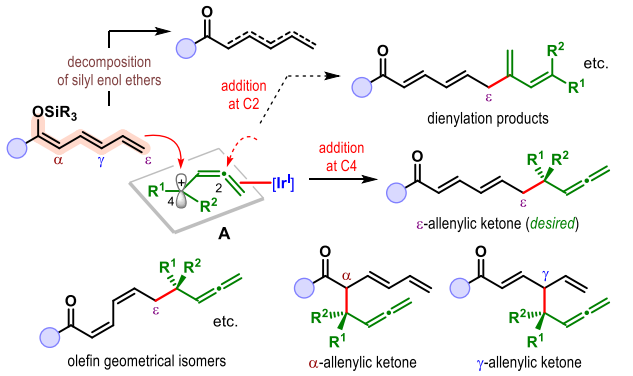
reaction.[28−31] Interestingly, no vinylogous or bisvinylogous nucleophile has ever been applied in any allenylic substitution reaction, let alone an enantioselective variant.[32−35]

Considering the potential of extended silyl enol ethers in creating remote stereocenters,[24,36−42] we sought to apply them as nucleophiles in Ir-catalyzed allenylic substitution. While the immediate products of this reaction would be highly unsaturated, it should be possible to access compounds with the desired degree of saturation, bearing a remote stereocenter, through selective reduction.

Although silyl enol ethers have been extensively utilized as nucleophiles in catalytic asymmetric synthesis, the application of extended silyl enol ethers, as bisvinylogous nucleophiles, in enantioselective catalysis has been scarce.[24,36−42] The examples known to date have mostly been confined to aldol or Mannich reactions and dominated by organocatalysis or Lewis acid catalysis.[24,36−42] The application of trienolsilanes as bisvinylogous nucleophiles in transition-metal catalysis remained curiously absent. A recent study by Xu and co-workers described the first Cu-catalyzed enantioselective propargylic substitution with extended silyl ketene acetals as nucleophiles.[43] We now report the first catalytic enantioselective allenylic substitution with extended silyl enol ethers as vinylogous and bisvinylogous nucleophiles (Scheme 1C).[44]

Our strategy hinges on harnessing the electrophilicity of the putative η^2-Ir(I)-bound allenylic carbocation intermediate[27] **A** (Scheme 1B) through the nucleophilic addition of dienol and trienol silyl ethers. However, this seemingly simple transformation can become complicated by both stereo- and regioselectivity issues (Scheme 2).

Scheme 2. Potential Challenges of Ir-Catalyzed Bisvinylogous Allenylic Substitution



The difference in nucleophilicity between the competing reactive sites (i.e., α- vs γ- vs ε-) in these extended silyl enol ethers is known to decrease with increasing conjugation.[24] Apart from the possible regioisomeric products arising out of less distinct site-selectivity on the nucleophile, diastereomers originating from the geometry of olefin(s) can further complicate the scenario. In addition, the instability of these silyl enol ethers is yet another cause of concern as they are known to decompose to the corresponding unsaturated ketones under a variety of conditions.

Through the judicious choice of reaction partners, promoter, and conditions, it was indeed possible to overcome most of these challenges. We herein present the successful outcome of this study, which culminated in the first enantioselective synthesis of γ- and ε-allenylic unsaturated ketones, bearing δ- and ζ-stereocenters, through an efficient and regioselective Ir-catalyzed allenylic substitution with vinylogous and bisvinylogous silyl enol ethers, respectively.

2. RESULTS AND DISCUSSION

To assess the feasibility of this distal functionalization strategy, catalytic enantioselective vinylogous allenylic alkylation of silyl dienol ether was initially undertaken. To begin with, we focused on finding an appropriate combination of substrates with a ligand, promoter, and solvent to achieve the desired γ-

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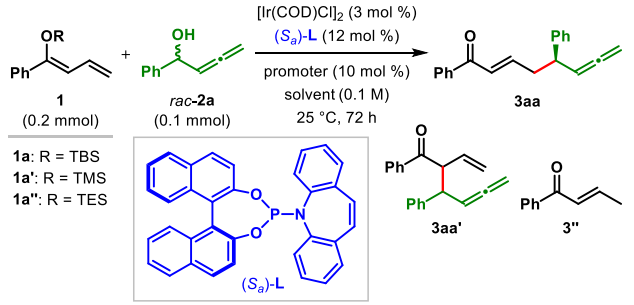
selectivity in addition to high diastereo- and enantioselectivity. For this purpose, vinylogous TBS-dienol ether **1a** derived from 1-phenyl-but-2-en-1-one was chosen as the nucleophile for reaction with racemic allenylic alcohol *rac*-**2a** (Table 1). To

Table 1. Optimization of Reaction Conditions for Enantioselective Vinylogous Allenylic Alkylation[a]



			yield[b]			
	promoter	solvent	3aa	3aa'	3''	er[c]
1	$Bi(OTf)_3$	THF	38	<5	16	98:2
2[d]	$Zn(OTf)_2$	THF	46	<5	15	99:1
3[d]	$Fe(OTf)_2$	THF	54	<5	12	98.5:1.5
4	$Sc(OTf)_3$	THF	48	<5	7	99:1
5	$La(OTf)_3$	THF	48	<5	<5	98:2
6[e]	$La(OTf)_3$	THF	32	<5	<5	98.5:1.5
7[f,g]	$La(OTf)_3$	THF	54	<5	<5	95.5:4.5
8[f,h]	$La(OTf)_3$	THF	43	<5	<5	97.5:2.5
9[f,g]	$La(OTf)_3$	toluene	16	<5	<5	n.d.
10[f,g]	$La(OTf)_3$	Et_2O	65	<5	6	99:1
11[f,g]	$La(OTf)_3$	$(CH_2Cl)_2$	(64)	<5	<5	97.5:2.5
12[f,i]	$La(OTf)_3$	$(CH_2Cl)_2$	(70)	<5	<5	97.5:2.5
13[f,i,j]	$La(OTf)_3$	$(CH_2Cl)_2$	(73)	<5	<5	97.5:2.5
14[f,g,k]	$La(OTf)_3$	$(CH_2Cl)_2$	63	<5	33	97.5:2.5
15[l]	$La(OTf)_3$	$(CH_2Cl)_2$	42	<5	<5	96:4
16[m]	$La(OTf)_3$	$(CH_2Cl)_2$	44	<5	<5	97:3

