Construction of Vicinal Quaternary Centers via Iridium-Catalyzed Asymmetric Allenylic Alkylation of Racemic Tertiary Alcohols

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ABSTRACT

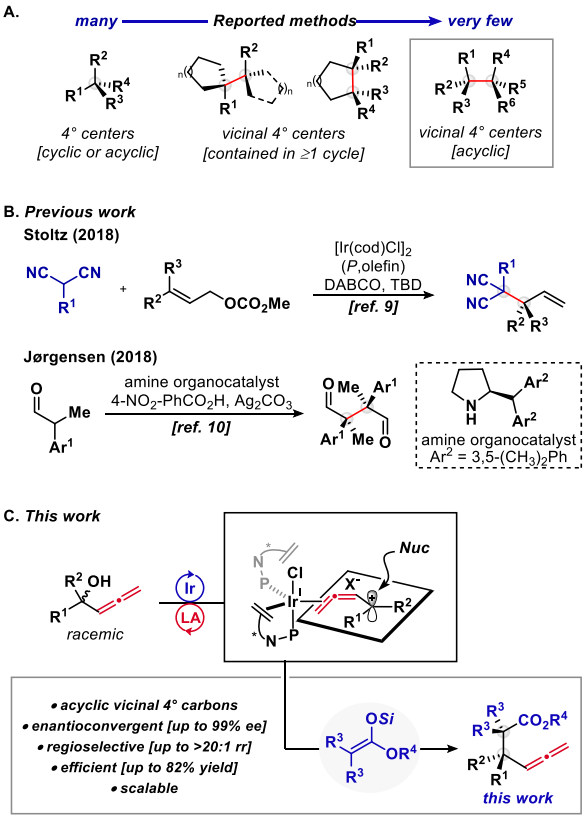
Enantioselective bond formation between sterically hindered fragments to furnish acyclic products with vicinal quaternary centers is a formidable challenge. We report a solution that involves co-catalysis between a chiral Ir-(phosphoramidite,olefin) complex and $La(OTf)_3$. This robust catalytic system effects highly enantioconvergent and regioselective alkylation of racemic tertiary α-allenyl alcohols with tetrasubstituted silyl ketene acetals. The transformation displays broad functional group tolerance for both reaction components and allows efficient generation of β-allenyl ester products in good yield and with excellent enantioselectivity. Furthermore, both the allene and ester functionalities were leveraged to upgrade the structural complexity of the products via a series of stereoselective metal-catalyzed functionalization reactions.

The asymmetric generation of quaternary stereocenters is of particular interest due to their presence in scaffolds of natural products and bioactive molecules.[1] While the past two decades have witnessed significant advances, they largely have addressed difficulties associated with setting a single quaternary stereocenter.[2] Yet, direct access to vicinal quaternary carbons stereoselectively remains a formidable challenge,[3] inspiring clever approaches, involving cycloadditions,[4] electrophilic substitutions,[5] or allylations.[6,7] In many methods reported, at least one of the quaternary stereocenters is endocyclic. By contrast, the synthesis of fragments incorporating vicinal acyclic quaternary carbons represents a more difficult task because of the higher entropic and enthalpic penalties during bond formation (Scheme 1A).[8] Stoltz has documented catalytic, enantioselective substitution of 3,3-disubstituted allylic carbonates with substituted malonodinitriles (Scheme 1B).[9] Concurrently, Jørgensen reported oxidative, stereoselective aldehyde homocoupling, furnishing 1,4-dialdehydes bearing vicinal quaternary stereocenters (Scheme 1B).[10,11,12,13]

Tertiary carbocations represent convenient synthetic access points for the asymmetric synthesis of quaternary centers.[14,15,16] However, attempts to gain stereocontrol over these intermediates have been scarce.[17] In 2004, Braun showed that chiral Ti(IV) complexes could be used to catalyze the asymmetric allylation of tertiary-benzylic carbocations.[17a] Jacobsen has reported that chiral hydrogen-bond donor-acceptor catalysts facilitate asymmetric allylation of tertiary propargylic carbocations in 2018.[17b] Our

group entered this area with the substitutions of racemic secondary allenylic alcohols by amines and organozinc reagents using a chiral Ir-bis(phosphoramidite,olefin) complex.[18,19] More recently, we demonstrated that η^2-coordination to iridium catalyst by allenes in racemic tertiary allenylic alcohols, leads to ionization and generation of an intermediate, metal-bound tertiary carbocation that underwent stereoselective reduction.[20]

