Akzeptierter Artikel

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Enantioselective Rhodium-Catalyzed Allylic Alkylation of β,γ -Unsaturated α -Amino Nitriles: Synthetic Homoenolate Equivalents

Timothy B. Wright, Ben W. H. Turnbull and P. Andrew Evans*

Abstract: An enantioselective rhodium-catalyzed allylic alkylation of β,γ -unsaturated α -amino nitriles is described. This protocol provides a novel approach for the construction of β -stereogenic carbonyl derivatives *via* the catalytic asymmetric alkylation of a homoenolate equivalent. The particularly challenging nature of this transformation is highlighted by the fact that *three* modes of selectivity must be manipulated, namely regio- and enantioselectivity, in addition to geometrical control. The γ -stereogenic cyanoenamine products can be readily hydrolyzed *in situ* to afford the β -substituted carboxylic acids, which in turn provide expedient access to a number of related carbonyl derivatives. In addition, control experiments indicate that the chiral rhodium-allyl intermediate facilitates the selective formation of the *E*-cyanoenamine products, which is critical since the *Z*-isomer affords significantly lower enantiocontrol. As a consequence, garnering excellent *E*-selectivity in the alkylation step is vital for the development of a practical process.

Polarity reversal of a conventional functional group often provides a strategic advantage in synthesis, which can circumvent the inherent limitations associated with a more traditional bond-forming reaction.^[1] For instance, heteroatom-stabilized allylic anions constitute useful homoenolate synthons for the construction of β -substituted carbonyl compounds.^[2] Nevertheless, the utility of these masked homoenolate equivalents is complicated by their ambident nature, which often leads to the formation of regioisomeric products (Scheme 1A).^[3,4] Notwithstanding this limitation, the asymmetric functionalization of allylic amines, carbamates and α -amino nitriles has been successfully described, albeit these approaches employ a chiral auxiliary^[5] or require a stoichiometric chiral base^[6,7] to promote the formation of a chiral nonracemic lithium carbanion (Scheme 1B).^[8] We envisioned the development of an enantioselective transition metal-catalyzed variant, in which a heteroatom-stabilized allylic anion with a simple allyl electrophile would constitute an attractive approach to the asymmetric construction of β -stereogenic carbonyl derivatives. Although there have been several elegant advances in the development of asymmetric transition metal-catalyzed allyl-allyl cross-coupling reactions using achiral allyl nucleophiles (Scheme 1C),^[9] the analogous process with a heteroatom-stabilized allylic anion has not been forthcoming. Furthermore, in contrast to the aforementioned allyl-allyl cross-coupling methods, which involve the enantioselective allylation of either prochiral or racemic electrophiles, our strategy would

Scheme 1. Factors affecting the development of the asymmetric alkylation of β,γ -unsaturated α -amino nitriles.

employ an achiral allyl alcohol derivative in accord with our earlier efforts with more conventional pronucleophiles. For instance, we recently reported the enantioselective rhodium-catalyzed allylic alkylation reactions of prochiral ketones, nitriles and aldehydes.^[10–13] Nevertheless, the adaptation of this approach to encompass a homoenolate equivalent^[14] is significantly more challenging based on the fact that this process requires the coordination of three distinct modes of selectivity, namely, the regio- and enantioselectivity in conjunction with geometrical control. Herein, we now describe the first highly enantioselective rhodium-catalyzed allylic alkylation of β,γ -unsaturated α -amino nitriles, which serve as synthetic homoenolate equivalents for the construction of β -stereogenic carboxylic acid derivatives (Scheme 1D). In this regard, this study delineates the importance of allylic anion geometry on the level of enantioselectivity in the rhodium-catalyzed process (*vide infra*).

Preliminary studies focused on the rhodium-catalyzed alkylation of the allylic α -amino nitrile **1a'** ($R = \text{Me}$), which is readily prepared *via* a one-pot Strecker reaction of cinnamaldehyde and *N*-methylaniline in the presence of trimethylsilyl cyanide. Treatment of the lithium anion of **1a'** with allyl acetate (**2**) in the presence of the chiral complex derived from Wilkinson's catalyst and (*R*)-BINOL-POMe^[15] at -10°C in tetrahydrofuran (THF), led to the exclusive formation of the γ -alkylation product as predominantly the *E*-isomer (Table 1, entry 1). Interestingly, while