[a]Unless stated otherwise, the reactions were performed using 2.0 equiv of **1a** and 1.0 equiv of **2a** on a 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis with mesitylene as the internal standard. Isolated yield is given in parentheses. [c]The enantiomeric ratio (er) of the major product **3aa** was determined by HPLC analysis using a stationary phase chiral column. [d]Reaction time 48 h. [e]Reaction with 1.0 equiv of **1a** and 1.5 equiv of **2a** for 90 h. [f]Reaction with 1.5 equiv of **1a** and 1.0 equiv of **2a**. [g]Reaction with 5 mol % $La(OTf)_3$. [h]Reaction with 10 μL of H_2O and 5 mol % $La(OTf)_3$ for 90 h. [i]Reaction with 20 mol % $La(OTf)_3$. [j]Reaction on a 0.2 mmol scale. [k]Reaction at 50 °C. [l]Reaction with 2.0 equiv of **1a'** and 1.0 equiv of **2a** under 5 mol % $La(OTf)_3$. [m]Reaction with 1.5 equiv of **1a''** and 1.0 equiv of **2a** under 5 mol % $La(OTf)_3$. TBS, *tert*-butyldimethylsilyl; TMS, trimethylsilyl; TES, triethylsilyl; n.d., not determined.

our delight, in the presence of 3 mol % $[Ir(COD)Cl]_2$ and 12 mol % Carreira's (*P*,olefin) ligand[45] (S_a)-**L** along with 10 mol % $Bi(OTf)_3$ as the Lewis acidic promoter in THF at 25 °C, the desired allenylic alkylation of **1a** took place to afford the γ-allenylic α,β-unsaturated ketone **3aa** as a single diastereomer in 38% yield and 98:2 er (entry 1). Although no regioisomeric α-allenylic alkylation product **3aa'** could be detected, considerable decomposition of **1a** was found to take place under the reaction conditions to generate enone **3''**. The formation of **3''** complicated the purification process due to its inseparability from **3aa**.[46] At this point, suppression of **3''** was deemed essential not only for the ease of product purification but also to enhance the overall efficiency of the process. An assessment of several Lewis acid promoters (entries 2−5) revealed the supremacy of $La(OTf)_3$, which significantly reduced the formation of **3''** and improved the yield of **3aa** (entry 5). An attempt to increase the yield of the desired product **3aa** by using excess allenylic alcohol **2a** proved futile (entry 6). However, the reaction with a 1.5:1 molar ratio of **1a** and **2a** under 5 mol % $La(OTf)_3$ afforded **3aa** in 54% yield, albeit at the expense of er (entry 7). Rigorous exclusion of moisture is not essential for this reaction as the presence of 10 μL of water resulted in only a slight drop in yield (entry 8). In fact, no **3''** could be detected, even with added water, under these conditions. Such a tolerance of moisture made this protocol robust and operationally simple. At this stage, screening of solvents (entries 9−11) unveiled 1,2-dichloroethane to be the optimum, delivering **3aa** in 64% isolated yield with 97.5:2.5 er (entry 11). The yield of **3aa** could be improved to 70% by using 20 mol % $La(OTf)_3$ under otherwise identical reaction conditions (entry 12).

The reaction on a 0.2 mmol scale under these conditions facilitated the product isolation and resulted in **3aa** in 73% yield (entry 13). Increasing the reaction temperature proved to be detrimental as it expedited the formation of **3''** and resulted in a substantial decrease in the yield of **3aa** (entry 14). Replacing the TBS group of **1a** with other silyl protecting groups (**1a'** and **1a''**) resulted in an inferior yield of **3aa** (entries 15−16).

Having optimized the catalyst, promoter, and other reaction parameters, we set out to showcase the generality of this Ir-catalyzed vinylogous allenylic alkylation reaction. Our optimized conditions (Table 1, entry 13) were found to be suitable for the reaction of TBS-dienol ether **1a** with an assortment of racemic allenylic alcohols (*rac*-**2**) bearing electronically diverse aryl groups (Scheme 3A). However, the reaction outcome clearly depends on the electronic nature of these aryl substituents. Allenylic alcohols (**2b−d** and **2g**) bearing an electron-donating group at the *para*- or *meta*-position of the aryl ring generally resulted in products with a higher yield compared to those having an electron-deficient aryl group (**2f**). Allenylic alcohols equipped with an electron-withdrawing group at the *meta*-position of the aryl ring (**2h−i**) are detrimental to this reaction, presumably due to their inability to stabilize the proposed carbocation intermediate. This tendency is further endorsed by a similar level of yield while using allenylic alcohols adorned with an aryl ring having two electron-withdrawing substituents (**2l−m**). The compliance of allenylic alcohol containing an *ortho*-substituted aryl ring is particularly noteworthy as it delivered the product **3aj** in 77% yield with high enantioselectivity. Heterocyclic substituents such as 1,3-benzodioxole, furan, and thiophene could also be incorporated into the product under our standard reaction conditions in moderate to good yield with good to excellent enantioselectivities (**3an−ap**). Among aliphatic allenylic alcohols, only the cyclopropyl-substituted one (**2q**) was found to be compatible and furnished the product **3aq** in excellent yield and enantioselectivity.

