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Stereospecific Rhodium-Catalyzed Allylic Substitution with Alkenyl Cyanohydrin Pronucleophiles: Construction of Acyclic Quaternary Substituted α,β-Unsaturated Ketones

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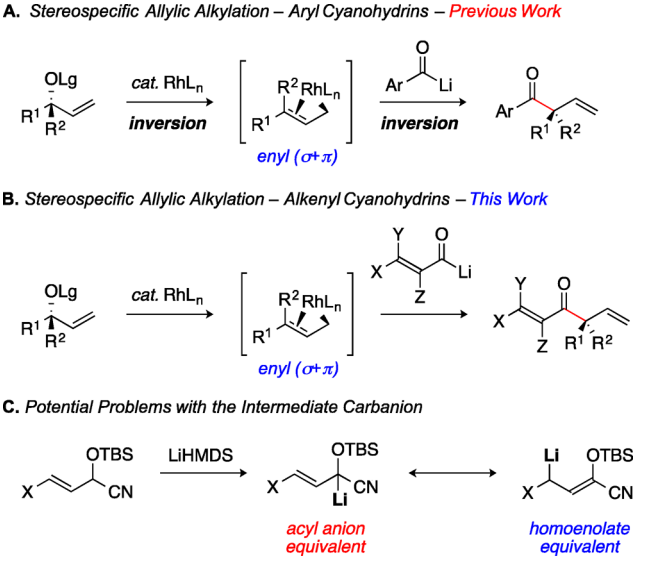
Supporting Information

ABSTRACT: A highly regio- and stereospecific rhodium-catalyzed allylic alkylation of tertiary allylic carbonates with alkenyl cyanohydrin pronucleophiles is described. This protocol offers a fundamentally novel approach toward the synthesis of acyclic quaternary-substituted α,β-unsaturated ketones and thereby provides a new cross-coupling strategy for target directed synthesis. A particularly attractive feature with this process is the ability to directly couple di-, tri, and tetrasubstituted alkenyl cyanohydrin pronucleophiles to prepare the corresponding α,β-unsaturated ketone derivatives in a highly selective manner. Additionally, the chemoselective 1,4-reduction of the enone products provides rapid access to acyclic enantiomerically enriched α,α′-dialkyl-substituted ketones, which are challenging motifs to prepare using conventional enolate alkylation.

The asymmetric construction of α-quaternary-substituted carbonyl compounds represents a vibrant area of investigation in organic synthesis due to the ubiquity of this motif in bioactive natural products, pharmaceuticals and various synthetic intermediates.[1,2] Although the venerable enolate alkylation remains an important carbon−carbon bond forming reaction, problems associated with regioselective enolate formation with unsymmetrical ketones, polyalkylation and the necessity to employ simple electrophiles have significantly hampered the development of asymmetric variants.[3,4] For instance, while the catalytic asymmetric alkylation,[5] arylation[6,7] and vinylation[8] of prochiral enolates have been described, they are generally optimal with cyclic substrates that circumvent the need to control the enolate geometry. Furthermore, while the enantioselective alkylation[9] of a mixture of acyclic enolate stereoisomers using a chiral chromium salen catalyst provides access to acyclic α-quaternary-substituted methyl ketones, this process is primarily restricted to simple electrophiles. Consequently, we anticipated the ability to directly utilize an acyl nucleophile would circumvent the formation of an enolate and thereby offer unparalleled scope and versatility, particularly with respect to the electrophile.[10−14]

To this end, we recently described the highly regio- and stereospecific rhodium-catalyzed allylic substitution reaction of chiral nonracemic tertiary allylic alcohol derivatives with an acyl anion equivalent (Scheme 1A).[15−17] The *tert*-butyldimethylsilyl-protected aryl cyanohydrin, which is readily prepared from the corresponding aldehyde,[18] provides a "masked" acyl anion equivalent that undergoes *in situ* deprotection with fluoride ion to furnish the corresponding quaternary-substituted acyclic aryl ketones via a classical double-inversion process. Although this work delineated important proof-of-principle, the aromatic ketone products are of relatively limited synthetic utility. Hence, we envisaged that the ability to utilize alkenyl cyanohydrin pronucleophiles would significantly expand the scope of this novel protocol and thereby access α,β-unsaturated ketones bearing an α-quaternary stereogenic center (Scheme 1B). The products produced from this process would be difficult to obtain via conventional enolate alkylation and are of particular importance as synthetic intermediates due to the presence of two functional groups that exhibit bimodal reactivity. A key feature of this strategy is the ability to control the reactivity of the lithiated alkenyl cyanohydrin, which can either undergo the desired alkylation at the α-position to function as an acyl anion