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Table 1. Optimization of the enantioselective rhodium-catalyzed allylation of β,γ -unsaturated α -amino nitriles^[a]

entry	1, R =	solvent	T (°C)	selectivity ^[b]		yield (%) ^[c]	ee (%) ^[d]
				3:4	E:Z (3)		
1	Me (a')	THF	-10	≥19:1	83:17	71	87 ^[e]
2	"	DMF	"	≥19:1	39:61	30	76 ^[e]
3	"	DME	"	2:1	92:8	49	95 ^[e]
4	Ph (a'')	"	"	6:1	91:9 ^[f]	63	88
5	Et (a)	"	"	5:1	94:6	68	94
6	"	"	0	9:1	95:5	76	94
7 ^[g]	"	DME/THF	0	≥19:1	95:5	81	89
8 ^[h]	Et (a)	DME/THF	0	≥19:1	95:5	81	93

[a] All reactions were performed on a 0.25 mmol scale using 10 mol% RhCl(PPh₃)₃, 40 mol% (R)-BINOL-POMe, 1.7 equiv **1** and 1.6 equiv of LiHMDS in solvent (5 mL) for ca. 16 h. [b] Regioselectivity was determined by 500 MHz ¹H NMR analysis of the crude reaction mixture; E/Z selectivity was determined by GC analysis of the crude reaction mixture. [c] Isolated yield of (E)-**3**. [d] Determined by HPLC analysis of (E)-**3**. [e] HPLC analysis of (Z)-**3** showed low ee (20–25%). [f] Determined by 500 MHz ¹H NMR analysis. [g] DME/THF (1:1). [h] DME/THF (4:1).

the major geometrical isomer (E)-**3a'** was isolated with 87% enantiomeric excess, the minor derivative (Z)-**3a'** was formed with significantly lower enantioselectivity (20–25% ee), thereby indicating that the geometrical selectivity in the alkylation is *critical* for garnering useful selectivity (*vide infra*). In an effort to determine the impact of various reaction parameters on selectivity, we elected to initially investigate the effect of solvent. To this end, *N,N*-dimethylformamide (DMF) afforded poor geometrical selectivity favoring the Z-isomer, whereas 1,2-dimethoxyethane (DME) provided excellent geometrical and enantiocontrol for the formation of (E)-**3a'**, albeit significantly reduced regioselectivity (entries 2 vs 3). Encouraged by this result, we hypothesized that increased steric bulk on the α -amino substituent may disfavor α -alkylation, in which the more bulky α -amino nitrile **1a''** (R = Ph) provided slightly increases regioselectivity, albeit with lower enantioselectivity (entry 4). Gratifyingly, the ethyl substituted α -amino nitrile **1a** (R = Et) provided a similar improvement in regioselectivity in addition to slightly higher geometrical and enantiocontrol (entry 5). Further studies demonstrated that increasing the temperature to 0 °C offered a slight increase in the propensity for γ -alkylation (entry 6). Finally, given the excellent regiocontrol observed in THF, we envisioned that a mixed solvent system may provide the ideal combination to afford a highly efficient and selective process. Gratifyingly, a DME/THF (4:1) solvent mixture offered exquisite levels of regio- and enantioselectivity, in addition to complete geometrical control, thereby furnishing the cyanoenamine (E)-**3a** in 81% yield and with 93% enantiomeric excess (entry 7).

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 7) to a number of allylic α -amino nitriles with allyl acetate.^[16] The reaction is tolerant of a variety of electron-rich and electron-deficient aryl groups at the γ -position, albeit electron-donating substituents on the aryl ring lead to slightly lower levels of regioselectivity (entries 1–6). Nevertheless, a key and striking feature of this reaction is the exquisite levels of geometrical control and enantioselectivity regardless of the electronic nature of the aryl substituent, which makes this process

Table 2. Scope of the enantioselective rhodium-catalyzed allylation of β,γ -unsaturated α -amino nitriles^[a,b]