Tertiary allenylic alcohols (**2r−s**) could also be employed as an electrophile in this reaction. In this case, the desired γ-allenylic enones (**3ar−as**) were obtained as an inseparable mixture with achiral γ-dienyl enones, formed by nucleophilic addition at the C2 of **A** (Scheme 2).[27,46] Nonetheless, both **3ar** and **3as** were formed with good er (Scheme 3B). However,

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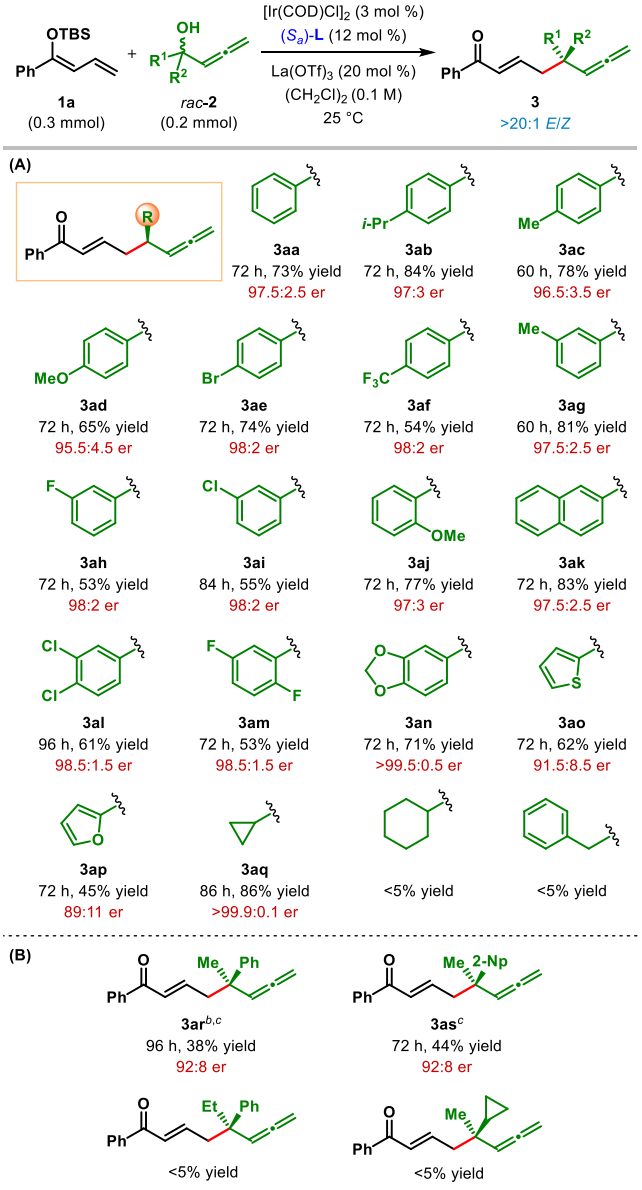
Scheme 3. Scope of Allenylic Alcohols in Enantioselective Vinylogous Allenylic Alkylation[a]



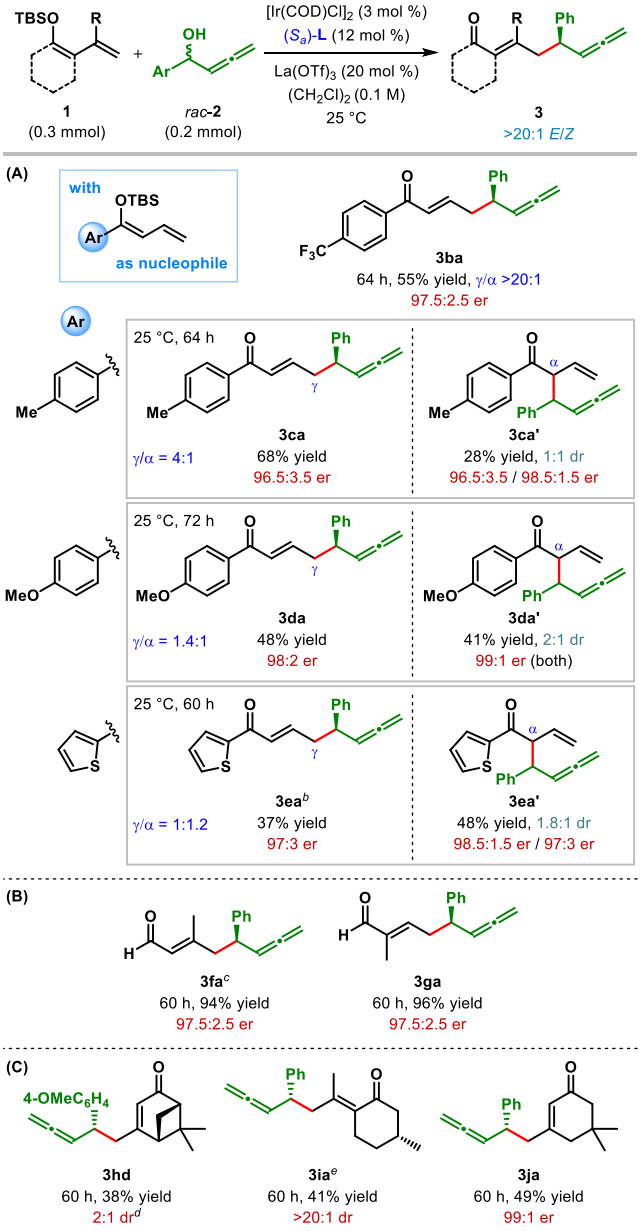
[a]Yields correspond to the isolated yield after chromatographic purification. Enantiomeric ratio (er) as determined by HPLC analysis using a stationary phase chiral column. [b]Reaction on a 0.4 mmol scale afforded **3ar** in 48% yield with 92:8 er. [c]Reaction was carried out with 10 mol % $La(OTf)_3$.

more hindered and dialkyl-substituted tertiary allenylic alcohols failed to react under our optimized conditions. Unfortunately, alkenyl-substituted allenylic alcohol led to a complicated regioisomeric mixture of products with almost no enantioinduction and remains a limitation of our protocol.

After demonstrating the generality and limitations of allenylic alcohols, we turned our attention to exploring the scope of silyl dienol ethers in this transformation (Scheme 4).