Scheme 1. Factors Affecting the Development of the Rhodium-Catalyzed Allylic Alkylation with Alkenyl Cyanohydrin Pronucleophiles



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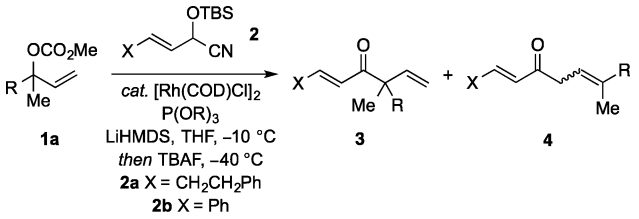
equivalent or react through the γ-position as a homoenolate equivalent (Scheme 1C). Herein, we now describe the first highly regio- and stereospecific rhodium-catalyzed allylic substitution of tertiary allylic carbonates with alkenyl cyanohydrin pronucleophiles to facilitate the construction of acyclic α-quaternary-substituted α,β-unsaturated ketones.

Preliminary studies focused on the γ-alkyl-substituted alkenyl cyanohydrin **2a** (X = $Ph(CH_2)_2$), since previous studies demonstrated that the anion of the unsubstituted derivative (X = H) is unstable under the reaction conditions.[17a] Treatment of the tertiary allylic carbonate **1a** with the lithium salt of **2a**, in the presence of triphenyl phosphite-modified $[RhCl(COD)]_2$ at −10 °C for ca. 16 h, followed by treatment with tetra-*n*-butylammonium fluoride (TBAF) at −40 °C[19] furnished the quaternary-substituted α,β-unsaturated ketone **3a** in 66% yield and with excellent regioselectivity (Table 1, entry 1). Gratifyingly, there was no evidence for nucleophilic attack at the γ-position of the alkenyl cyanohydrin **2a**. Although the stereoelectronics of the phosphite ligand generally play a critical role in the efficiency and selectivity of the rhodium-catalyzed allylic substitution reaction, screening various phosphites provided only modest improvement in the yield (entries 2−4). Hence, we elected to continue our studies using the readily available triphenyl phosphite as the optimum ligand. Additional studies demonstrated that increasing the stoichiometry of the cyanohydrin pronucleophile provides the desired acyclic ketone **3a** in excellent yield and with ≥19:1 regioselectivity (entry 5). Interestingly, the aryl-substituted alkenyl cyanohydrin **2b** (X = Ph) afforded the desired ketone **3b** in good yield and excellent regioselectivity regardless of stoichiometry (entry 6 vs entry 7). The difference in reaction stoichiometry was ascribed to the greater kinetic acidity of the α-proton in **2b**, which is supported by deuterium quenching experiments that demonstrate a higher concentration of the reactive nucleophile.[15]

Table 1. Optimization of the Rhodium-Catalyzed Allylic Substitution using Alkenyl Cyanohydrin 2 (R = $Ph(CH_2)_2$)[a,b]

