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Regio- and Enantiospecific Rhodium-Catalyzed Allylic Substitution with an Acyl Anion Equivalent

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ABSTRACT

The construction of enantiomerically enriched acyclic quaternary substituted ketones *via* the regio- and enantiospecific rhodium-catalyzed allylic alkylation reaction of chiral nonracemic tertiary alcohols with cyanohydrin pronucleophiles is described. This approach provides an alternative method to the α-arylation and vinylation of acyclic disubstituted ketone enolates, which remains a challenging endeavor. The combination of the allylic alkylation with ring-closing metathesis facilitates the preparation of enantiomerically enriched 2,2-disubstituted naphthalene-1-ones, which have proven very difficult to prepare using a more conventional dearomatization strategy.

The asymmetric synthesis of α-substituted carbonyl compounds, particularly those that contain quaternary carbon stereogenic centers, remains a particularly important area of investigation for synthetic organic chemistry.[1] This can be attributed to the challenges associated with the installation of this type of structural motif in important biologically active pharmaceutical agents and natural products.[2] In general, the most common approach towards the asymmetric construction of these types of compounds involves the functionalization of prochiral enolate nucleophiles, typically by alkylation,[3] arylation,[4] and vinylation.[5] However, in addition to the inherent stereoelectronic restrictions placed on the regioselective formation and alkylation of an unsymmetrical enolate, a critical limitation with these reactions is that they are generally optimal for cyclic substrates, which circumvents the problems associated with controlling the enolate geometry. For instance, the deprotonation of an acyclic α,α-disubstituted ketone almost invariably leads to a mixture of (*E*)- and (*Z*)-enolates, which upon facially selective electrophilic trapping generates a mixture of enantiomers. Although a couple of notable examples have been devised that successfully address the problem with acyclic α,α-disubstituted enolates, a universal solution to this problem has not been forthcoming. For example, the chiral auxiliary pseudoephedrine X_ψ facilitates the formation of a stereodefined enolate that undergoes diastereoselective alkylation (Scheme 1A),[6]

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(1) For recent reviews on the catalytic enantioselective construction of quaternary carbon stereogenic centers, see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (d) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593.

(2) For reviews on the asymmetric synthesis of natural products containing quaternary carbon stereogenic centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745.

(3) For recent reviews on the enantioselective enolate alkylation reaction, see: (a) Stoltz, B. M.; Mohr, J. T. In *Science of Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, 2010; Vol. 3, p 567. (b) Oliver, S.; Evans, P. A. *Synthesis* **2013**, *45*, doi: 10.1055/s-0033-1338538.

(4) For recent examples of asymmetric transition metal-catalyzed enolate arylation reactions, see: (a) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413. (c) García-Fortanet, J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8108. (d) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195. (e) Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330.

(5) For recent examples of asymmetric transition metal-catalyzed enolate vinylation reactions, see: (a) Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897. (b) Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343. (c) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900.

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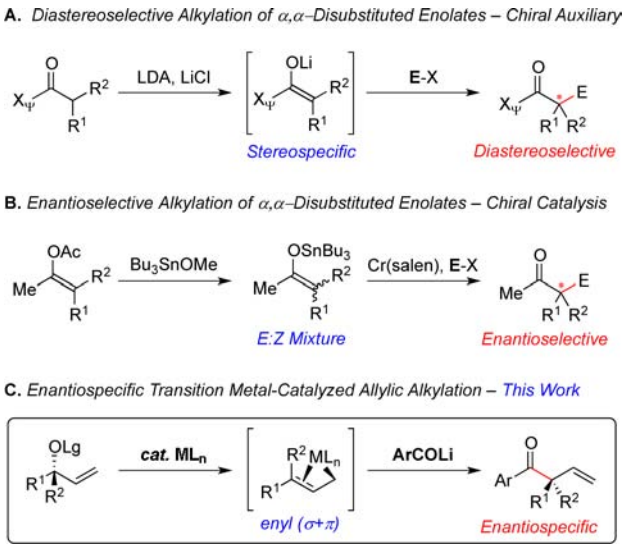
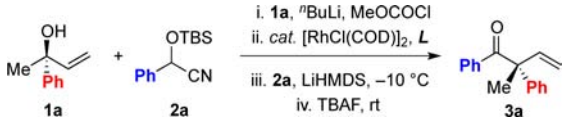
Scheme 1. Comparison of Stereoselective Enolate Alkylation with Metal-Catalyzed Allylic Substitution for the Preparation of Enantiomerically Enriched Acyclic Quaternary Stereocenters