With silyl dienol ethers, derived from acyclic α,β-unsaturated ketones, as the nucleophile, the regioselectivity (i.e., γ- vs α-selectivity) of the reaction was found to be dependent on the electronic nature of the aryl substituent (Scheme 4A). While exclusive γ-selectivity was observed with electron-deficient 4-trifluoromethylphenyl substituted silyl dienol ether **1b**,

Scheme 4. Scope of Silyl Dienol Ethers in Enantioselective Vinylogous Allenylic Alkylation[a]



[a]Yields correspond to the isolated yield after chromatographic purification. Enantiomeric ratio (er) as determined by HPLC analysis using a stationary-phase chiral column. Diastereomeric ratio (dr) as determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Reaction on a 0.61 mmol scale using 2 mol % $[Ir(COD)Cl]_2$ and 8 mol % (S_a)-**L**. [c]Reaction on a 1.0 mmol scale afforded **3fa** in 93% yield with 97:3 er. [d]The dr of the purified product. A verbenone sample with ~80:20 er was used for the preparation of the silyl dienol ether **1h** (see the Supporting Information). [e]Reaction using 0.2 mmol of *rac*-**2a** and 0.21 mmol of **1i**.

regioselectivity of the reaction shifted toward α- with an increase in electron density on silyl dienol ether. Thus, 4-methylphenyl substituted silyl dienol ether **1c** delivered a 4:1 mixture of γ- and α-regioisomeric products **3ca** and **3ca′**, respectively. Selectivity toward the α-allenylic alkylation product became more dominant when using further electron-donating 4-methoxyphenyl substituted silyl dienol ether **1d** as a nucleophile. Finally, a switchover was observed with silyl

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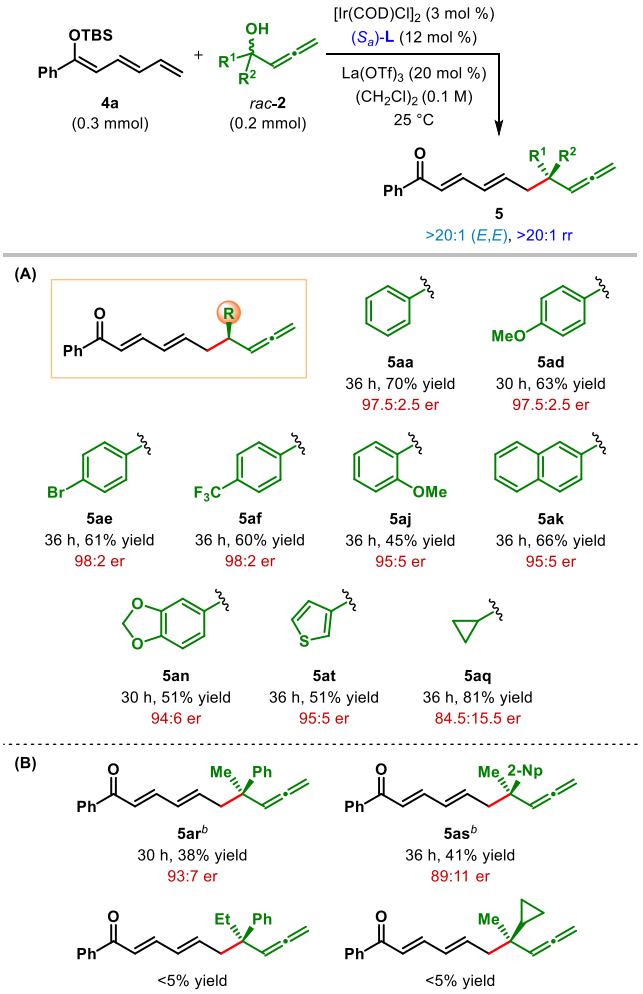
dienol ether **1e** bearing a 2-thienyl substituent, which favored α-allenylic alkylation over γ-, although only slightly. These findings highlight the role of electronics of silyl dienol ether in regulating its regioselectivity in allenylic alkylation. While the γ-selective products were generally formed with good to excellent enantioselectivity, the α-allenylic alkylation proceeded with poor diastereoselectivity. This is not surprising since the Ir(I)/(*P*,olefin) complex used as the catalyst in this study is known to impart excellent stereocontrol only on the electrophilic fragment.[27] Similarly, silyl dienol ether, bearing a phenyl group at the terminal position, furnished a 2:1 mixture of γ/α-allenylic products.[46] Although these regioisomers are separable and formed with excellent er, the influence of steric on the regioselectivity is evident from this example.

Silyl dienol ether derived from α,β-unsaturated aldehydes such as 3-methylbut-2-enal (**1f**) and 2-methylbut-2-enal (**1g**) proved to be excellent substrates for allenylic alkylation and delivered the corresponding γ-allenylic α,β-unsaturated aldehydes (**3fa**–**ga**) in excellent yields with high enantioselectivities (Scheme 4B).

We were delighted to find that our protocol is not restricted to acyclic silyl dienol ethers derived from the corresponding unsaturated ketones or aldehydes. Cyclic silyl dienol ether derived from natural products such as verbenone (**1h**) and (*R*)-pulegone (**1i**) fared reasonably well under our reaction conditions and furnished the peripherally modified γ-allenylic natural products (**3hd**, **3ia**) with similar levels of stereoselectivities.[47] The existing stereocenters in these substrates (**1h**–**i**) did not exert any influence on the stereochemical outcome as these reactions were found to be completely catalyst-controlled.[46] Structurally related γ-allenylic isophorone **3ja** could also be accessed in 49% yield with 99:1 er under the standard reaction conditions.

