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Communication

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 cocatalysis 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.[1,2] While the past two decades have witnessed significant advances in this area, they largely have addressed difficulties associated with setting a single quaternary stereocenter.[3−8] As such, direct access to vicinal quaternary carbons stereoselectively remains a formidable challenge[9−11] that has inspired clever approaches, involving cycloadditions,[12−19] electrophilic substitutions,[20−22] and allylations.[23−30] In many methods reported, at least one of the generated quaternary centers 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).[31−33] Toward this end, Stoltz has documented catalytic, enantioselective substitution of 3,3-disubstituted allylic carbonates with substituted malonodinitriles (Scheme 1B).[34] Concurrently, Jørgensen reported oxidative, stereoselective aldehyde homocoupling, furnishing 1,4-dialdehydes bearing vicinal quaternary stereocenters (Scheme 1B).[35−44]

Tertiary carbocations represent convenient synthetic access points for the asymmetric synthesis of quaternary centers.[45−55] However, attempts to gain stereocontrol over these intermediates have been scarce.[56−58] In 2004, Braun showed that chiral Ti(IV) complexes could be used to catalyze the asymmetric allylation of tertiary-benzylic carbocations.[56] Jacobsen has reported that chiral hydrogen-bond donor−acceptor catalysts facilitate asymmetric allylation of tertiary propargylic carbocations in 2018.[57] 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.[59−61] More recently, we demonstrated that η^2-coordination of the allene motifs in racemic tertiary allenylic alcohols to a chiral Ir(I) catalyst led to ionization and generation of an intermediate, metal-bound tertiary carbocation that underwent stereoselective reduction.[62]

We envisioned that by judicious choice of conditions, Ir-stabilized, tertiary 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[63] 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.

Our studies were initiated using α-allenyl alcohol (±)-**1a** as a model substrate. Silyl ketene acetals were selected as nucleophiles due to their synthetic versatility along with their facile preparation.[64−67] After extensive evaluation, a system comprising $[Ir(cod)Cl]_2$ (5 mol %), phosphorus−olefin ligand (*S*)-$\mathbf{L_1}$ (20 mol %), TBS 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 was isolated in 75% yield with 99% ee and >20:1 selectivity over the

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Scheme 1. (A) Various Motifs of Quaternary and Vicinal Quaternary Carbons; (B) Examples of Enantioselective Synthesis of Acyclic Vicinal Quaternary Carbons; (C) Enantioselective Generation of Vicinal Quaternary Carbons via Allenylic Alkylation with Tetrasubstituted Silyl Ketene Acetals

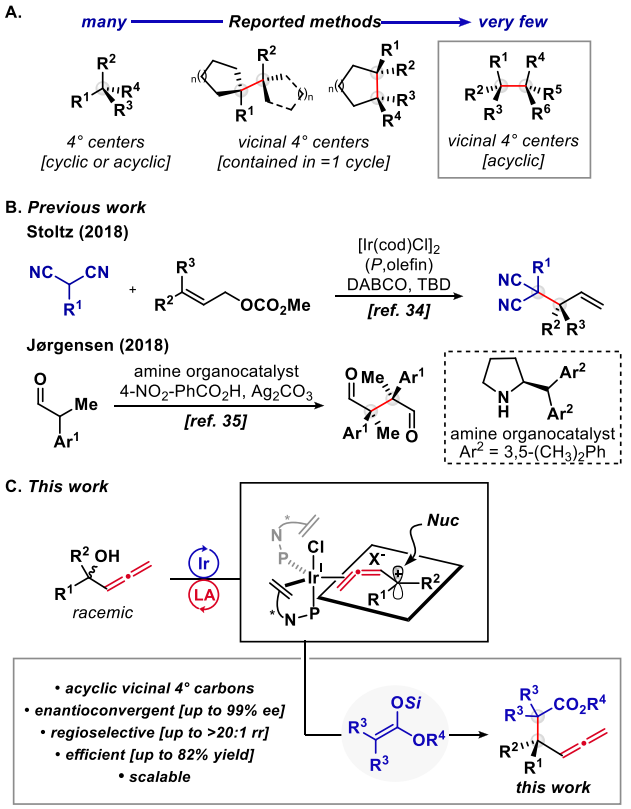
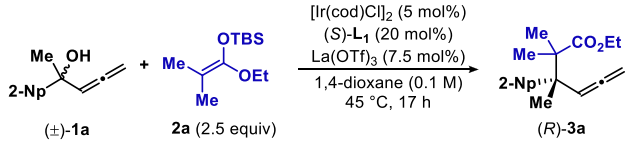
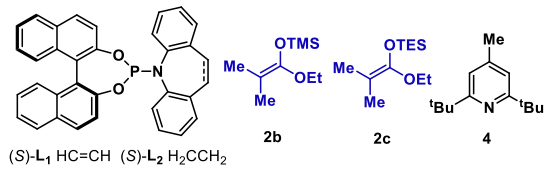