whereas a chiral chromium salen catalyst results in a highly enantioselective alkylation of a mixture of enolate stereoisomers (Scheme 1B).[7] Nevertheless, we envisioned an alternative approach to this problem, which circumvents the formation of an enolate and thereby provides almost unparalleled scope with respect to the electrophile.

In this context, we recently reported a novel method for the construction of acyclic quaternary carbon stereogenic centers *via* the rhodium-catalyzed allylic substitution of tertiary allylic alcohol derivatives with an acyl anion equivalent (Scheme 1C), namely a *tert*-butyldimethylsilyl-protected cyanohydrin.[8] The cyanohydrin pronucleophile is readily prepared by the addition of *tert*-butyldimethylsilyl cyanide to the corresponding aldehyde[9] and unmasked *in situ* with fluoride to afford the acyclic ketone. Additionally, this study also provided proof-of-concept for the first stereospecific rhodium-catalyzed allylic substitution of a chiral nonracemic tertiary allylic alcohol derivative, which proceeds *via* a classical double inversion process to facilitate good chirality transfer, albeit slightly lower than the corresponding secondary alcohol derivatives.[10−12] Herein, we describe a general method for the enantiospecific synthesis of a variety of acyclic quaternary α-aryl and

Table 1. Optimization of the *One-Pot* Regio- and Enantiospecific Rhodium-Catalyzed Allylic Substitution with an Acyl Anion Equivalent[a]



		acyclic ketone **3a**			
entry	*L*	*b*:*l*[b]	% yield[c]	*er*[d]	*cee*[15]
1	P(O-2,4-di-^{t}BuC$_6$H$_3$)$_3$	≥19:1	66	91:9	85
2	P(OTBS)$_3$	≥19:1	72	59:41	19
3	P(OPh)$_3$	≥19:1	78	79:21	61
4	P(OMe)$_3$	≥19:1	80	91:9	85
5	***P(OCH$_2$CF$_3$)$_3$***	***≥19:1***	***87***	***95:5***	***91***

[a] All reactions were performed on a 0.5 mmol reaction scale using 1 equiv of ^{n}BuLi, 1 equiv of MeOCOCl, 2.5 mol % [RhCl(COD)]$_2$, 10 mol % ***L***, 1.3 equiv of **2a**, and 1.8 equiv of LiHMDS in THF (5 mL) at −10 °C for *ca.* 16 h, followed by the addition of 4 equiv of TBAF at room temperature. [b] Regioselectivity was determined by 500 MHz ^{1}H NMR on the isolated product **3a**. [c] Isolated yields. [d] Determined by chiral HPLC on the isolated product **3a**.

α-vinyl ketones, which remain challenging substrates for conventional enolate alkylation reactions.

A critical component for this process is the ability to readily access highly enantiomerically enriched tertiary allylic alcohols. In this context, an array of chiral nonracemic aryl tertiary alcohols **1** were readily prepared by a three step procedure reported by Aggarwal and co-workers for the stereodivergent construction of aryl-substituted tertiary alcohols.[13] Interestingly, the attempted activation of the tertiary allylic alcohol **1a** (Ar = Ph) with methyl chloroformate led to the rearrangement to the achiral linear regioisomer during purification by column chromatography.[14] Hence, to circumvent this problem, we developed a convenient and efficient *one-pot* procedure in which the reactive allylic carbonate was generated *in situ*, and then directly treated with the anion of the cyanohydrin **2** in the presence of the rhodium catalyst, to provide the enantiomerically enriched ketone **3** upon deprotection of the resultant cyanohydrin adduct with fluoride.