entry	1, R =	3, R =	γ:α	E:Z	yield (%)	ee (%)
1.	H	H	≥19:1	95:5	81%	93% ee
2.	OMe	OMe	5:1	95:5	71%	92% ee
3.	Me	Me	5:1	97:3	75%	96% ee
4.	F	F	10:1	96:4	80%	95% ee
5.	Br	Br	≥19:1	≥95:5	82%	95% ee
6.	CF ₃	CF ₃	≥19:1	≥95:5	53%	94% ee
7.	OBn	OBn	11:1	≥95:5	82%	94% ee
8.	OPMB	OPMB	10:1	≥95:5	68%	90% ee
9.	benzofuran	benzofuran	9:1	≥95:5	79%	96% ee
10.	fluorene	fluorene	≥19:1	≥95:5	86%	94% ee
11.	indole	indole	2:1	≥95:5	56%	91% ee
12.	thiophene	thiophene	≥19:1	≥95:5	84%	95% ee
13.	furan	furan	14:1	96:4	80%	95% ee
14.	pyrrole	pyrrole	≥19:1	≥95:5	80%	96% ee
15.	oxazole	oxazole	3:1	96:4	71%	96% ee
16.	H	H	≥19:1	90:10	84%	94% ee
17.	OMe	OMe	≥19:1	91:9	70%	92% ee
18.	F	F	≥19:1	88:12	82%	94% ee

[a] All reactions were performed on a 0.25 mmol scale using 10 mol% RhCl(PPh₃)₃, 40 mol% (R)-BINOL-POMe, 1.7 equiv **1** and 1.6 equiv of LiHMDS in DME/THF (5 mL) at 0 °C for ca. 16 h; 5 mol% Rh and 20 mol% L* were used where indicated. [b] Enantiomeric excess was determined by HPLC analysis of isolated (E)-**3a-r**. [c] Reported yields are based on the isolated yield of a single regio- and geometrical isomer. [d] Crude regioselectivity was determined by 500 MHz ¹H NMR analysis; crude E/Z selectivity was determined by GC or NMR analysis. [e] Isolated as a mixture of E/Z isomers.

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amenable to the direct one-pot synthesis of β -stereogenic carboxylic acids (*vide infra*). The reaction is also tolerant of disubstituted aromatic groups, which afford good efficiency and excellent levels of enantiomeric excess (entries 7-9). Additionally, bicyclic aromatic groups as well as nitrogen, sulfur and oxygen based heterocycles can be incorporated with comparable levels of stereocontrol (entries 10-15). Remarkably, γ -vinyl substituted allylic α -amino nitriles **1p-1r** also undergo selective alkylation with excellent levels of regio- and stereocontrol (entries 16-18), thereby extending the scope beyond aryl and heteroaryl groups.^[17] Interestingly, in the aforementioned examples there is no evidence for alkylation at the ε -position, which significantly expands the synthetic utility of this process. Overall, the ability to achieve high levels of regio- and enantioselectivity, in conjunction with exquisite geometrical control, makes the allylation of β,γ -unsaturated α -amino nitriles a powerful method for the asymmetric construction of γ -stereogenic α -cyanoenamines, which offer a myriad of potential synthetic applications.

Scheme 2 highlights the potential utility of the current process in target-directed synthesis. For example, Scheme 2A illustrates the use of reduced catalyst loading in a gram-scale reaction, which furnishes cyanoenamine **3a** with commensurable levels of efficiency and selectivity. Schemes 2B and C demonstrate the efficacy of allylic α -amino nitriles **1** for the enantioselective construction of β -stereogenic carbonyl derivatives. In this regard, the allylation of **1a** followed by *in situ* hydrolysis of the resulting cyanoenamine **3a** furnished the carboxylic acid **5a**^[18] in good yield and with excellent enantioselectivity (Scheme 2A). Moreover, the carboxylic acid can be readily converted to a variety of other β -substituted carbonyl derivatives. For example, treatment with methyllithium affords the methyl ketone **6a** with complete conservation of enantiomeric excess (Scheme 2B). Alternatively, the acid-catalyzed esterification with methanol provides the β -stereogenic methyl hydrocinnamate **7a**, while standard amide-

bond forming conditions furnish the benzyl amide **8a** to further highlight the synthetic utility of this process. The expedient formation of β -stereogenic esters and amides by this method is significant, given the challenges associated with their formation *via* catalytic Michael addition strategies.^[19] For example, there is a paucity of methods available for the direct asymmetric addition of allyl nucleophiles to α,β -unsaturated esters,^[20] and the analogous process with enamides is unknown at present.^[21] Furthermore, the alternative disconnection involving the catalytic 1,4-arylation would require a challenging skipped dienoate or dienamide derivatives as the Michael acceptor.^[22] Overall, the excellent level of enantioselectivity in the one-pot synthesis of **5a**^[23] illustrates the importance of garnering high geometrical control in the catalytic allylation given that (*Z*)-**3a** is formed with significantly lower levels of asymmetric induction (Table 1, entries 1-3). Hence, the inability to control the geometry of **3** would require a tedious separation of the *Z*-isomer in order to access the β -stereogenic acid **5** with high levels of enantiomeric excess.