We next turned to ε-allenylic alkylation of $\alpha,\beta,\gamma,\delta$-unsaturated ketones through the bisvinylogous allenylic alkylation of silyl trienol ethers. The reaction conditions optimized for vinylogous allenylic alkylation proved to be suitable for the bisvinylogous allenylic alkylation reaction between silyl trienol ether **4a** and allenylic alcohol *rac*-**2a** (Scheme 5A). The desired ε-allenylic ketone **5aa** was isolated in 70% yield with 97.5:2.5 er. Elucidation of the scope of this transformation demonstrated that a range of sterically and electronically diverse substituents on the arene ring of allenylic alcohols are compatible with these reaction conditions. Electronically varied allenylic alcohols (**2d**–**f**) bearing a methoxy, bromo, or trifluoromethyl group at the *para*-position of the aryl ring fared reasonably well and afforded the products **5ad**–**af** with excellent enantioselectivity. Placing a methoxy group at the *ortho*-position of the aryl ring in allenylic alcohol (**2j**) did not deter the reaction, even though the product (**5aj**) was obtained in only 45% yield with reduced enantioselectivity. Similar levels of enantioselectivity were also obtained with allenylic alcohols substituted with 2-naphthyl (**2k**), 5-benzo[1,3]dioxole (**2n**), and 3-thienyl (**2t**). However, the reaction with cyclopropyl-substituted allenylic alcohol (**2q**) was found to be only moderately enantioselective, although the product **5aq** formed in good yield. Most notably, this protocol is applicable to sterically encumbered tertiary allenylic alcohols **2r**–**s** (Scheme 5B). However, these reactions are less efficient and, as discussed above (see Scheme 3B), products **5ar**–**as** were obtained, along with ε-dienyl $\alpha,\beta,\gamma,\delta$-unsaturated ketones as an inseparable mixture, in moderate to good er.[46] In general, bisvinylogous allenylic alkylation reactions were found to be

Scheme 5. Scope of Enantioselective Bisvinylogous Allenylic Alkylation[a]



[a]Unless noted otherwise, reaction conditions indicated above were followed. Yields correspond to the isolated yield after chromatographic purification. The ers were determined by HPLC analysis using a stationary phase chiral column. [b]Reaction was carried out with 10 mol % $La(OTf)_3$.

faster compared to the vinylogous variant discussed above. The low yield of the products on many occasions is primarily due to the instability of silyl trienol ethers under the reaction conditions. Nonetheless, these reactions are highly regioselective since no α- or γ-allenylic ketone could be detected in any of these cases. Similarly, the products were formed as a single diastereomer with respect to the dienone geometry.

In order to determine the absolute configuration, some of the allenylic alkylation products (**3aa**/**5aa** and **3ar**/**5ar**) were exposed to ozonolytic conditions followed by a reductive workup with $NaBH_4$ (Scheme 6). This manipulation led to the formation of a common 2-substituted butane-1,4-diol from each set of starting materials, i.e., **6** from **3aa**/**5aa** and **7** from **3ar**/**5ar**. The enantioselective syntheses of **6** and **7** have previously been reported.[48−50] Comparison of specific rotations of **6** and **7** with those reported in the literature[48−50] established the absolute configuration of **6** and **7** and, in retrospect, the corresponding allenylic alkylation products **3aa**/**5aa** and **3ar**/**5ar**, respectively. The absolute stereochemistry of the other products (**3** and **5**), shown in Schemes

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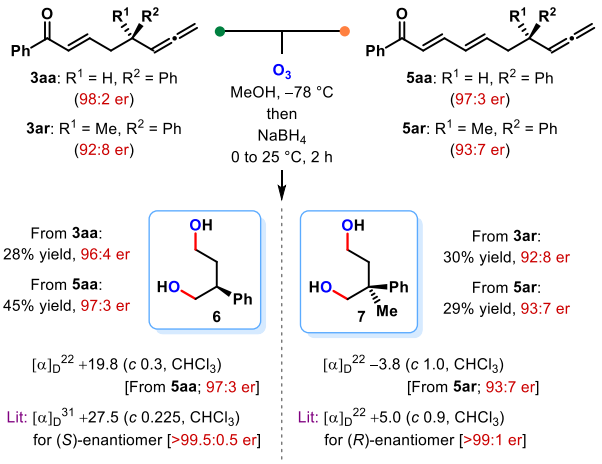
Scheme 6. Determination of the Absolute Configuration of Allenylic Alkylation Products



3−5, was inferred as the same by analogy. As expected, the same sense of enantioinduction was observed in vinylogous and bisvinylogous allenylic alkylation reactions.

The scalability of our protocols was displayed by larger-scale experiments on vinylogous (Scheme 7A) as well as bisvinylogous allenylic alkylation (Scheme 8A). Using a slightly lower catalyst loading, these reactions afforded the desired γ- and ε-allenylic unsaturated ketones with levels of yields and enantioselectivities similar to those of the smaller-scale reactions shown in Schemes 3 and 5.

Synthetically versatile allene and unsaturated carbonyl functionalities in the products provide ample opportunities for their elaboration into other important building blocks. A few such derivatizations of intricately functionalized α,β-unsaturated ketone **3aa** are illustrated in Scheme 7B. Selective conjugate reduction of the electron-deficient olefin in **3aa** was achieved with 5 mol % Stryker's reagent and 1.5 equiv of $PhSiH_3$, and the resulting γ-allenylic ketone **8** was obtained in 50% yield.[51] Conversion of ketone **8** to the corresponding oxime **9** followed by *p*-TsOH/$ZnCl_2$-mediated Beckmann rearrangement[52] furnished γ-allenylic amide **10**, having a remote δ-stereocenter, in high yield without any loss of its stereochemical integrity. The overall process represents a formal γ-allenylic alkylation of an amide — a challenging transformation indeed. Although Ir-catalyzed hydroboration[53] of the terminal olefin could not be performed directly on **3aa**, the reaction proceeded efficiently on the reduced ketone **8** to furnish the alkyl boronate **11** in 51% yield, along with a separable side product **12**. Alkyl boronate **11** is presumably generated through double hydroboration of allene in **8** coupled with protodeboronation of the intermediate alkyl bisboronate species. Similarly, the formation of **12** could be explained via hydroboration of the terminal double bond of allene followed by protodeboration. Oxidation of **11** with sodium perborate led to the corresponding primary alcohol **13** in 91% yield. Luche reduction of **3aa** delivered the corresponding allylic alcohol **14** as an equimolar mixture of diastereomers in 74% yield. Selective reduction of the functionalities in **3aa** is possible with controlled hydrogenation conditions under Pd/C. Thus, hydrogenation of the allene and conjugated olefin was achieved in EtOAc within 2 h, which allowed for the formal introduction of a stereocenter four carbons away from the parent carbonyl group (**15**). On the other hand, global reduction of all the functionalities in **3aa** in dry methanol after prolonged exposure to hydrogen afforded a chiral hydrocarbon **16**, bearing an "orphaned stereocenter", in 88% yield.