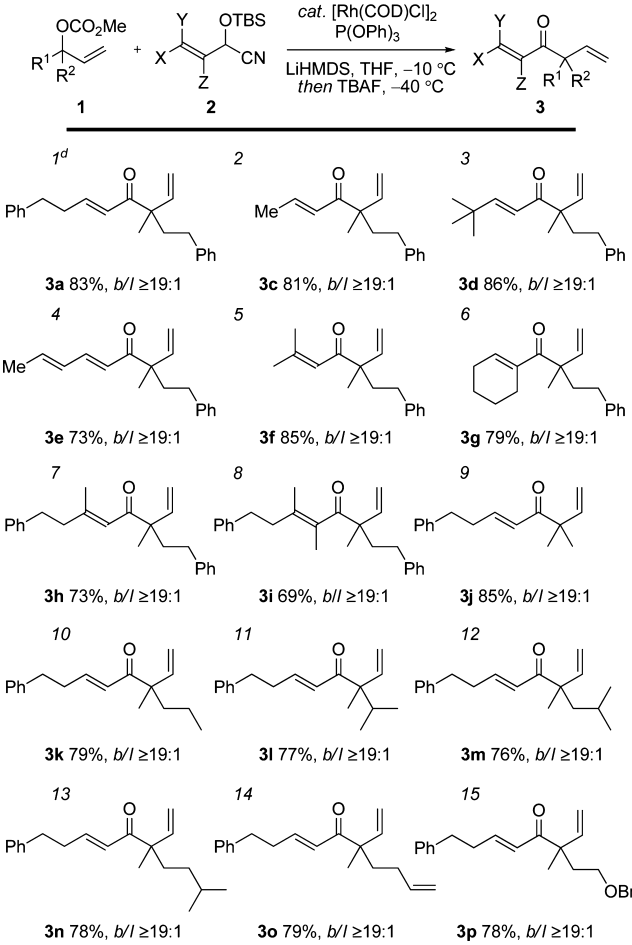


entry	phosphite L =	Nu	method	3:4 (b/l)[c]	yield of 3 (%)[d]
1	$P(OPh)_3$	**2a**	A	≥19:1	66
2	$P(OMe)_3$	**2a**	A	≥19:1	67
3	$P(OCH_2CF_3)_3$	**2a**	A	≥19:1	67
4	$P(O\text{-}2,4\text{-}di^tBuC_6H_3)_3$	**2a**	A	≥19:1	68
5	***$P(OPh)_3$***	***2a***	***B***	***≥19:1***	***83***
6	***$P(OPh)_3$***	***2b***	***A***	***≥19:1***	***75***
7	$P(OPh)_3$	**2b**	B	≥19:1	75

[a]All reactions were performed on a 0.5 mmol reaction scale using 2.5 mol % $[Rh(COD)Cl]_2$ and 10 mol % ligand (L) in 5 mL THF at −10 °C for ca. 16 h, followed by the addition of TBAF at −40 °C. [b]Method A: 1.3 equiv **2**, 1.8 equiv LiHMDS, and 4.0 equiv TBAF were employed; Method B: 2.0 equiv **2**, 2.8 equiv LiHMDS, and 6.0 equiv TBAF were employed. [c]Regioselectivity was determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures prior to deprotection of the cyanohydrin adducts, which are obtained as a 1:1 mixture of diastereomers. [d]Isolated yields of the desired regioisomer **3**.

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 5) to a number of alkyl-substituted alkenyl cyanohydrins and tertiary allylic carbonates. In the first instance, the study focused on the pronucleophile component. To this end, the reaction is tolerant of 1,2-disubstituted alkenyl cyanohydrins bearing both long and short alkyl chains, generating the α,β-unsaturated ketones in excellent yields and with exceptional regioselectivity (entries 1−2). Furthermore, the *tert*-butyl derivative and a cyanohydrin containing a potentially reactive 1,3-diene proceed with excellent selectivity (entries 3−4). Additionally, trisubstituted alkenyl cyanohydrins bearing a *gem*-dimethyl or cyclohexene motif also provide competent substrates (entries 5−6). Nevertheless, a particularly attractive feature of the current work is the ability to employ differentially tri- and tetra-substituted alkenyl cyanohydrins, which furnish the α-quaternary-substituted ketones with complete retention of geometrical selectivity in the double bond (entries 7−8).[20] Remarkably, the *cis*-1,2-disubstituted cyanohydrin (**Z**)-**2a** (X/Z = H, Y = $Ph(CH_2)_2$) undergoes complete isomerization under

Table 2. Scope of the Rhodium-Catalyzed Allylic Substitution with Alkyl-Substituted Alkenyl Cyanohydrins (Method B)[a,b,c]



[a]All reactions were performed on a 0.5 mmol reaction scale using 2.5 mol % $[Rh(COD)Cl]_2$, 10 mol % $P(OPh)_3$, 2.0 equiv **2**, and 2.8 equiv LiHMDS in THF (5 mL) at −10 °C for ca. 16 h, followed by the addition of 6.0 equiv TBAF at −40 °C. [b]Regioselectivity was determined by 500 MHz ^{1}H NMR analysis of the isolated ketones **3**. [c]Isolated yields. [d]79% yield ($b/l \geq 19:1$, $E/Z \geq 19:1$) using (**Z**)-**2a** (E/Z = 1:7).