A. Gram-Scale Allylation of **1a** B. One-Pot Synthesis of β -Stereogenic Carboxylic Acid **5a** C. Further Transformations of Carboxylic Acid **5a**

Scheme 2. (a) Gram-scale allylation of **1a** with reduced catalyst loading; crude regio- and E/Z selectivity reported. (b) One-pot synthesis of β -stereogenic carboxylic acid **5a**. (c) Further transformations of acid **5a**.

A. E/Z Selectivity in the Protonation/Methylation of Lithiated **1a** B. Rhodium-Catalyzed Resolution of Allylic Anions Derived from **1a**

Scheme 3. (a) Geometrical outcome in the protonation and methylation of the lithium anion derived from **1a**. (b) Proposed model for the origin of geometrical control in the rhodium-catalyzed allylation of **1a**.

In order to provide further insight into the role of geometrical selectivity in the rhodium-catalyzed allylic alkylation, we investigated the protonation and methylation of the anion derived from **1a**. The deprotonation of **1a** under the previously optimized conditions (Table 1, entry 7), followed by the addition of either aqueous ammonium chloride solution or methyl iodide resulted in significantly reduced geometrical selectivity compared to the catalytic asymmetric allylic alkylation reaction (Scheme 3). Indeed, the γ -substitution products were formed with poor geometrical selectivity in favor of the *Z*-isomer (Scheme 3A),^[24] which contrasts the excellent geometrical selectivity obtained for (*E*)-**3a** ($E/Z \geq 95:5$) in the rhodium-catalyzed allylic alkylation (Table 2, entry 1). Furthermore, the alkylation with methyl iodide affords the same level of geometrical selectivity ($E/Z = 33:64$) in the presence of the chiral rhodium catalyst, suggesting that the geometry of the allylic anion is not altered in the presence of the metal complex, but the nature of the electrophile.^[25] This data suggests that the deprotonation of **1a** affords a geometrical

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mixture of fluxional allylic anions, wherein the *E*-isomer preferentially reacts with the chiral nonracemic rhodium-allyl intermediate to furnish (*E*)-**3a** (Scheme 3B). Furthermore, the π -facial alkylation of the two geometrical isomers is a critical component to controlling enantioselectivity, which is not immediately evident from the one-pot process, thereby making the isolation of the cyanomenamines **3** an important feature for the development of this process.

In conclusion, we have developed a direct and highly enantioselective rhodium-catalyzed allylic alkylation of β,γ -unsaturated α -amino nitriles, which serve as synthetic homoenolate equivalents. A critical aspect to the development of this methodology is the ability to control the geometrical outcome of the transformation, given that the rhodium-catalyzed allylation of discrete allylic anion isomers does not proceed with uniform enantiocontrol in the formation of *E*- and *Z*-alkylation products. Overall, the ability to govern a highly regio- and enantioselective reaction provides efficient access to γ -stereogenic α -cyanoenamines, which represent potentially interesting synthetic intermediates that will be the subject of future studies. For example, the cyanoenamine adducts are readily hydrolyzed *in situ* to provide a convenient approach to the carboxylic acids that can be readily converted to β -substituted carbonyl derivatives. Finally, in light of the paucity of methods that employ homoenolate nucleophiles in asymmetric transition metal-mediated cross-coupling reactions, we anticipate that this approach will promote the examination of related pronucleophiles.

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Conflict of interest

The authors declare no competing financial interest.

Keywords: allylic substitution • α -amino nitrile • asymmetric catalysis • homoenolate • rhodium-catalyzed

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- [17] Alkyl-substituted allylic α -amino nitriles undergo alkylation with poor regiocontrol. Studies on these systems are the subject of further investigation in our laboratory.

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- [25] Methylation of the anion derived from **1a** in the presence of $\text{RhCl}(\text{PPh}_3)_3$ and (*R*)-BINOL-POMe affords **9a** with the same *E/Z* ratio, which is consistent with two distinct allylic anions reacting at different rates in the rhodium-catalyzed allylation; please see SI for details.

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**Enantioselective Rhodium-Catalyzed
Allylic Alkylation of β,γ -Unsaturated
 α -Amino Nitriles: Synthetic
Homoenolate Equivalents**

We report the first example of a catalytic asymmetric allylic alkylation of β,γ -unsaturated α -amino nitriles, which function as synthetic homoenolate equivalents.