Unlike the ketone in **3aa**, the presence of an α,β-unsaturated aldehyde functionality in **3fa** and **3ga** opens up additional possibilities for synthetic elaborations (Scheme 7C). Chain homologation through Horner−Wadsworth−Emmons (HWE) olefination and related reactions presents one such possibility, with the potential to introduce further unsaturation in a stereocontrolled manner. HWE olefination of α,β-unsaturated aldehydes in **3ga** and **3fa** with triethylphosphonoacetate (**17**) turned out to be completely diastereoselective and provided ε-allenylic (*E*,*E*)-α,β,γ,δ-unsaturated esters **18** and **19**, respectively. The corresponding (*Z*)-selective olefination of **3fa** was accomplished under Still−Gennari conditions[54] with bis(trifluoroethyl) phosphonoacetate (**20**) and afforded ε-allenylic (*Z*,*E*)-α,β,γ,δ-unsaturated ester **21**, exclusively as a single diastereomer, in 63% yield. Notwithstanding the moderate yield and slight erosion of its enantiopurity, the formation of **21** further emphasized the synthetic utility of these γ-allenylic α,β-unsaturated aldehydes. Enantioselective synthesis of such chiral (*Z*,*E*)-α,β,γ,δ-unsaturated ester **21** may not be straightforward by other means. Similar HWE olefinations of **3fa** with α-keto phosphonate (**22**) and α-cyano phosphonate (**24**) were found to be less diastereoselective, although the respective products ε-allenylic (*E*,*E*)-α,β,γ,δ-unsaturated ketone **23** and nitrile **25** could be isolated in high yield. Despite the modest diastereoselectivity, these two examples pave the way for other ε-allenylic α,β,γ,δ-unsaturated compounds with diverse functionalities. These two-step sequences consisting of allenylic alkylation and HWE olefination reactions represent an enantioselective formal ε-allenylic alkylation of α,β,γ,δ-unsaturated compounds.

Lee's group, as well as our laboratory, has demonstrated the utility of β-methyl α,β-unsaturated aldehydes as a four-carbon building block in the de novo construction of arenes from cyclic enediones under dienamine catalysis.[55−57] The presence of the α,β-unsaturated aldehyde functionality in **3fa** was exploited for this oxidative [4 + 2]-cycloaddition with 1,4-naphthoquinone (**26**) using pyrrolidine as a catalyst to furnish 2-homoallenylic anthraquinone **27** in decent yield and 96.5:3.5 er (Scheme 7C). This process epitomizes an enantioselective formal allenylic alkylation of an electron-deficient aromatic compound at its benzylic position.

As shown in the case of γ-allenylic α,β-unsaturated ketone **3aa** (Scheme 7B), functionalities present in ε-allenylic α,β,γ,δ-unsaturated ketone **5aa** could also be selectively reduced under similarly regulated hydrogenation conditions and resulted in either ζ-chiral ketone **28** or chiral hydrocarbon **29**, containing an "orphaned stereocenter", in good yield (Scheme 8B).

A tentative catalytic cycle shown in Scheme 9 is proposed based on the previous literature precedence.[27−31] η^2-Coordination of racemic allenylic alcohol *rac*-**2** through its terminal double bond to the Ir(I)[(S_a)-**L**]$_2$ complex results in a 1:1 mixture of diastereomeric complexes (R,S_a,S_a)-**30** and (S,S_a,S_a)-**31**. Lewis acidic La(OTf)$_3$ is believed to trigger the ionization of intermediates **30** and **31** to generate diastereomeric allenylic carbocations **32** and **33**, respectively. In complex **32**, the larger substituent (R^L) stays *anti* to the iridium center, whereas in complex **33**, it is *syn*.

Even though butadienylium cations *anti*-**32** and *syn*-**33** arise directly from (*R*)- and (*S*)-**2**, respectively, this stereochemical information can be expected to disappear due to the facile rotation around the C3−C4 bond. Consequently, the final