We envisioned that by judicious choice of conditions, Ir-stabilized allenylic carbocations could act as convenient linchpins for the enantioselective construction of vicinal quaternary centers. Herein, we report the realization of this goal with the enantioconvergent alkylation of racemic, tertiary allenylic alcohols with fully substituted silyl ketene acetals (Scheme 1C). This transformation represents the first application of *allenylic* substitution in the enantioselective construction of quaternary centers[21] as well as the first instance of its use for the enantioselective formation of vicinal quaternary centers. Furthermore, exploiting our η^2-coordination-induced S_N1-type ionization mechanism allows *unprotected* tertiary alcohols to be used as substrates in an Ir-catalyzed asymmetric carbon-carbon formation for the first time. This powerful methodology provides access to hindered, acyclic β-allenyl ester products with good yields and excellent regio- and enantioselectivity.

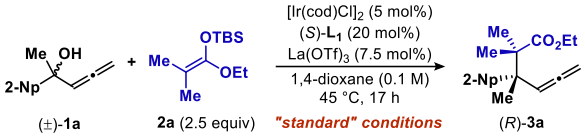


Scheme 1. A. Various motifs of quaternary and vicinal quaternary carbons; **B.** Examples of enantioselective synthesis of vicinal quaternary carbons centers using Ir-catalysis; **C.** Enantioselective generation of vicinal quaternary carbons center motif via allenylic alkylation of disubstituted silyl ketene acetals.

Our studies were initiated using α-allenyl alcohol (±)-**1a** as model substrate. Silyl ketene acetals were selected as nucleophiles[22] due to their synthetic versatility along with their facile, preparation. After extensive evaluation, a system comprising $[Ir(cod)Cl]_2$ (5 mol%), phosphorous–olefin ligand (*S*)-**L_1** (20 mol%), TBS-silyl ketene acetal **2a** (2.5 equiv), and $La(OTf)_3$ (7.5 mol%) in 1,4-dioxane ([(±)-**1a**] 0.1 M) at 45 °C was found to be optimal. Under these conditions, β-allenyl ester (*R*)-**3a** bearing vicinal quaternary carbons were isolated in 75% yield with 99% ee and >20:1 selectivity over the corresponding 1,3-diene regioisomer (Table 1, entry 1). The effect of each parameter on the reaction outcome was also examined. Less bulky trimethylsilyl ketene acetal **2b** afforded product in higher yield (88% vs. 75%) but lower enantioselectivity (89% vs. 99% ee), while TES derivative **2c** resulted in lower enantiomeric excess with no improvement of yield (entries 2 and 3).

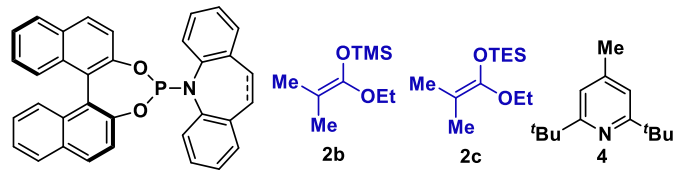
When the reaction was conducted at 23 ^{o}C, product yield remained unchanged while resulting in attenuation of enantiocontrol (97% ee) (entry 4). Considerable decrease in yield was observed at 60 ^{o}C (entry 5). Addition of Lewis acid was found to be crucial; in the absence of $La(OTf)_3$ co-catalyst, only starting material was recovered (entry 6). When $Zn(OTf)_2$ was employed, product was obtained in 73% yield and 99% ee (entry 7). When the reduced ligand analog (*S*)-**L_2** was employed, no product was observed, highlighting the importance of the olefin ligand (entry 8). Control experiments showed that the reaction shuts down in the absence of $[Ir(cod)Cl]_2$/(*S*)-**L_1** or either of its individual components (entries 9-11). When the [Ir]:(*S*)-**L_1** ratio was changed from 1:2 to 1:1, a drop in both yield (39%) and enantiomeric excess (78% ee) were observed, in line with the notion that a 1:2 [Ir]:(phosphoramidite,olefin)-ligand complex is operative (entry 12).[23] You and co-workers recently reported that a catalyst comprised of $[Rh(cod)Cl]_2$ and **L_1** is effective for enantioselective allylation of 1,3-diketones using racemic allylic alcohol derivatives.[24] However, when $[Ir(cod)Cl]_2$ was replaced by $[Rh(cod)Cl]_2$ in this reaction, decomposition of starting allene was observed under otherwise similar reaction conditions (entry 13). It is well precedented that triflic acid can be generated in the presence of adventitious moisture through hydrolysis of metal triflate salts.[25] With this in mind, we conducted an experiment with 10 mol% 2,6-di-tertbutyl-4-methyl-pyridine **4** as Brønsted acid scavenger (entry 14),[26] whereupon, essentially no change in the reaction outcome was observed, suggesting the role of $La(OTf)_3$ as Lewis acid.

