

Rhodium-Catalyzed Allylic Substitution with an Acyl Anion Equivalent: Stereospecific Construction of Acyclic Quaternary Carbon Stereogenic Centers

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S Supporting Information

ABSTRACT: A highly regio- and stereospecific rhodium-catalyzed allylic alkylation of tertiary allylic alcohol derivatives with a cyanohydrin pronucleophile is described. This direct and operationally simple protocol provides a fundamentally novel approach toward the synthesis of α -quaternary substituted ketones and circumvents many of the inherent problems associated with conventional enolate alkylation reactions. The stereospecific variant of this reaction provides the enantiomerically enriched α -quaternary substituted allylic aryl ketone, which is a particularly challenging intermediate for more conventional enolate-based strategies.

The stereoselective construction of all-carbon quaternary stereogenic centers remains both an important and challenging area of investigation.¹ In this context, the synthesis of this motif in acyclic systems remains arguably the greatest challenge, despite the development of a number of elegant approaches over the past decade.² Among these methods, enolate alkylation represents a particularly powerful synthetic strategy and remains one of the most fundamentally important carbon–carbon bond-forming reactions in synthetic organic chemistry.³ This can be attributed to the ubiquity and versatility of carbonyl compounds as synthetic intermediates, and their presence in an array of pharmacologically important agents. For example, chiral auxiliaries are frequently employed in this manner, albeit this approach is now being superseded by catalytic variants, which utilize organocatalysts and transition metal complexes for the enantioselective alkylation of a wide range of carbonyl compounds.^{4–6} Furthermore, these methods have been extended to non-traditional electrophiles for the arylation and vinylation of enolates.^{7–9} Nevertheless, the stereocontrolled construction of acyclic quaternary carbon centers via enolate alkylation has a number of inherent limitations (Scheme 1A). For instance, the ability to regioselectively form an enolate from an unsymmetrical ketone, polyalkylation via enolate equilibration, and the necessity to employ simple electrophiles adversely impact the chiral and achiral versions of this venerable process. Additionally, this process generally requires a specific enolate geometry, since the origin of enantioselectivity is defined by a combination of enolate geometry and π -facial selectivity in the alkylation.

We envisioned an alternative strategy for the construction of enantiomerically enriched acyclic α -quaternary substituted ketones (Scheme 1B), which involves the stereospecific

Scheme 1. Comparison of Conventional Alkylation of a Ketone Enolate with Allylic Substitution Using an Acyl Anion

A. Classical Alkylation - Challenging - Three Modes of Selectivity



B. Allylic Alkylation - Umpolung - Two Modes of Selectivity - This Work



rhodium-catalyzed allylic substitution of chiral nonracemic acyclic tertiary allylic carbonates with an acyl anion equivalent.^{10–13} Hence, a critical component for the successful implementation of this process is the ability to intercept the putative rhodium-*enyl* intermediate in an analogous manner to the corresponding secondary allylic carbonates.^{14,15} The potential advantage to this strategy is the ability to employ an array of diverse substituents (R_1/R_2), which obviates the inherent stereoelectronic restrictions associated with conventional electrophiles. In this context, we expect the inherent stability of the nucleophile to be an important component, since a stabilized nucleophile would provide retention of configuration, whereas an unstabilized version would promote direct attack on the metal center and afford the opposite enantiomer.¹⁴ Herein, we now describe the successful implementation of the first regioselective rhodium-catalyzed allylic alkylation of tertiary allylic carbonates with an acyl anion equivalent to facilitate the construction of acyclic α -quaternary substituted ketones and the first stereospecific example using a chiral nonracemic allylic carbonate (Scheme 1).

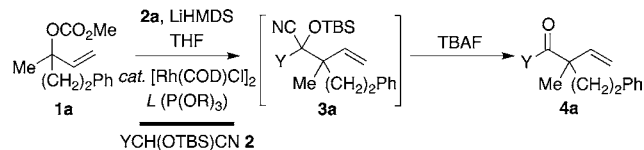
In accord with our hypothesis, the *tert*-butyldimethylsilyl-protected cyanohydrin **2** was selected as the acyl anion equivalent,¹⁶ which is readily prepared by the addition of *tert*-butyldimethylsilyl cyanide to the corresponding aldehyde¹⁷ and unmasked in the presence of fluoride. Additionally, we envisioned that the anion derived from **2** would be sufficiently

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stabilized to permit the double inversion process outlined in Scheme 1B.¹⁸ Treatment of the tertiary allylic carbonate **1a** with the lithium salt of **2a** (Y = Ph) in the presence of [RhCl(COD)]₂, modified with triphenyl phosphite, followed by the addition of tetra-*n*-butylammonium fluoride (TBAF) furnished the α -quaternary substituted acyclic aryl ketone **4a** in 77% yield, albeit with modest regioselectivity (Table 1, entry