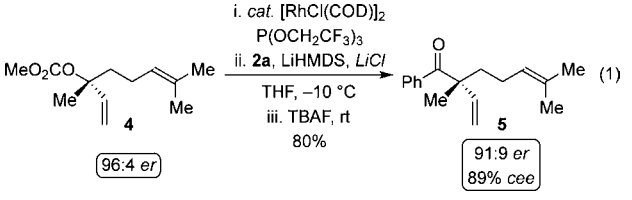
Table 1 outlines the effect of the phosphite ligand on enantiospecificity. Interestingly, the bulky aryl phosphite that was optimal for regioselectivity in the previous study afforded the acyclic ketone **3a** in moderate yield and stereospecificity (entry 1). A survey of various phosphite ligands indicates that the regioselectivity is consistent with an array of stereoelectronically diverse ligands, whereas the level of stereospecificity is optimal with a smaller electron-deficient phosphite ligand, namely tris(2,2,2-trifluoroethyl) phosphite (entry 5). Presumably, the

(6) Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231.
(7) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701.
(8) Evans, P. A.; Oliver, S.; Chae, J. *J. Am. Chem. Soc.* **2012**, *134*, 19314.
(9) Kurono, N.; Yamaguchi, M.; Suzuki, K.; Ohkuma, T. *J. Org. Chem.* **2005**, *70*, 6530.
(10) Evans, P. A.; Leahy, D. K. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 10, pp 191−214.
(11) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.
(12) For an example of a stereospecific iron-catalyzed allylic substitution of a tertiary allylic carbonate, see: Jegelka, M.; Plietker, B. *Org. Lett.* **2009**, *11*, 3462.
(13) (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778. (b) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142.
(14) For a related process involving allylic acetates, see: Serra-Muns, A.; Guérinot, A.; Reymond, S.; Cossy, J. *Chem. Commun.* **2010**, *46*, 4178.

relatively small size and increased π-acidity of this ligand serves to increase the rate of nucleophilic alkylation relative to $\pi-\sigma-\pi$ isomerization and thereby minimize the equilibration of the *enyl* intermediate.