Table 1. Effect of Reaction Parameters.[a]



Entry	Variation from "standard conditions"	yield (*R*)-**3a** (%)[b]	ee (%)[c]
1	None	83(75)[d]	99
2	**2b** instead of **2a**	92(88)[d]	89
3	**2c** instead of **2a**	80	96
4	23 °C instead of 45 °C	85	97
5	60 °C instead of 45 °C	58	99
6	no $La(OTf)_3$	0	-
7	$Zn(OTf)_2$ instead of $La(OTf)_3$	73	99
8	(*S*)-$\mathbf{L_2}$ instead of (*S*)-$\mathbf{L_1}$	0	-
9	no [Ir] nor (*S*)-$\mathbf{L_1}$	3	-
10	no [Ir]	1	-
11	no (*S*)-$\mathbf{L_1}$	1	-
12	1:1 [Ir]:$\mathbf{L_1}$	39	78
13	[Rh] instead of [Ir][e]	3	-
14	additive **4**[f]	73	99

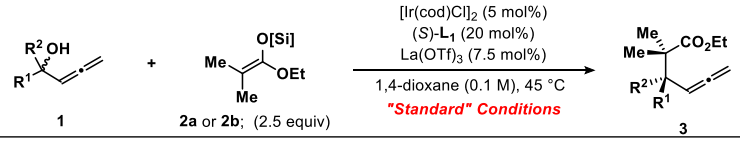
[a] Reactions conducted on 0.4 mmol scale. [b] Determined by analysis of ^{1}H NMR spectra of the unpurified reaction mixture using $(CHCl_2)_2$ as internal standard. [c] Determined by HPLC with chiral stationary phase. [d] Isolated yield of (*R*)-**3a**. [e] $[Rh(cod)Cl]_2$ in lieu of $[Ir(cod)Cl]_2$. [f] 10 mol% was used. cod = 1,5-cyclooctadiene; 2-Np = 2-naphthyl; OTf = O_3SCF_3; TBS = *t*-$BuMe_2Si$; TMS = Me_3Si; Et_3Si = triethylsilyl; – = not determined.