Table 1. Effect of Reaction Parameters[a]



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	add **4** (10 mol %)	73	99

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



corresponding 1,3-diene regioisomer (Table 1, entry 1). The effect of each parameter on the reaction outcome was also examined. Less bulky TMS ketene acetal **2b** afforded the 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 °C, product yield remained unchanged and a slight attenuation of enantiocontrol was observed (97% ee) (entry 4), while a considerable decrease in yield was observed at 60 °C (entry 5). Addition of Lewis acid was found to be crucial, and only starting material was recovered in the absence of $La(OTf)_3$ (entry 6). When $Zn(OTf)_2$ was employed, the product was obtained in 73% yield and 99% ee (entry 7). When the reduced ligand analog (*S*)-$\mathbf{L_2}$ was employed, no product was observed, highlighting the importance of the olefin ligand (entry 8). Control experiments showed that the reaction fails in the absence of $[Ir(cod)Cl]_2$/(*S*)-$\mathbf{L_1}$ or either of its individual components (entries 9–11). When the [Ir]:(*S*)-$\mathbf{L_1}$ ratio was changed from 1:2 to 1:1, a decrease 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).[68] You and co-workers reported that a catalyst comprised of $[Rh(cod)Cl]_2$ and (*S*)-$\mathbf{L_1}$ is effective for enantioselective allylation of 1,3-diketones using racemic allylic alcohol derivatives.[69,70] However, when $[Ir(cod)Cl]_2$ was replaced by $[Rh(cod)Cl]_2$ in this reaction, decomposition of the allene substrate was observed under otherwise similar reaction conditions (entry 13). It is well precedented that triflic acid can be generated via the hydrolysis of metal triflate salts in the presence of adventitious moisture.[71−75] With this in mind, we conducted an experiment with using 10 mol % of 2,6-di-*tert*-butyl-4-methyl-pyridine as a non-coordinating Brønsted acid scavenger (entry 14).[76] Therein essentially no change in the reaction outcome was observed, which suggests that the main role of $La(OTf)_3$ is that of a Lewis acid.

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 processes scalability was tested by conducting the transformation on a 1 g scale using substrate **1a**. This led to the desired product being isolated in 76% yield with excellent selectivity (99% ee and >20:1 rr). Substrates possessing a 2-naphthyl group bearing electron-withdrawing or -donating substituents were examined, and these led to products **3b** and **3c** 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

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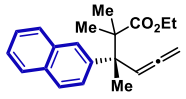
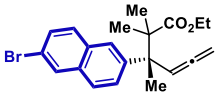
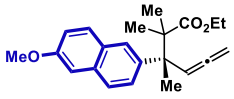
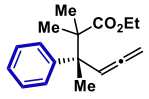
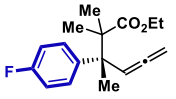
Table 2. Scope of Racemic Electrophiles in the Ir-Catalyzed Enantioselective Alkylation Reaction[a]

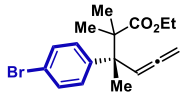

3a; 76% yield, 99% ee
>20:1 rr (17 h)
1 gram scale

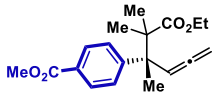

3b; 77% yield, 92% ee
>20:1 rr (20 h)[b]

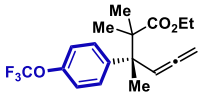

3c; 73% yield, 97% ee
>20:1 rr (7 h)

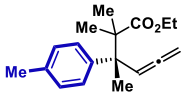

3d; 65% yield, 96% ee
>20:1 rr (20 h)

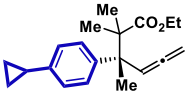

3e; 76% yield, 92% ee
>20:1 rr (14 h)[b]

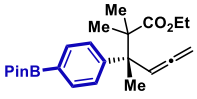

3f; 68% yield, 91% ee
>20:1 rr (27 h)[b]