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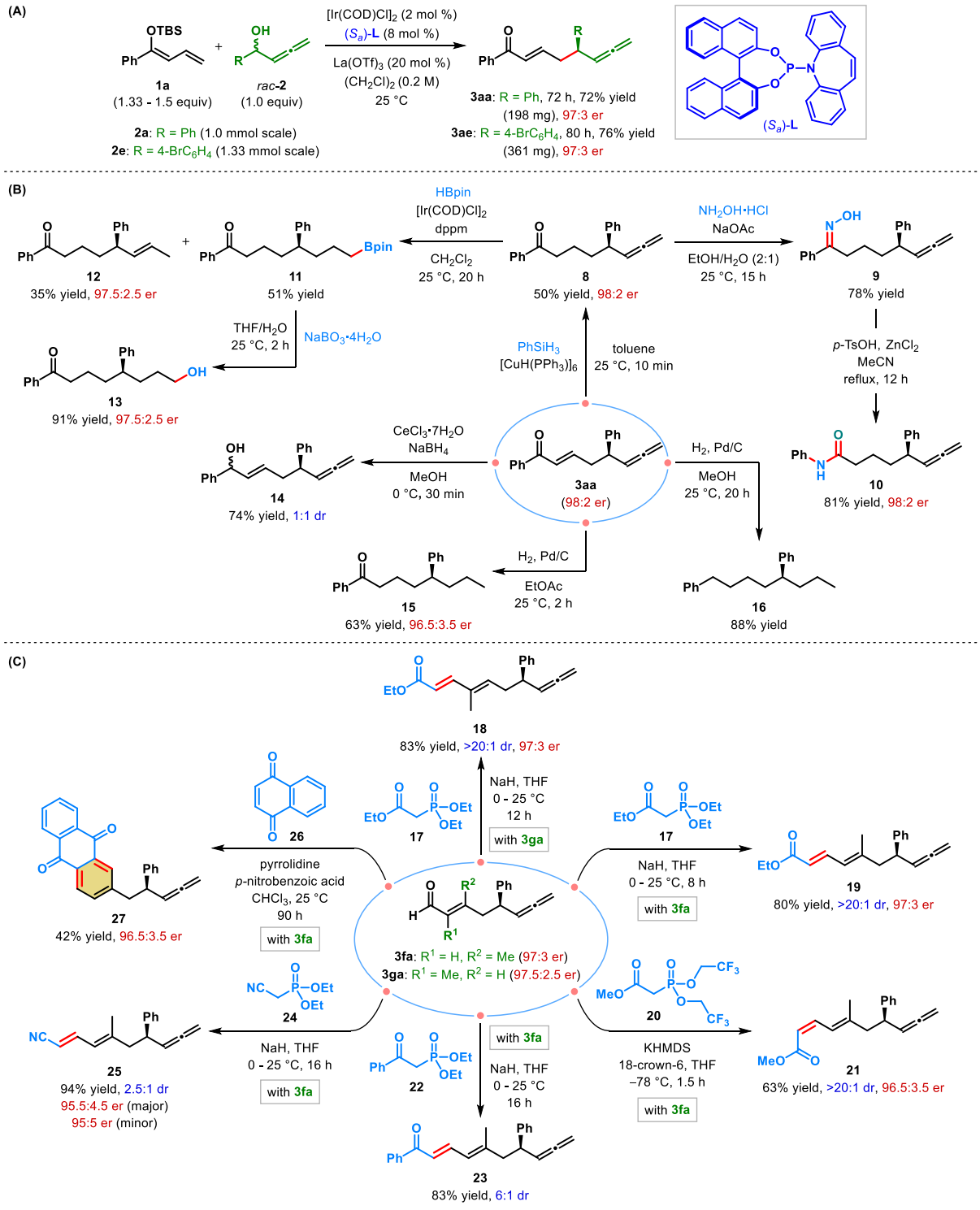
Scheme 7. Scale-up Synthesis and Synthetic Elaborations of γ-Allenylic Ketone and Aldehydes



stereochemical outcome is solely dictated by the configuration of the (*P*,olefin) ligand (**L**) on iridium during the irreversible C−C bond-formation step. With (S_a)-**L**, shielding of the *si*-face of the planar cationic butadienylium fragment in *anti*-**32** by the binaphthyl moiety of the axially bound **L** on Ir(I) leaves its *re*-face exposed for nucleophilic attack. In contrast, the *si*-face of *syn*-**33** is sterically more accessible. Between these two carbocationic intermediates, *syn*-**33** is notably more crowded due to the proximity of R^L to the already sterically hindered iridium center. As a result, the reaction predominantly proceeds through the *re*-face addition of (bis)vinylogous silyl enol ethers **1** or **4** to the C4 of *anti*-**32**, making the reaction enantioconvergent. Hydroxide-assisted cleavage of the O−Si bond in **34** regenerates $La(OTf)_3$ and an allene exchange in product-bound Ir(I) complex **35** with **2** releases γ- or ε-allenylic unsaturated ketones (*R*)-**3** or (*R*)-**5**, respectively.

The presence of bulky (*P*,olefin) ligands on the Ir center generally leaves the C2 position in **32** or **33** inaccessible to nucleophiles and prevents the formation of dienylation products (see Scheme 2). However, in reactions with tertiary

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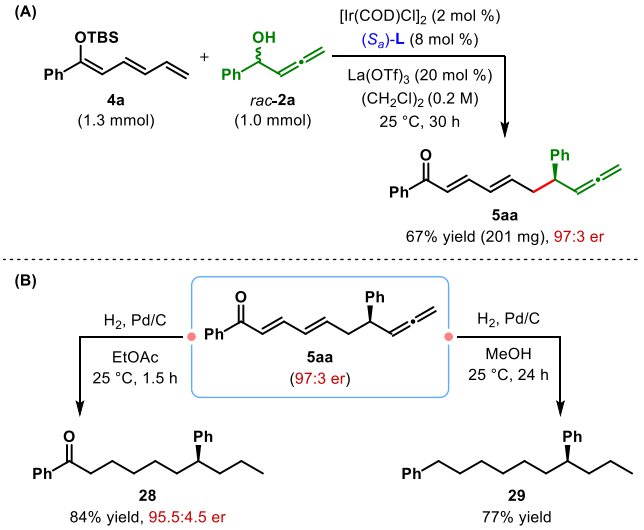
Scheme 8. Scale-up Synthesis and Synthetic Elaborations of ε-Allenylic (*E*,*E*)-α,β,γ,δ-Unsaturated Ketone 5aa



allenylic alcohols (**2r**–**s**), the higher stability of the tertiary carbocations and the relatively greater steric crowding at C4 opens the dienylation pathway to produce a small amount of achiral γ-dienyl enones.[27,46]