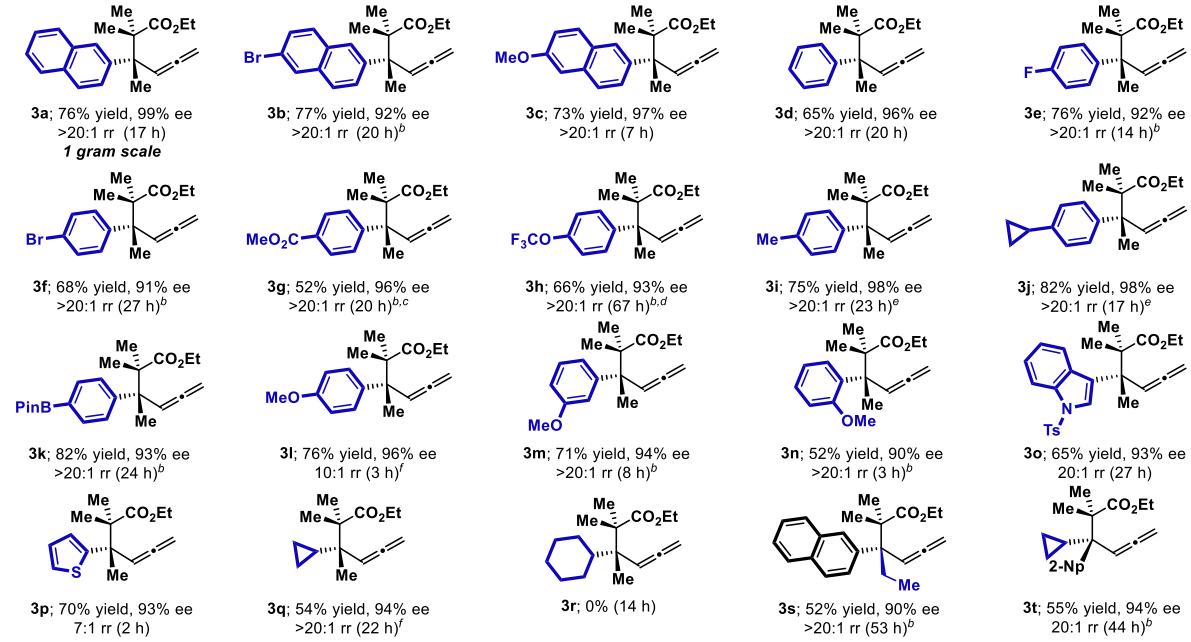


(*S*)-$\mathbf{L_1}$ HC=CH (*S*)-$\mathbf{L_2}$ H_2CCH_2

A wide variety of racemic tertiary α-allenyl alcohols (±)-**1** and silyl ketene acetals **2** were found to undergo the transformation to afford products with high enantiomeric excess and regiocontrol (Tables 2 and 3). The scalability of the reaction was confirmed at 1-gram scale, using 2-naphthyl substrate (**1a**). The corresponding product was obtained in 76% yield and selectivity (99% ee and >20:1 rr). Substrates possessing 2-naphthyl group with electron-withdrawing (**3b**) or electron-donating (**3c**) substituent were examined, and these led to products in 77% and 73% yield with 92% and 97% ee, respectively. The replacement of the 2-naphthyl motif with phenyl was tolerated, and led to the corresponding product being obtained in 65% yield with 96% ee and >20:1 rr (**3d**). Substrates bearing electron-withdrawing or -donating groups at the *para*-position of the aryl substituent also participated in the transformation. For example, products bearing halogens (**3e**, **3f**), ester (**3g**), trifluoromethoxy (**3h**), or alkyl groups (**3i**, **3j**) were obtained in 52-82% yield with 91-98% ee and >20:1 rr. We also found that a substrate bearing a pinacolborane group furnsihed corresponding product **3k** in 82% yield with 93% ee and >20:1 rr. Unexpectedly, given the nature of the hindered nucleophiles, the enantioselectivity of this reaction was much less sensitive to the position of substituents for substrates bearing methoxy groups than the asymmetric reductive deoxygenation reaction we previously reported.[20] Accordingly, the reaction with *para*-, *meta-,* or *ortho*-methoxy substituted analogs (**3l**-**3n**) all provided the respective products in 52-76% yield with 90-96% ee and 10->20:1 rr. Heteroaromatic substrates were also examined, and the products containing *N*-tosyl indole (**3o**) and thiophene (**3p**) were obtained with 65% and 70% yield with 93% and 93% ee and 20:1 and 7:1 rr, respectively. When the arene in the substrate was be replaced with a cyclopropane group, product **3q** was obtained in 54% yield with 94% ee and >20:1 rr. The cyclopropyl group is thought to provide the requisite stabilization for the tertiary carbocation generated under the reaction conditions.[27] In stark contrast to this finding, no reaction was observed when the arene was replaced by a cyclohexyl group (**3r**). Furthermore, alkyl groups other than methyl could be tolerated at the allenylic position. For example, subjecting the substrates containing ethyl group or cyclopropyl group to the reaction conditions furnished products **3s** and **3t** in 52% and 55% yield with 90% and 94% ee, respectively. Interestingly, the cyclopropane-containing product **3t** was obtained with the opposite absolute configuration than that of parent methyl-containing product **3a**.[20]

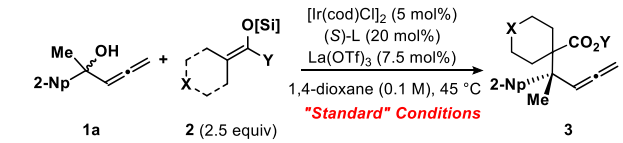
Table 2. Scope of Racemic Electrophiles for Ir-Catalyzed Enantioselective Alkylation Reaction[a]