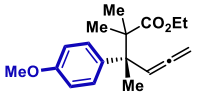

3g; 52% yield, 96% ee
>20:1 rr (20 h)[b,c]

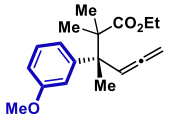

3h; 66% yield, 93% ee
>20:1 rr (67 h)[b,d]

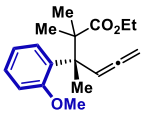

3i; 75% yield, 98% ee
>20:1 rr (23 h)[e]

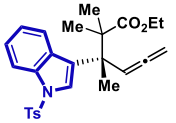

3j; 82% yield, 98% ee
>20:1 rr (17 h)[e]

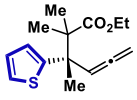

3k; 82% yield, 93% ee
>20:1 rr (24 h)[b]

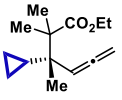

3l; 76% yield, 96% ee
10:1 rr (3 h)[f]

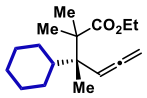

3m; 71% yield, 94% ee
>20:1 rr (8 h)[b]

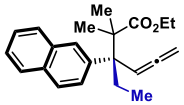

3n; 52% yield, 90% ee
>20:1 rr (3 h)[b]

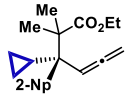

3o; 65% yield, 93% ee
20:1 rr (27 h)


3p; 70% yield, 93% ee
7:1 rr (2 h)


3q; 54% yield, 94% ee
>20:1 rr (22 h)[f]


3r; 0% (14 h)


3s; 52% yield, 90% ee
>20:1 rr (53 h)[b]


3t; 55% yield, 94% ee
20:1 rr (44 h)[b]

[a]Reaction conditions: $[Ir(cod)Cl]_2$ (5.0 mol %), (*S*)-$\mathbf{L_1}$ (20 mol %), (±)-**1** (0.4 mmol), **2a** (2.5 equiv), $La(OTf)_3$ (7.5 mol %), 1,4-dioxane (*c* 0.1 M), and 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}H NMR analysis of the unpurified reaction mixtures. [b]Reaction conducted using **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.

in 52−82% yield with 91−98% ee and >20:1 rr. Substrates bearing a pinacolborane group were also well-tolerated, and the corresponding product (**3k**) could be obtained in 82% yield with 93% ee and >20:1 rr. In contrast to our previously reported asymmetric reductive deoxygenation reaction, substrates bearing para-, meta-, or ortho-methoxy groups (**3l**−**3n**) all provided the respective products with high enantioselectivity (90−96% ee). Heteroaromatic substrates were also examined, and 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 replaced with a cyclopropyl 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.[77] 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 substrates containing ethyl 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 cyclopropyl-containing product **3t** was obtained with the absolute configuration opposite that of parent methyl-containing product **3a**.[62]

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 the *tert*-butyl derivative was employed, none of the desired *β*-allenyl ester was observed.[78] 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 tertiary-quaternary stereocenter arrangement was obtained in 72% yield and with 85% ee and >20:1 rr, albeit with a dr of 2.4:1.[79] 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 six-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 a means to increase their structural complexity (Scheme 2). Asako and Takai's Mo-catalyzed regioselective hydrosilylation afforded allylsilane (*Z*)-**5** in 73% yield with >20:1 rr and >20:1 *Z*:*E*.[80] Tsuji's palladium-catalyzed arylamination also worked well to give amine (*Z*)-**6** in 70% yield with >20:1 rr and >20:1 *Z*:*E*.[81] After the transformation of ester to carboxylic acid **7**, Curtius rearrangement followed by

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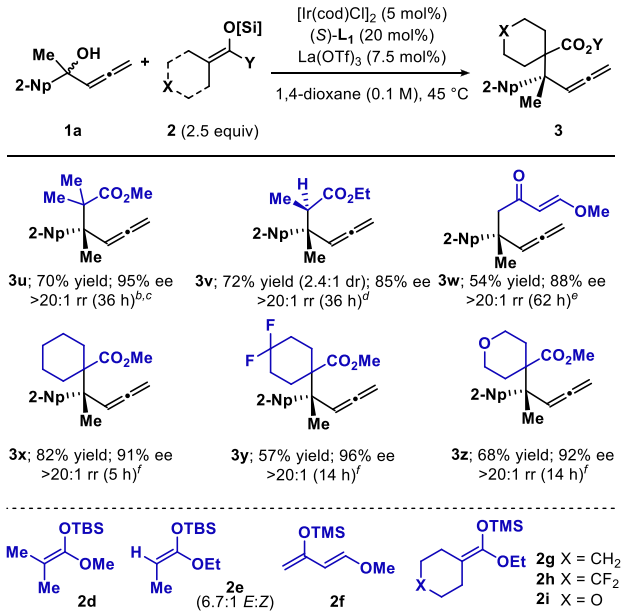
Table 3. Scope of Silyl Ketene Acetal Nucleophiles[a]