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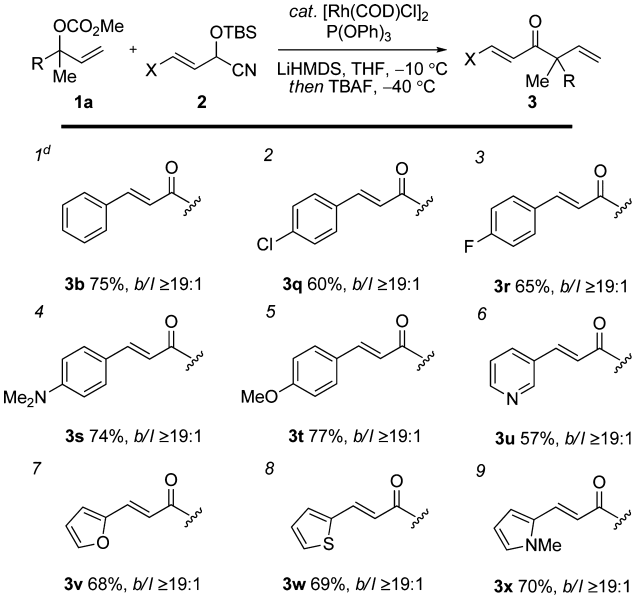
the reaction conditions to furnish the *trans*-substituted enone **3a** in comparable yield. This unexpected observation most likely arises from olefin equilibration triggered by the relief of $A^{1,3}$-strain between the phenethyl substituent and the large *tert*-butyldimethylsilyl group.[21] It is interesting to note that despite this isomerization, alkylation at the γ-position is not evident.

Nevertheless, the scope with respect to the tertiary allylic carbonate provides significant flexibility with this approach. For instance, while both short and long chain alkyl substituents are well tolerated (entries 9−10), branched and functionalized side-chains provide the acyclic ketones in good yields and excellent regioselectivity (entries 11−15). This is particularly noteworthy due to the problems associated with the introduction of these groups via conventional alkylation reactions, i.e., isopropyl and hydroxyethyl groups.

Table 3 outlines the examination of a range of aryl-substituted alkenyl cyanohydrins to further illustrate the scope of the

Table 3. Scope of the Rhodium-Catalyzed Allylic Substitution with Aryl-Substituted Alkenyl Cyanohydrins (Method A) (R = $Ph(CH_2)_2$)[a,b,c]

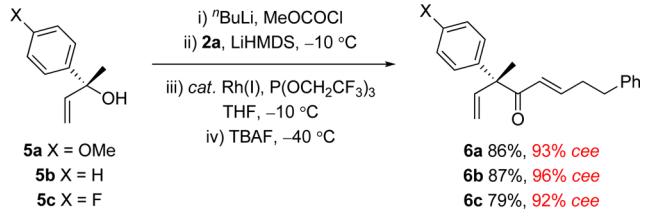


[a]All reactions were performed on a 0.5 mmol reaction scale using 2.5 mol % $[Rh(COD)Cl]_2$, 10 mol % $P(OPh)_3$, 1.3 equiv **2**, and 1.8 equiv LiHMDS in THF (5 mL) at −10 °C for ca. 16 h, followed by the addition of 4.0 equiv TBAF at −40 °C. [b]Regioselectivity was determined by 500 MHz ^1H NMR analysis of the isolated ketones **3**. [c]Isolated yields. [d]73% yield ($b/l \geq 19:1$) on a 10 mmol (2.3 g) scale using 0.5 mol % $[Rh(COD)Cl]_2$ and 2 mol % $P(OPh)_3$.

reaction using slightly modified reaction conditions (Table 1, entry 6). In addition to the unsubstituted phenyl substituent (entry 1), the reaction is tolerant of a number of electron-deficient and electron-rich aryl groups (entries 2−5). Gratifyingly, a number of alkenyl cyanohydrins bearing heterocyclic substituents also undergo the alkylation in good yield and with comparable selectivity for the branched regioisomer (entries 6−9). Finally, the ability to conduct the reaction on gram-scale using 1 mol % of the rhodium catalyst demonstrates the viability of this methodology for target-directed synthesis. Overall, this work provides access to an array of acyclic quaternary-substituted α,β-unsaturated ketones bearing both an electron-rich and an electron-deficient olefin, which would be difficult to access via conventional enolate alkylation reactions.