Table 1. Optimization of the Rhodium-Catalyzed Allylic Substitution Using the Cyanohydrin **2a (Y = Ph)^a**



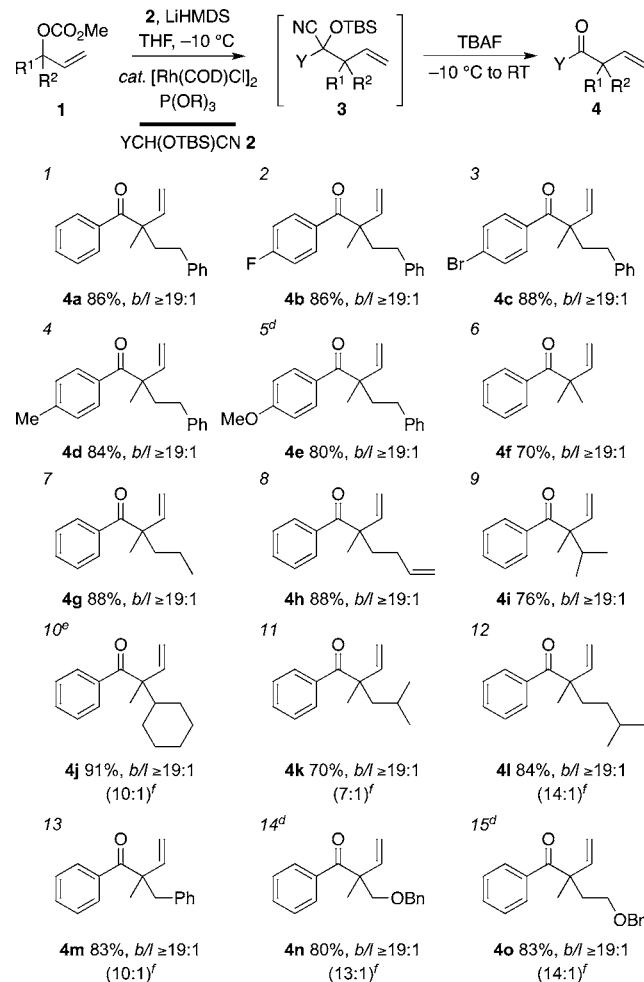
entry	phosphite L	L:M	temp (°C)	b/l for 3a ^b	yield of 4a (%) ^c
1	P(OPh) ₃	4:1	21	5:1	77
2	P(OPh) ₃	3:1	21	7:1	82
3	P(OPh) ₃	2:1	21	7:1	82
4	P(OMe) ₃	2:1	21	4:1	78
5	P(OCH ₂ CF ₃) ₃	2:1	21	6:1	82
6	P(OTBS) ₃	2:1	21	10:1	54
7	P(O-2,4-di ^t BuC ₆ H ₃) ₃	2:1	21	11:1	84
8	P(O-2,4-di ^t BuC ₆ H ₃) ₃	2:1	0	17:1	82
9	P(O-2,4-di ^t BuC ₆ H ₃) ₃	2:1	-10	≥19:1	93

^aAll reactions were performed on a 0.5 mmol reaction scale using 2.5 mol % [Rh(COD)Cl]₂, 1.3 equiv of **2a**, and 1.8 equiv of LiHMDS in THF for ca. 16 h, which was followed by the addition of 2.5 equiv of TBAF at room temperature. ^bRegioselectivity was determined by 500 MHz ¹H NMR analysis of the crude reaction mixtures before deprotection of the cyanohydrin adduct **3a**, which is obtained as a 1:1 mixture of diastereoisomers. ^cGC yields of **4a**.

1).¹⁹ Although prior studies demonstrated that the ligand stoichiometry was an important factor for improving selectivity, a reduction in ligand stoichiometry provided only a modest improvement in the formation of the branched isomer (entries 2 and 3).²⁰ A particularly attractive feature of the rhodium-catalyzed allylic substitution is the ability to readily modify the stereoelectronics of the phosphite ligand, which allows ligands to be readily interchanged without having to prepare a new precatalyst. In this context, modifying the phosphite led to further improvement in the branched selectivity (entries 4–7), wherein the bulky phosphites provide optimal selectivity (entry 6 and 7). Although the bulky tris(*tert*-butyldimethylsilyl)-phosphite and tris(2,4-di-*tert*-butylphenyl)phosphite ligands provided similar levels of regioselectivity, the latter provides a more efficient process. Finally, the selectivity could be further improved by lowering the temperature to -10 °C (entries 8 and 9), which afforded the acyclic ketone **4a** in 93% yield and with ≥19:1 regioselectivity.