[a]Reaction conditions: $[Ir(cod)Cl]_2$ (5.0 mol %), (*S*)-**L**$_1$ (20 mol %), (±)-**1a** (0.4 mmol), **2** (2.5 equiv), $La(OTf)_3$ (7.5 mol %), 1,4-dioxane (*c* 0.1 M), and 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]**2d** was used. [d](*E*)-**2e** was used. [e]**2f** was used. [f]**2g**, **2h**, or **2i** was used.

quenching with BnOH furnished carbamate **8** in good yield. Finally, Breit's Rh-catalyzed intramolecular cyclization reaction between carboxylic acid and allene delivered lactone **9** in 94% yield with 5.2:1 dr.[82] In all cases, no erosion of enantiomeric purity was observed.

In conclusion, we have developed an enantioselective method that permits facile access to the vicinal quaternary carbon centers within acyclic motifs. This cocatalytic process utilizes the simple and robust Ir−(phosphoramidite,olefin) catalyst system and $La(OTf)_3$ 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 shown to perform well even on a 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00609.

Experimental details of synthetic procedures, characterization data for all new compounds, NMR spectra, crystal data, ORTEP diagrams (PDF)

Accession Codes

CCDC 2056432, 2056443, 2056444, 2056454, and 2056457 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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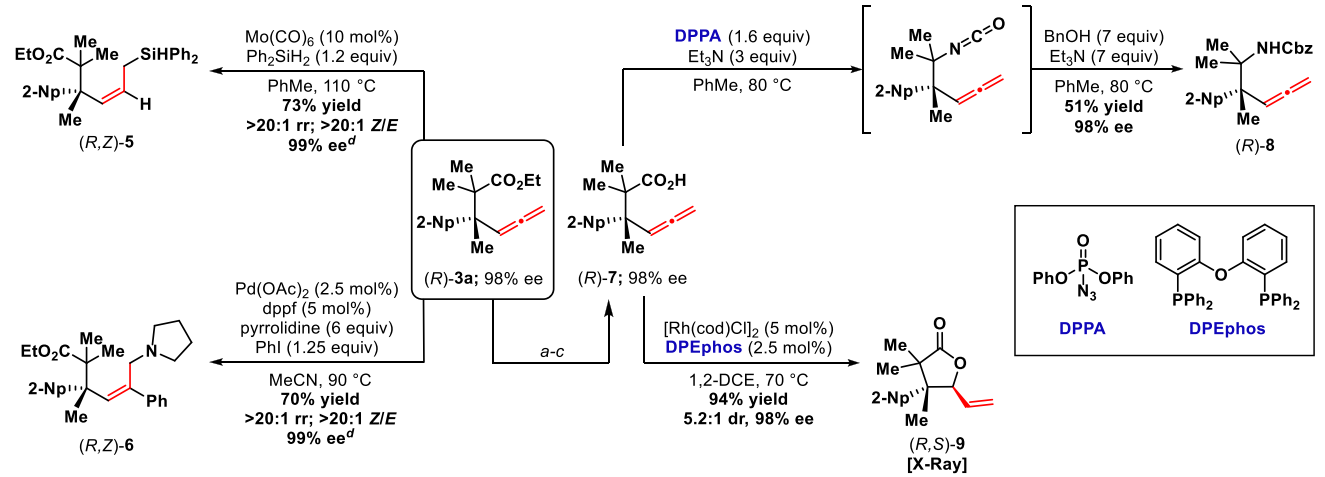
Scheme 2. Synthetic Application of the β-Allenyl Ester Products



[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), ^{t}BuOH/H_2O, 0 °C to rt, 11 h. [d]Product was derived from (*R*)-**3a** possessing 99% ee.

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Notes

The authors declare no competing financial interest.

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