3. CONCLUSIONS

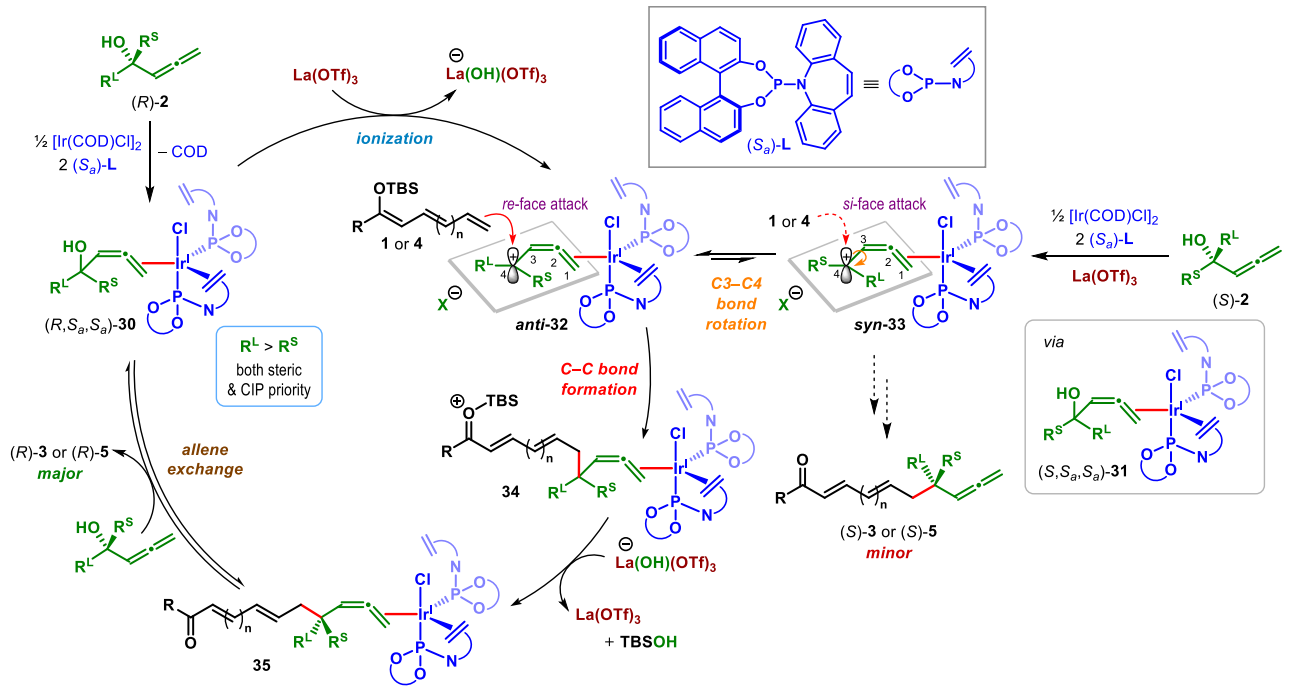
In summary, we have developed the first catalytic enantioselective vinylogous and bisvinylogous allenylic substitution using extended silyl enol ethers as the nucleophile. With racemic allenylic alcohols as the alkylating agent, these reactions are cooperatively catalyzed by an Ir(I)/(phosphoramidite,olefin) complex and Lewis acidic $La(OTf)_3$ and proceed in an enantioconvergent fashion. Depending on the choice of nucleophile (i.e., silyl dienol and trienol ether), γ- and ε-allenylic unsaturated ketones, bearing δ- and ζ-stereocenters, respectively, are generally obtained in a regio- and diastereoselective manner in moderate to high yields with good to excellent enantioselectivity. Extension of the scope to tertiary allenylic alcohols enabled the creation of an all-carbon quaternary stereogenic center at a position distant (δ- or ζ-) from the carbonyl group with promising enantioselectivity. The products of these reactions, unsaturated carbonyls bearing an allene moiety, are densely functionalized and can be transformed into synthetically useful building blocks through controlled reduction and stereoselective olefination. Besides carbonyls with varying degrees of unsaturation and chain homologated carbonyls, unfunctionalized hydrocarbons bearing an "orphaned stereocenter" can also be accessed. Overall, this study highlights the power of (bis)vinylogous reactions in the distant functionalization and creation of remote stereocenters. Further investigations in this direction are currently underway in our laboratory.

4. METHODS

4.1. General Procedure for the (Bis)vinylogous Allenylic Substitution

In an oven- and vacuum-dried reaction tube equipped with a magnetic stir bar, $[Ir(COD)Cl]_2$ (4 mg, 0.006 mmol, 3 mol %) and (S_a)-**L** (12.2 mg, 0.024 mmol, 12 mol %) were taken in 0.3 mL of dry $(CH_2Cl)_2$ under positive argon pressure. The resulting solution was then stirred vigorously at 25 °C for 15 min to obtain a deep-red solution. To this was added a solution of allenylic alcohol *rac*-**2** (0.2 mmol, 1.0 equiv) in 0.7 mL of dry $(CH_2Cl)_2$ and stirred at 25 °C for 5 min. Subsequently, extended silyl enol ether **1** or **4a** (0.3 mmol, 1.5 equiv) in 1.0 mL of dry $(CH_2Cl)_2$ was added followed by $La(OTf)_3$ (14.2 mg, 0.04 mmol, 0.2 equiv) in one portion. The reaction tube was purged with argon, closed with a glass stopper, and stirred at 25 °C until TLC (5% EtOAc in petroleum ether) revealed the complete consumption of **2**. The reaction mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure. This residue was purified by silica-gel flash column

Scheme 9. Proposed Mechanism of Ir-Catalyzed Enantioselective (Bis)vinylogous Allenylic Alkylation



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chromatography (2−4% Et_2O in petroleum ether) to obtain γ- or ε-allenylic unsaturated ketones **3** or **5**, respectively.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00640.

Experimental details and characterization data, NMR spectra, and HPLC chromatograms (PDF)

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Author Contributions

CRediT: **Sankash Mitra** data curation, formal analysis, investigation, methodology, writing - original draft, writing - review & editing; **Santanu Mukherjee** conceptualization, funding acquisition, project administration, supervision, writing - original draft, writing - review & editing.

Notes

The authors declare no competing financial interest.

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