In order to further highlight the scope of this transformation, we elected to examine the stereospecific rhodium-catalyzed allylic alkylation of the chiral nonracemic tertiary allylic alcohols **5a−c**, readily prepared following the three-step protocol described by Aggarwal et al. (Scheme 2).[22] In accord with our

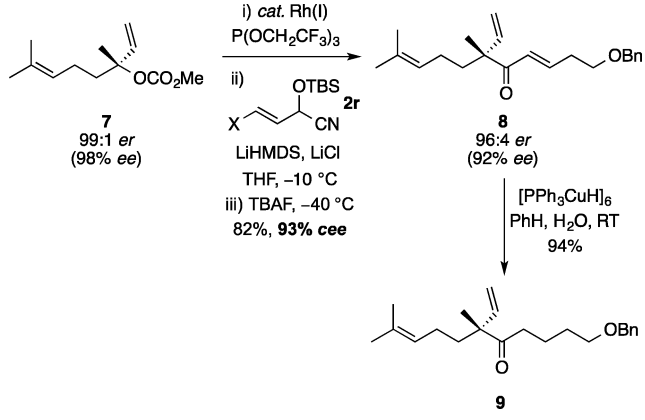
Scheme 2. Stereospecific Allylic Substitution of Chiral Nonracemic Allylic Alcohols 5a−c



previous studies, the use of the electron-poor tris(2,2,2-trifluoroethyl)-phosphite ligand proved optimal, affording the acyclic ketones **6a−c** with excellent levels of regiocontrol ($b/l \geq$ 19:1) and conservation of enantiomeric excess (≥92% cee).[23] Additionally, the preparation of a compound of known absolute configuration provided confirmation that the alkylation proceeds with overall retention, which illustrates the cyanohydrin is behaving as a soft nucleophile in this process.[24]

The asymmetric synthesis of α,α'-dialkyl acyclic ketones is particularly challenging for conventional enolate alkylation reactions, due to the problems associated with regioselective enolate formation from an unsymmetrical ketone. Hence, we envisaged an alternate approach to these compounds outlined in Scheme 3, which combines the stereospecific allylic alkylation

Scheme 3. Asymmetric Synthesis of α,α'-Dialkyl Ketone 9 via Stereospecific Rhodium-Catalyzed Allylic Substitution/ Chemoselective 1,4-Reduction (X = CH_2CH_2OBn)



with a chemoselective 1,4-reduction. In this context, the rhodium-catalyzed allylic alkylation of the linalool-derived allylic carbonate **7** (99:1 er) furnished the α,β-unsaturated ketone **8** in good yield and excellent regio- and stereospecificity ($b/l \geq$ 19:1, 93% cee). Treatment of the acyclic ketone **8** with Stryker's reagent[25] affords the α,α'-dialkyl acyclic ketone **9** in excellent yield to further illustrate the potential utility of this approach.

In conclusion, we have developed the regio- and stereospecific rhodium-catalyzed allylic substitution of chiral nonracemic allylic carbonates with trialkylsilyl-protected alkenyl cyanohydrins,

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which permits the construction of acyclic quaternary-substituted α,β-unsaturated ketones bearing both an electron-rich and electron-deficient olefin. Additionally, the use of branched and functionalized alkyl substituents in the allylic alcohol moiety provides access to products that would be challenging for conventional enolate alkylation reactions. The ability to construct di-, tri-, and tetrasubstituted enones, with complete transposition of *E*-geometrical selectivity, further demonstrates the broad scope of this methodology. Finally, the two-step sequence involving the allylic alkylation and chemoselective 1,4-reduction to give a α,α'-dialkyl acyclic ketone highlights the synthetic potential of this process. Hence, given the utility of the acyclic quaternary-substituted α,β-unsaturated ketone products, we anticipate that this approach will permit the construction of this important and challenging motif in target-directed synthetic applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10270.

Experimental procedures, spectral data, and copies of spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(19) The fluoride ion deprotection was conducted at low temperature to suppress competitive Michael addition of the liberated cyanide to the α,β-unsaturated ketone.

(20) In all cases the alkylation proceeds with complete retention of the (*E*)-cyanohydrin stereochemistry ($E/Z \geq 19{:}1$).

(21) Although the 1,2-disubstituted cyanohydrin (**Z**)-**2a** underwent complete isomerization under the reaction conditions, a mixture of *E*/*Z* isomers (1:1) of the tri- and tetra-substituted alkenyl cyanohydrins **2h**/**2i** provided the ketones **3h**/**3i** as a mixture of isomers (E/Z = 3:1 and 4:1, respectively), albeit favoring the *trans* derivative.

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