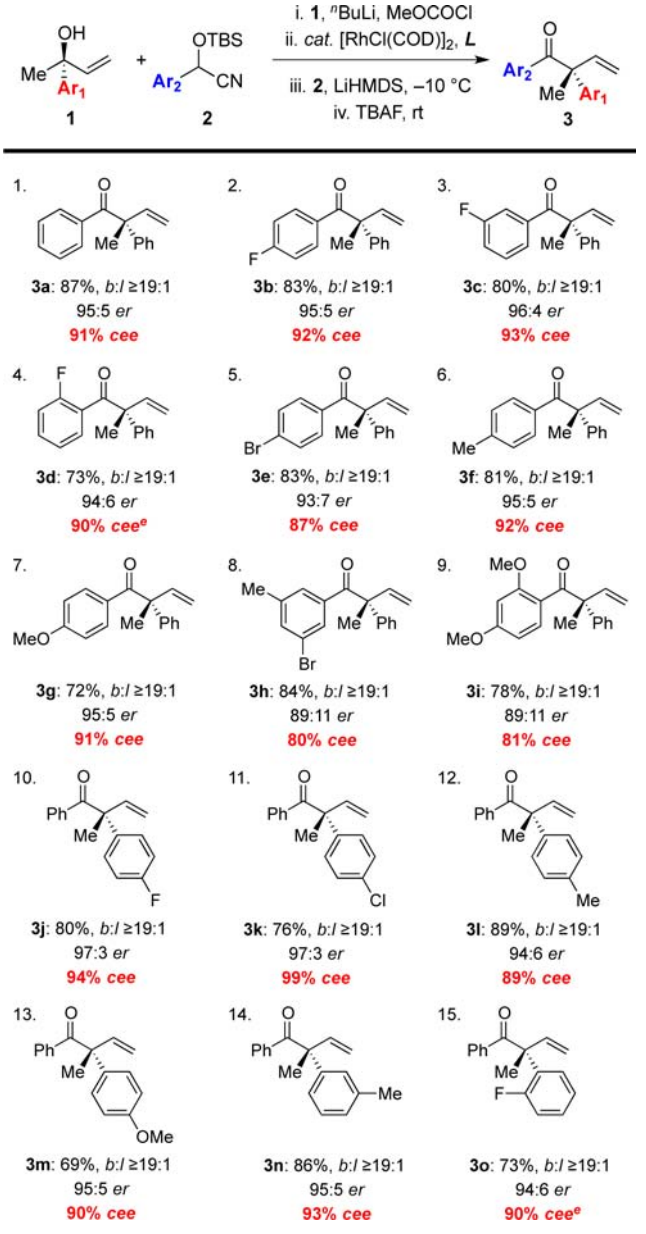
Scheme 2 summarizes the application of the optimized reaction conditions (Table 1, entry 5) to aryl cyanohydrins and tertiary allylic alcohol derivatives. A range of electron-rich and electron-poor aryl cyanohydrins provide the acyclic ketones **3a**–**i** in good to excellent yield and with uniformly high conservation of enantiomeric excess (entries 1–9),[15] albiet disubstituted derivatives provide slightly lower stereospecificities (entries 8 and 9). In addition, several tertiary aryl allylic alcohols **1** provide excellent stereoretention in this process (entries 10–15). Interestingly, in the case of both the *ortho*-fluorinated aryl cyanohydrin and tertiary aryl allylic alcohol, trimethyl phosphite provided optimal selectivity at room temperature (entries 4 and 15). A particularly attractive feature with this method is the ability to obtain consistently high chirality transfer for an array of α-quaternary substituted aryl ketones, which is almost independent of the substitution pattern of cross-coupling components. Overall, this reaction currently provides access to a diverse array of acyclic α-quaternary ketones bearing pendant alkyl, aryl and vinyl groups, in which the latter provides a particularly versatile functional handle for target directed synthesis.

To highlight the substrate scope of this method further, we elected to examine the rhodium-catalyzed allylic alkylation of the linalool-derived allylic carbonate **4** (96:4 *er*) with the cyanohydrin **2a** (eq 1). Gratifyingly, the alkyl-substituted allylic carbonate **4** was as efficient as the aryl-substituted analogs, providing the ketone **5** in excellent yield and enantiospecificity (91:9 *er*, 89% *cee*) in the presence of lithium chloride. Interestingly, in the absence of lithium chloride the reaction furnished **5** with slightly reduced stereospecificity (88:12 *er*, 85% *cee*). This additive presumably serves to deaggregate the lithiated cyanohydrin, thereby providing a more reactive nucleophile, which undergoes alkylation at an increased rate relative to $\pi-\sigma-\pi$ isomerization of the chiral allylic electrophile to afford enhanced stereospecificity. In contrast, the *one-pot* protocol serendipitously generates lithium chloride from the acylation of the allylic alcohol **1**, which presumably explains the consistently high stereospecificities (Scheme 2). Although alkyl-substituted tertiary allylic alcohols are generally more difficult to prepare than the corresponding aryl derivatives, this reaction provides proof-of-concept for this important process.