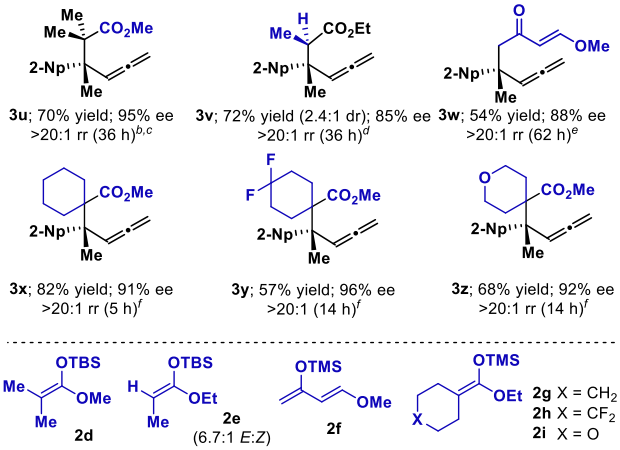




[a] Reaction conditions: $[Ir(cod)Cl]_2$ (5.0 mol%), (*S*)-**L**$_1$ (20 mol%), (±)-**1** (0.4 mmol), **2a** (2.5 equiv), $La(OTf)_3$ (7.5 mol%), 1,4-dioxane (*c* 0.1 M), 45 °C unless otherwise noted. Isolated yields shown. Enantiomeric excess (ee) was determined by HPLC, SFC, or GC analysis using a chiral stationary phase. Regiochemical ratios (rr) were determined by ^{1}HNMR analysis of the unpurified reaction mixtures. [b] Reaction conducted using TMS-ketene acetal **2b** (2.5 equiv). [c] 20 mol% of $La(OTf)_3$ was used. [d] 10 mol% of $La(OTf)_3$ was used. [e] 4.0 equiv of **2a** was used. [f] Reaction was run at 23 °C.

Table 3. Scope of Silyl Ketene Acetal Nucleophiles[a]



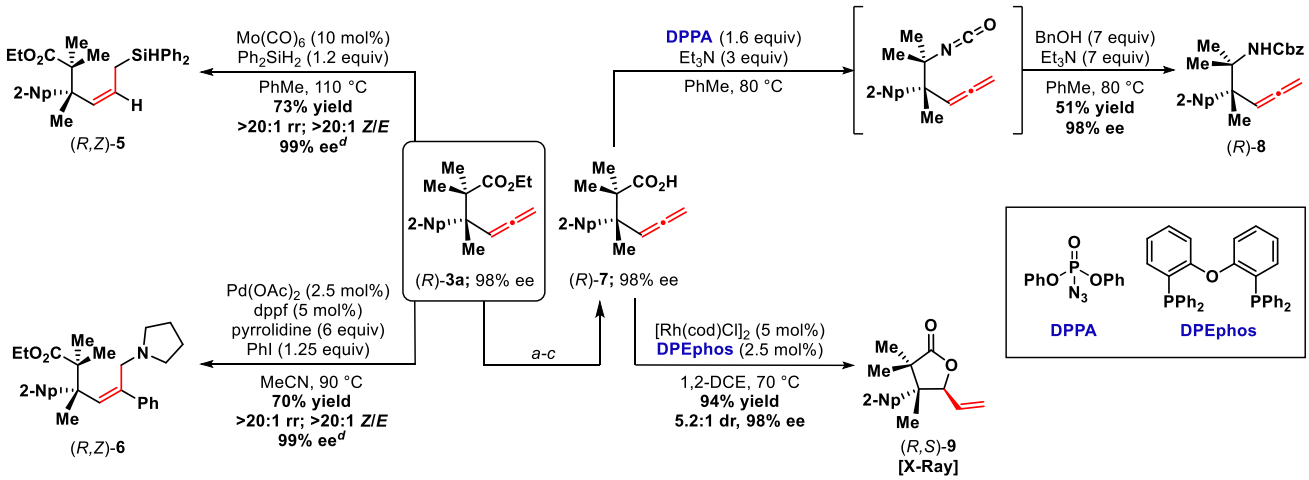


[a] Reaction conditions: $[Ir(cod)Cl]_2$ (5.0 mol%), (*S*)-**L**$_1$ (20 mol%), (±)-**1** (0.4 mmol), **2** (2.5 equiv), $La(OTf)_3$ (7.5 mol%), 1,4-dioxane (*c* 0.1 M), 45 °C. Isolated yields shown. Enantiomeric excess value (ee) was determined by HPLC or SFC analysis using a chiral stationary phase. Regiochemical ratios (rr) were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b] 10 mol% of $La(OTf)_3$ was used. [c] TBS-ketene acetal **2d** was used. [d] TBS-ketene acetal (*E*)-**2e** was used. [e] Danishefsky's diene **2f** was used. [f] TMS-ketene acetal **2g**, **2h**, or **2i** was used.