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 9) to a range of racemic tertiary allylic carbonates and aryl cyanohydrin derivatives. The alkylation is clearly tolerant of a range of electron-poor and electron-rich aryl cyanohydrins (entries 1–5). Additionally, the allylic carbonate provides access to an array of substituents, some of which would prove extremely challenging for conventional alkylation reactions. For instance, simple alkyl and alkenyl groups afford the acyclic ketones **4** in good to excellent yield with exquisite selectivity for the branched isomer

Table 2. Scope of the Rhodium-Catalyzed Allylic Substitution Using the Cyanohydrin **2^{a,b,c}**

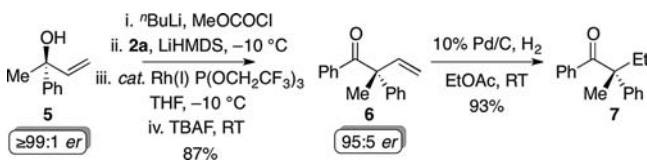


^aAll reactions were performed on a 0.5 mmol reaction scale using 2.5 mol % [Rh(COD)Cl]₂, 10 mol % P(O-2,4-di-^tBuC₆H₃)₃, 1.3 equiv of **2**, and 1.8 equiv of LiHMDS in THF (5 mL) at -10 °C for ca. 16 h, followed by the addition of 2.5 equiv of TBAF at room temperature. ^bRegioselectivity was determined by 500 MHz ¹H NMR analysis of the isolated aryl ketones **4**. ^cIsolated yields. ^dP(OTBS)₃ was used. ^eP(OPh)₃ was used. ^fCrude selectivity on the cyanohydrin adduct **3**.

(entries 6–8). The ability to directly install *gem*-dimethyl groups is particularly attractive, since this can often be quite challenging for conventional alkylation reactions. Nevertheless, the most impressive feature, as noted above, is the ability to introduce branched and functionalized alkyl groups (entries 9–15), which are notoriously challenging electrophiles in conventional enolate alkylation reactions. Although these substrates sometimes afford slightly reduced selectivity, the ability to tailor the phosphite to improve reactivity and selectivity makes this a particularly attractive process. Additionally, the introduction of a simple vinyl group provides an extremely useful functional handle. Overall, this work provides a versatile alternative to conventional enolate alkylation, which is likely to provide a convenient disconnection for an array of synthetic applications.

In order to showcase the synthetic utility of this transformation, we elected to examine the stereospecific version (Scheme 2). Although the alkylation of chiral nonracemic secondary carbonates is well established for a range of stabilized

Scheme 2. Stereospecific Allylic Substitution through a Double Inversion Process Using a Stabilized Cyanohydrin Pronucleophile



and unstabilized nucleophiles, the tertiary variants are potentially more challenging.²¹ We envisioned that this process would also proceed through an electronically biased configurationally stable *enyl* intermediate in accord with our previous studies, to facilitate the alkylation with overall retention of configuration.¹⁵ Although enantiomerically pure tertiary allylic alcohol derivatives were historically challenging intermediates, a number of new methods have recently emerged for their construction. For example, the enantiomerically enriched tertiary allylic alcohol **5** was readily prepared using the method reported by Aggarwal and co-workers.²²

Interestingly, the conversion of the alcohol **5** to the corresponding allylic carbonate resulted in significant rearrangement to the achiral linear allylic carbonate. Although this problem could be readily circumvented by *in situ* acylation and subsequent allylic alkylation,²³ the optimal reaction conditions furnished the acyclic ketone **6** with poor stereospecificity, which prompted the re-examination of the other phosphite ligands. Gratifyingly, the electron-poor tris(2,2,2-trifluoroethyl)-phosphite proved optimal in terms of both regio- and stereospecificity, affording the acyclic ketone **6** in 87% yield and with 91% conservation of enantiomeric excess (*b/l* ≥ 19:1, 95:5 *er*). Although the chirality transfer is slightly lower than that obtained with secondary derivatives, this reaction provides proof-of-concept for this novel process. Additionally, the absolute configuration of the major enantiomer was determined by hydrogenation of the terminal alkene, to provide a compound of known absolute configuration, thereby confirming that the process proceeds with overall retention.²⁴

In conclusion, we have developed the first regio- and stereospecific metal-catalyzed allylic alkylation of tertiary allylic carbonates with a trialkylsilyl-protected cyanohydrin pronucleophile. This process provides a direct and operationally simple method for the construction of α -quaternary substituted ketones, and thereby circumvents the inherent problems associated with conventional enolate alkylation reactions. Moreover, it provides broad substrate scope by facilitating the introduction of branched and functionalized alkyl groups, which are generally very challenging electrophiles for conventional enolate alkylation reactions. The application of this methodology to the preparation of the enantiomerically enriched α -quaternary substituted acyclic ketone is particularly significant since it represents the first stereospecific rhodium-catalyzed allylic alkylation of a chiral nonracemic tertiary allylic carbonate. Future studies will focus on further development of this important transformation, since we anticipate that this will be applied to the preparation of complex bioactive biologically important agents that contain quaternary carbon stereogenic centers.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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