The asymmetric construction of cyclohexadienone derivatives *via* the enantioselective oxidative dearomatization of phenols and naphthols provides an important strategy for the total synthesis of a variety of natural products.[16] Nevertheless, despite some exciting developments in this field, particularly in the area of hypervalent iodine

Scheme 2. Scope for the Stereospecific Rhodium-Catalyzed Allylic Substitution with an Acyl Anion Equivalent[a–d]



[a] All reactions were performed on a 0.5 mmol reaction scale using 1 equiv of ^{n}BuLi, 1 equiv of MeOCOCl, 2.5 mol % $[RhCl(COD)]_2$, 10 mol % $P(OCH_2CF_3)_3$, 1.3 equiv of **2**, and 1.8 equiv of LiHMDS in THF (5 mL) at −10 °C for *ca.* 16 h, followed by the addition of 4 equiv of TBAF at room temperature. [b] Regioselectivity was determined by 500 MHz ^{1}H NMR on the isolated products. [c] Isolated yields. [d] Enantiomeric ratios (*er*) values were determined by chiral HPLC on the isolated products. [e] $P(OMe)_3$ was used at room temperature.

(15) The term conservation of enantiomeric excess (cee) = (ee of product/ee of starting material) × 100. Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761.

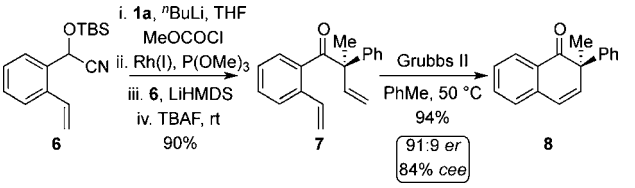
(16) For a recent review, see: Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235.

chemistry, the asymmetric alkylation reactions are particularly challenging both in terms of efficiency and selectivity.[17]

We envisaged an alternative approach to these compounds, as outlined in Scheme 3, which combines the allylic alkylation with ring-closing metathesis. In this context, the rhodium-catalyzed allylic alkylation of the chiral nonracemic tertiary carbonate derived from **1a** with the carbanion of the vinyl-substituted cyanohydrin **6** furnished, upon deprotection, the diene **7**, which was treated with Grubbs second-generation catalyst to afford the naphthoid cyclohexa-2,4-dienone **8** in 85% overall yield and with 84% *cee*.[18]

In conclusion, the regio- and enantiospecific rhodium-catalyzed allylic substitution of chiral nonracemic tertiary alcohols with trialkylsilyl-protected cyanohydrins provides a general and convenient method for the construction of enantiomerically enriched acyclic α-quaternary substituted ketones. Additionally, the ability to extend the scope of this transformation to acyclic alkyl-substituted tertiary allylic alcohols illustrates the synthetic utility beyond aryl-substituted allylic alcohol derivatives. The asymmetric synthesis of a dearomatized naphthoid cyclohexa-2,4-dienone, which remains a challenging endeavor for more conventional dearomatization strategies, further highlights the synthetic potential for this process. Hence, this method provides a viable alternative to the catalytic asymmetric α-arylation and vinylation of acyclic disubstituted ketone enolates, which are particularly challenging substrates.

Scheme 3. Asymmetric Synthesis of Naphthoid Cyclohexa-2,4-dienone **8** *via* the Sequential Stereospecific Rhodium-Catalyzed Allylic Substitution/Ring-Closing Metathesis Reaction



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Supporting Information Available. Experimental procedures, characterization data, and spectra are included. This material is available free of charge *via* the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) For a recent example of asymmetric spirolactonization of 1-naphthols catalyzed by a spirobiindane-based chiral hypervalent iodine species, see: Dohi, T.; Takenaga, N.; Nakae, T.; Toyoda, Y.; Yamasaki, M.; Shiro, M.; Fujioka, H.; Maruyama, A.; Kita, Y. *J. Am. Chem. Soc.* **2013**, *135*, 4558.

(18) Although this particular compound has been prepared in racemic form by the oxidative arylation of 1-naphthol using Ph_2ICl, the efficiency of this reaction is poor; see: Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7065.