Encouraged by the wide substrate scope of racemic allenylic electrophiles, we next investigated the silyl ketene acetal component (Table 3). The use of the methyl ester derived silyl ketene acetal **2d** furnished **3u** in 70% yield with 95% ee and >20:1 rr. However, when *tert*-butyl derivative was employed, none of the desired β-allenyl ester was observed.[28] A reaction employing the propionate derived silyl ketene acetal **2e** enriched in the *E* isomer (*E*:*Z* = 6.7:1) was also examined. In the experiment, product **3v** bearing a vicinal quaternary-tertiary stereocenter arrangement was obtained in 72% yield and with 85% ee and >20:1 rr, albeit with a dr of 2.4:1.[29] Danishefsky's diene **2f** was also found to be a competent nucleophile, and its use resulted in the formation of the corresponding α,β-unsaturated ketone product (**3w**) in 54% yield and 88% ee. Finally, silyl ketene acetals derived from cyclohexane (**2g**), 4,4-difluorocyclohexane (**2h**) and tetrahydropyran (**2i**) carboxylic acids were tested. Products (**3x-z**) bearing unsubstituted, difluoro-substituted, and oxygen-containing 6-membered rings were obtained in good yields (57-82%) with uniformly high enantioselectivities (91-96%) and regioselectivities (>20:1 rr).

The retention of the allene unit in the products obtained from the allenylic alkylation reaction makes them prime candidates for synthetic diversification. As such, we examined a series of metal-catalyzed functionalization reactions as means to increase their structural complexity (Scheme 2). Asako and Takai's Mo-catalyzed regioselective hydrosilylation afforded allyl silane (*Z*)-**5** in 73% yield **(**>20:1 rr, >20:1 *E:Z)*.[30] Tsuji's Pd-catalyzed arylamination also worked well to give amine product (*Z*)-**6** in 70% yield with >20:1 rr and >20:1 *E:Z*.[31] After the transformation of ester to carboxylic acid **7**, Curtius rearrangement followed by quenching with BnOH furnished carbamate **8** in good yield. Finally, Breit's Rh- catalyzed

Scheme 2. Synthetic application of the γ-allenylic ester products.



[a] DIBAL-H (3 equiv), DCM, –78 °C to rt, 30 min. [b] DMP (1.5 equiv), DCM, 0 °C, 30 min. [c] $NaClO_2$ (3.0 equiv), KH_2PO_4 (3.0 equiv), 2-methyl-2-butene (6.6 equiv), $^tBuOH/H_2O$, 0 °C to rt, 11 h. [d] Product was derived from a batch of ester substrate (*R*)-**3a** possessing 99% ee.

intramolecular cyclization reaction between carboxylic acid and allene delivered lactone **9** in 94% yield with 5.2:1 dr.[32] In all cases, no erosion of enantiomeric purity was observed.

In conclusion, we have developed an enantioselective method, permitting facile access to the vicinal quaternary carbon centers acyclic motifs. This co-catalytic process utilizes the simple and robust Ir-(phosphoramidite,olefin) catalyst in the presence of $La(OTf)_3$ to afford highly enantioconvergent, regioselective alkylation of racemic tertiary α-allenyl alcohols with tetrasubstituted silyl ketene acetal nucleophiles. This intermolecular transformation displays broad functional group tolerance for both reaction components, and it allows rapid generation of sterically congested β-allenyl esters in good yield (up to 82%) and excellent enantioselectivity (up to 99% ee). The reaction was also shown to perform well even on gram-scale without any effect on efficiency or selectivity. Furthermore, by taking advantage of both the allene and ester, we utilized a series of stereoselective transition metal-catalyzed reactions to add additional complexity to the enantioenriched allenylic alkylation products. We are currently in the process of expanding the scope of enantioselective reactions with this catalytic system. More broadly, the transformation we disclose begins to expand the scope of asymmetric allenylic substitution, which has otherwise lagged behind the more extensively studied allylation counterpart.

Experimental details of synthetic procedures, X-ray data, and computational details (PDF).

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Notes

The authors declare no competing financial interests.

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TOC Graphic: