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Enantioselective Rhodium-Catalyzed Allylic Substitution with a Nitrile Anion: Construction of Acyclic Quaternary Carbon Stereogenic Centers

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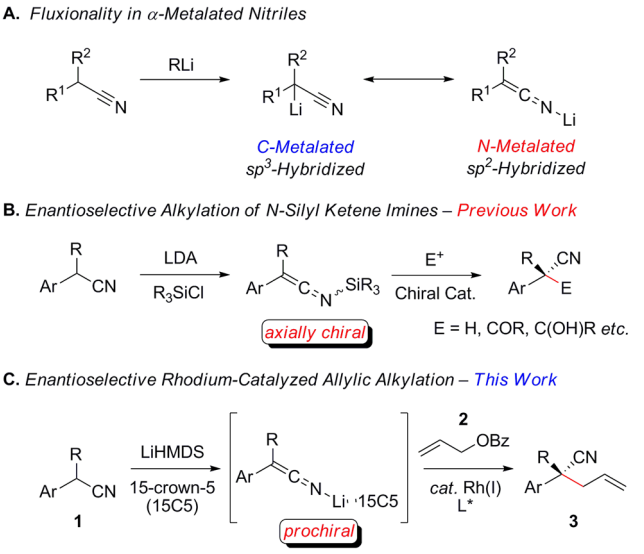
Supporting Information

ABSTRACT: A direct and highly enantioselective rhodium-catalyzed allylic alkylation of allyl benzoate with α-substituted benzyl nitrile pronucleophiles is described. This simple protocol provides a new approach toward the synthesis of acyclic quaternary carbon stereogenic centers and provides the first example of the direct asymmetric alkylation of a nitrile anion. The synthetic utility of the nitrile products is amply demonstrated through conversion to various functional groups and the synthesis of a bioactive aryl piperazine in an expeditious four-step sequence.

The enantioselective construction of quaternary carbon stereogenic centers, particularly in acyclic systems, remains one of the most significant challenges facing modern synthetic chemistry.[1,2] Although the catalytic asymmetric alkylation using classical activating groups, namely ketones, aldehydes, esters, and amides[3,4] has been described, the analogous process with a nitrile anion has not been forthcoming.[5] Despite the inherent versatility of these anions, the fluxional nature of the α-metalated nitrile, due to the interconversion between the *C*- and *N*-metalated forms, makes the development of the asymmetric process particularly challenging (Scheme 1A).[6] Consequently, several elegant methods have been developed centered around the electrophilic "trapping" of the *N*-metalated form using silicon to form axially chiral *N*-silyl ketene imines (SKIs)[7] that are able to undergo asymmetric acylation[8a] and aldol-type[8b−d] addition reactions *via* a dynamic kinetic asymmetric transformation (DYKAT) (Scheme 1B).[9] Nevertheless, the direct asymmetric alkylation of an α-metalated nitrile would clearly be advantageous. Although the diastereoselective alkylation[10] and enantiospecific acylation[11] of such anions has been reported, the enantioselective variant has so far proven elusive.[12]

In a program directed toward the development of rhodium-catalyzed allylic substitution reactions,[13−15] we recently disclosed the direct and enantioselective allylic alkylation of prochiral α-alkoxy ketone enolates with allyl benzoate utilizing the complex derived from Wilkinson's catalyst and a chiral monodentate phosphite.[16] We envisaged that a similar strategy could facilitate the asymmetric alkylation of α-substituted benzyl nitrile anions to construct challenging quaternary carbon stereogenic centers. Central to this strategy would be the ability to control the aforementioned equilibrium between the *C*- and *N*-metalated derivatives. Interestingly, density functional theory

Scheme 1. Factors Affecting the Development of the Enantioselective Rhodium-Catalyzed Allylic Alkylation with a Nitrile Anion



(DFT)[17] and X-ray crystallography[18] indicates that lithiated phenylacetonitrile, solvated with a crown ether, stabilizes the *N*-metalated resonance structure to provide a prochiral nucleophile that we envisioned would promote the asymmetric alkylation by π-facial discrimination.[19] Herein, we now describe the first direct and highly enantioselective metal-catalyzed allylic alkylation of the benzyl nitrile pronucleophiles **1** with allyl benzoate (**2**) to afford chiral nonracemic quaternary carbon-substituted nitriles **3** (Scheme 1C).[20]

Table 1 outlines the preliminary studies toward the development of the enantioselective rhodium-catalyzed allylic alkylation with α-substituted benzyl nitrile anions. Treatment of allyl benzoate (**2**) with the lithium salt of the commercially available benzyl nitrile **1a**, in the presence of the chiral complex derived from $RhCl(PPh_3)_3$ and (*R*)-BINOL-MeOP at 0 °C for *ca.* 16 hours furnished the enantioenriched nitrile **3a** in excellent yield and with 46% enantiomeric excess (entry 1). Given the encouraging efficiency and selectivity, we elected to examine the effect of temperature on the enantioselectivity, which we envisioned may impact the fluxionality of the nitrile

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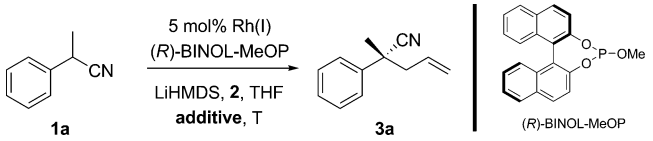
Table 1. Optimization of the Rhodium-Catalyzed Allylic Substitution Using the Benzyl Nitrile 1a[a]



1a 3a

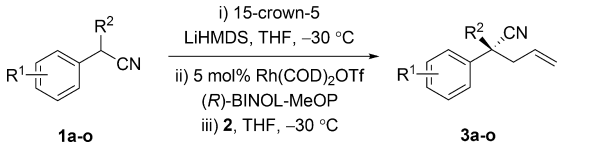
entry	rhodium precatalyst	T (°C)	additive	yield of **3a** (%)[b]	ee (%)[c]
1	$RhCl(PPh_3)_3$	0	–	89	46
2	"	−10	–	90	52
3	"	−30	–	88	72
4	"	−50	–	89	70
5	"	−30	HMPA[d]	89	78
6	"	"	DMPU[d]	92	74
7	"	"	15-crown-5[e]	87	84
8[f]	"	"	"	90	88
9[f]	***Rh(COD)$_2$OTf***	***−30***	***15-crown-5***[e]	***88 (86)***[g]	***92***

[a]All reactions were performed on a 0.25 mmol reaction scale using 5 mol % Rh(I), 20 mol % (*R*)-BINOL-MeOP, 1.3 equiv **1a**, and 1.2 equiv LiHMDS in THF (0.1 M) for *ca.* 16 h. [b]GC yields of **3a**. [c]Enantiomeric excess was determined by chiral GC on the crude reaction mixtures. [d]9:1 ratio of THF/additive. [e]1.2 equiv of 15-crown-5. [f]Reaction conducted at 0.05 M in THF. [g]Isolated yield.

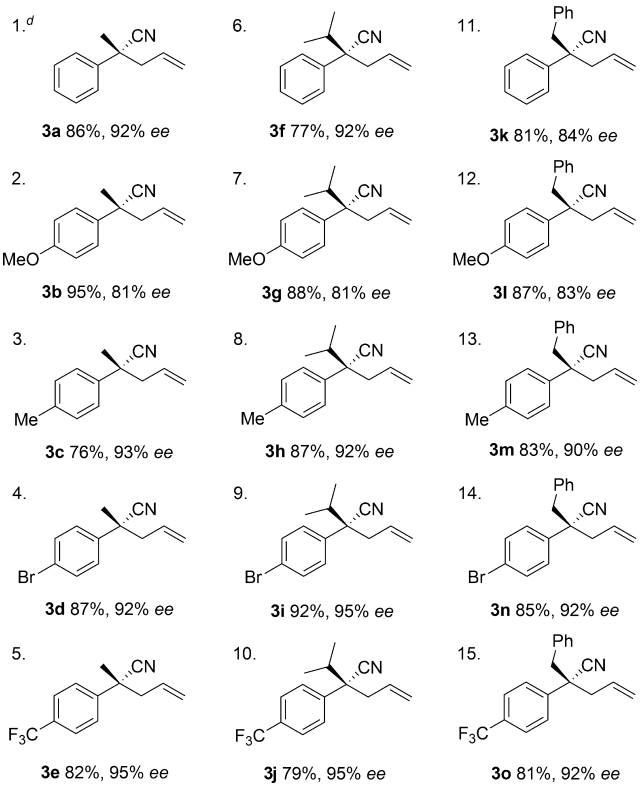
anion. Although reducing the temperature from 0 to −30 °C improved the asymmetric induction, affording **3a** in 88% yield and with 72% enantiomeric excess (entries 2 and 3), further reduction in the reaction temperature did not provide additional benefit (entry 4). Nevertheless, it is interesting to note that temperature did not impact the overall yield of the reaction, which can presumably be attributed to the high reactivity of the α-metalated nitrile **1a** with the unsubstituted rhodium-allyl intermediate derived from allyl benzoate (**2**). In accord with our hypothesis that the use of deaggregating agents may affect the equilibrium between *C*- and *N*-metalated forms, HMPA or DMPU led to modest improvement in enantioselectivity (entries 5 and 6), whereas 15-crown-5 provided a significant improvement in the selectivity, furnishing **3a** in 87% yield and with 84% enantiomeric excess (entry 7). Further optimization examined the effect of concentration and the nature of the rhodium(I) precatalyst. Although reducing the concentration from 0.1 to 0.05 M provided a small improvement in selectivity (entry 8), switching to the cationic rhodium(I) precatalyst afforded the nitrile **3a** in 86% isolated yield and with 92% enantiomeric excess (entry 9).

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 9) to a number of α-alkyl benzyl nitriles. Gratifyingly, the reaction is tolerant of a range of electron-withdrawing and electron-donating aryl substituents, albeit the strongly electron-donating *p*-methoxy derivative gave lower enantioselectivity (entries 1−5). This is in stark contrast to our previous work with α-alkoxy ketone enolates, wherein the strongly electron-withdrawing *p*-trifluoromethyl substituent gave the lowest enantiomeric excess. Nevertheless, the ability to introduce different alkyl substituents at the benzylic position provides significant flexibility with this approach. For instance, the isopropyl group proceeded with comparable selectivity (entries 6−10), and offered an efficient approach to more challenging quaternary carbon centers. Alternatively, a benzyl substituent also provides a competent substrate, albeit with slightly lower selectivity in this case (entry 11 *vs* entries 1 and 6). Nevertheless, the substituted phenyl derivatives afforded

Table 2. Scope of the Enantioselective Rhodium-Catalyzed Allylic Substitution[a,b,c]



1a-o 3a-o



[a]All reactions were performed on a 0.25 mmol reaction scale using 5 mol % Rh(COD)$_2$OTf, 20 mol % (*R*)-BINOL-MeOP, 1.3 equiv **1**, 1.2 equiv LiHMDS, and 1.2 equiv 15-crown-5 in THF (5.0 mL) at −30 °C for *ca.* 16 h. [b]Isolated yields. [c]Enantiomeric excess was determined by chiral GC or HPLC analysis on the purified products and derivatives. [d]79% yield and 91% ee on a 10 mmol (1.7 g) scale.

analogous results to the methyl and isopropyl examples (entries 12−15). Finally, the ability to conduct the reaction on gram-scale, with comparable efficiency and selectivity, highlights the applicability of this method to large-scale synthesis. *Overall, this work provides the first example of an asymmetric alkylation of a nitrile anion to prepare acyclic quaternary carbon stereogenic centers, which should permit the expedient construction of this motif in target directed synthesis applications.*

Scheme 2 illustrates the inherent utility of the nitrile products, which can be readily converted to a number of important derivatives in a selective and efficient manner. For instance, DIBAL-H reduction of the enantioenriched nitrile **3a** furnished the aldehyde **4** in excellent yield and with complete retention of stereochemistry. Similarly, reduction of the nitrile to the primary amine **5** was accomplished with lithium aluminum hydride. Alternatively, the addition of methyllithium to **3a**, followed by hydrolysis of the intermediate imine, furnished the methyl ketone **6** in good yield. Finally, hydrolysis of the nitrile to the corresponding amide **7** using hydrogen peroxide under basic conditions, proceeded in excellent yield and conservation of enantiomeric excess. Gratifyingly, the

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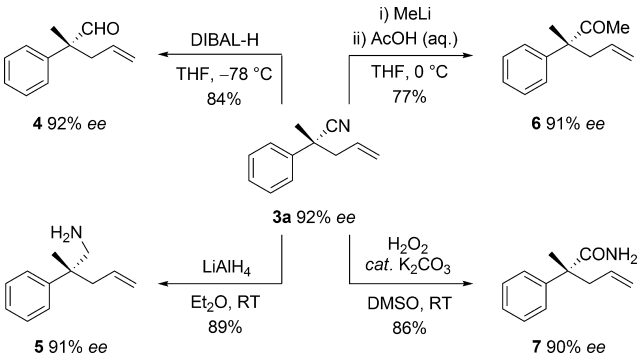
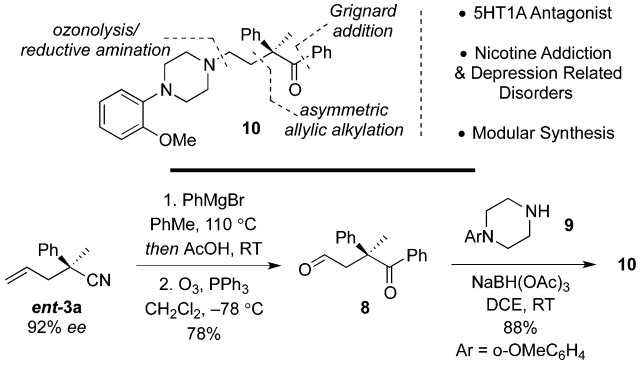
Scheme 2. Transformations of Enantioenriched Nitrile 3a



nitrile was converted to an array of useful functionality with complete retention of stereochemistry, thereby illustrating the potential utility of this process for synthetic applications.

To further highlight the suitability of this methodology for target directed synthesis and to establish the absolute configuration of the products, the serotonin antagonist **10** was prepared (Scheme 3). Interestingly, this agent is a member of a family of synthetic aryl piperazines that are selective antagonists of the 5-HT1A receptor and have been touted as possible treatments for smoking cessation and depression related disorders.[21] Hence, the enantioenriched nitrile ***ent*-3a** was prepared under the standard reaction conditions from 1-phenylacetonitrile **1a** in 83% yield, albeit using the (*S*)-BINOL-MeOP. Treatment of the nitrile ***ent*-3a** with phenyl Grignard followed by acid hydrolysis gave the phenyl ketone, which was subjected to ozonolysis to afford the aldehyde **8** in 78% overall yield. Reductive amination of the aldehyde **8** with the commercially available aryl piperazine **9** gave **10** in 88% yield, which allowed the absolute configuration of the asymmetric alkylation to be determined.[22a] Overall, the four-step sequence from 1-phenylacetonitrile afforded the serotonin antagonist **10** in 57% yield, thereby providing the most efficient route to this target reported to date.[22]

Scheme 3. Enantioselective Synthesis of Bioactive Phenyl Piperazine 10



In conclusion, we have developed the direct and highly enantioselective rhodium-catalyzed allylic alkylation of α-substituted benzyl nitrile anions with allyl benzoate (**2**). This process provides the first example of a direct, enantioselective alkylation of a nitrile anion, which is driven by the ability to control the *C*- versus *N*-metalated equilibrium with a crown ether. We anticipate that this finding will be critical for the further development of asymmetric nitrile anion alkylation reactions. Furthermore, we demonstrate the synthetic utility of the nitrile products through functional group interconversion to a number of important motifs and in the concise and efficient synthesis of a serotonin antagonist. Hence, given the ubiquity of the nitrile pharmacophore in medicinal chemistry[23] and their utility as synthetic intermediates, we envisage that this work will be of significant interest to the broader community.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and spectra for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02810.

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Notes

The authors declare no competing financial interest.

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