

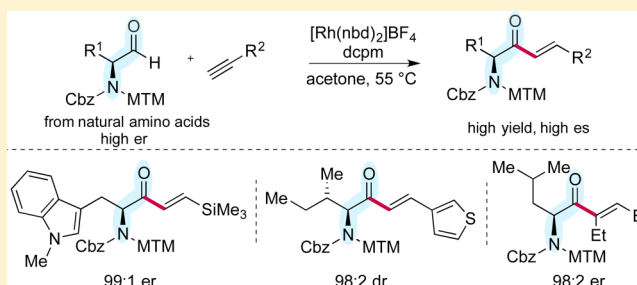
α -Amino Aldehydes as Readily Available Chiral Aldehydes for Rh-Catalyzed Alkyne Hydroacylation

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S Supporting Information

ABSTRACT: Readily available α -amino aldehydes, incorporating a methylthiomethyl (MTM) protecting group on nitrogen, are shown to be efficient substrates in Rh-catalyzed alkyne hydroacylation reactions. The reactions are performed under mild conditions, employing a small-bite-angle bisphosphine ligand, allowing for good functional group tolerance with high stereospecificity. Amino aldehydes derived from glycine, alanine, valine, leucine, phenylalanine, isoleucine, serine, tryptophan, methionine, and cysteine were successfully employed, as was an enantiomerically enriched α -OMTM-aldehyde derived from phenyllactic acid. The synthetic utility of the α -amino enone products is demonstrated in a short enantioselective synthesis of the natural product sphingosine.



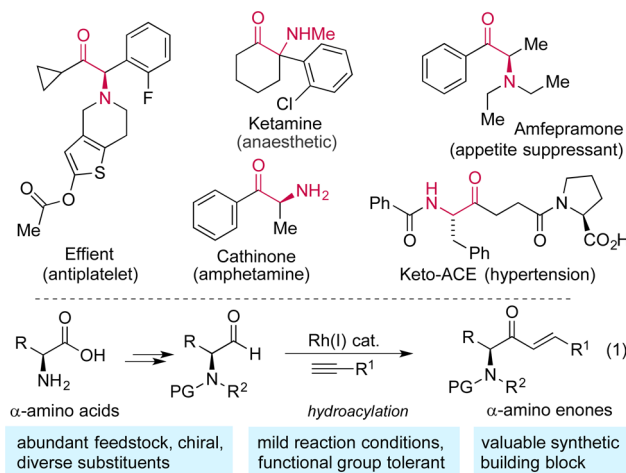
INTRODUCTION

Alkene and alkyne hydroacylation reactions represent powerful methods for the preparation of ketones and enones, respectively.¹ These processes offer an atom economical and, in many cases, highly efficient method for the construction of carbon–carbon bonds using a variety of transition-metal and also nonmetal catalysts.² Reactions that achieve high levels of regio- and enantioselectivity have been developed,^{3,4} and applications to target synthesis are being reported.⁵

Despite the advent of a number of non-chelation-controlled hydroacylation processes,^{6–9} the subclass of intermolecular hydroacylation (HA) reactions that has enjoyed the most success is that based on some form of substrate chelation, be it originating from the aldehyde^{10–14} or alkene or alkyne.¹⁵ A consequence of such a strategy is that the coordinating group needed to achieve the desired reactivity and selectivity is necessarily present in both the substrate and the product. Methods that utilize the coordinating group directly in a subsequent transformation, resulting in “traceless” processes, go some way to addressing these limitations.¹⁶ However, a more attractive scenario would be one in which the coordinating group was a simple, useful substituent the presence of which would be desired in the final product. In this context, the ability to exploit a simple amino group would be appealing. Although aniline-derived benzaldehyde-type substrates have recently been reported as effective substrates for intermolecular HA reactions, by both us^{17a} and others,^{17b} these substrates by their nature are limited to aromatic examples. Alkyl aldehydes featuring amino-substituents are notable by their absence in the HA literature, presumably a consequence of their strong coordinating ability and basic character. Conversely, these are precisely the properties that result in amino groups being so prevalent in bioactive molecules.¹⁸

The α -amino carbonyl motif is present in a number of medicinal agents and natural products (Scheme 1)¹⁹ and features in intermediates for the synthesis of heterocycles and, in particular, enantiomerically enriched amino alcohols.²⁰ To target these important structures, we were attracted to the use of naturally occurring α -amino acids as a readily available feedstock for chiral amino aldehydes to use in HA reactions (eq 1, Scheme 1). Although enantioselective HA reactions have

Scheme 1. The α -Amino Ketone Motif in Biologically Relevant Molecules, Together with a Rh-Catalyzed Hydroacylation Route Exploiting Amino Acids To Access α -Amino Enones (eq 1)



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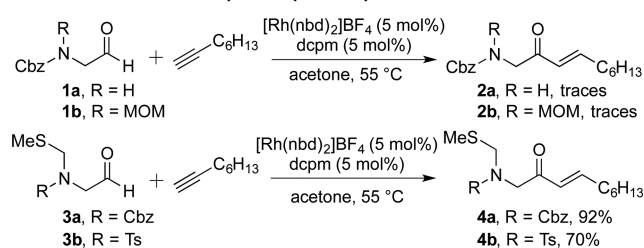
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been reported,⁴ examples of enantioenriched aldehydes being employed as substrates in intermolecular reactions are scarce.^{15a,21} Given the mild reaction conditions employed with our recently reported, highly active small-bite-angle catalysts,²² we were confident that we should be able to maintain the enantiomeric purity of such aldehydes in HA reactions. In this paper we show that it is possible to utilize α -amino-substituted alkyl aldehydes in HA reactions and describe the application of chiral α -amino aldehydes as effective substrates for the synthesis of synthetically appealing chiral α -amino enones.

RESULTS AND DISCUSSION

We have previously shown that nonchiral α -hydroxy aldehydes could be effectively employed in HA reactions provided that the alcohol was protected as a methylthiomethyl (MTM) ether.²³ We postulated that the corresponding MTM-protected amino aldehydes should also be viable HA substrates, with the MTM group functioning as a simple, removable, chelating substituent. Using a glycine derivative, we quickly established that both a MTM group and an electron-withdrawing protecting group were necessary to achieve reactivity (Scheme 2). For example,

Scheme 2. Initial Evaluation of Glycine-Derived Aldehydes 1a,b and 3a,b in Alkyne Hydroacylation



aldehyde **1a**, featuring only a Cbz protecting group on the amine, was essentially inert in a reaction with 1-octyne and a Rh(I)/dcpm catalyst, delivering only trace quantities of the desired HA adduct (**2a**). Aldehyde **1b**, combining a Cbz group with a MOM group on the N atom, was similarly unreactive. For both of these substrates the majority of the starting aldehydes were recovered, suggesting that reductive decarbonylation generates a nonactive Rh-complex. However, aldehydes **3a** and **3b**, featuring a MTM group and either a Cbz or Ts group, respectively, delivered the desired enones (**4a,b**) in good yields. We attribute the success of the MTM-bearing aldehydes to the S-atom both directing the Rh-complex to the aldehyde C–H bond for rapid oxidative addition and also stabilizing the resultant acyl rhodium hydride intermediate toward reductive decarbonylation.^{22a,b} The corresponding aldehyde bearing only a MTM group, but without an accompanying electron-withdrawing group, was unstable and could not be isolated in pure form.

With the key reactivity principle in place, we next explored the scope of the alkyne component in combination with aldehyde **3a** (Table 1). In all cases, a catalyst generated from the combination of $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ and the bis-phosphine ligand dcpm was employed. Both linear and branched aliphatic alkynes (entries 1–3) as well as carbocyclic alkynes (entries 4 and 5) could be employed. Aromatic alkynes, including a 3-thiophene example, were excellent substrates (entries 6–8), giving the enone products in high yields. The exceptional functional group tolerance of this reaction was demonstrated

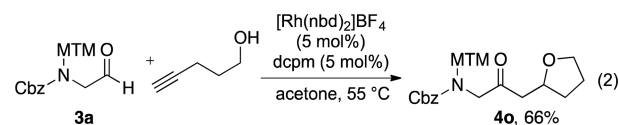
Table 1. Alkyne Scope in Hydroacylation Reactions with Aldehyde 3a^a

entry	alkyne	yield	entry	alkyne	yield
1		94%	7		99%
2		73%	8		76%
3		80%	9		93%
4		87%	10		75%
5		75%	11		86%
6		99%	12		71%

^aReaction conditions: **3a** (1.0 equiv), alkyne (1.5 equiv), $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ (5 mol %), dcpm (5 mol %), acetone, 55 °C.

through the use of ferrocenyl (entry 9), enyne (entry 10), alkyl iodide (entry 11), and unprotected alcohol (entry 12) substrates, all giving the corresponding products in good yields.

The reaction between glycine-derived aldehyde **3a** and 5-pentynol proceeded smoothly; however, the product isolated was tetrahydrofuran-substituted ketone **4o**, resulting from intramolecular conjugate addition of the hydroxyl group into the initially formed enone (eq 2).



Having established mild and effective conditions for alkyne hydroacylation using MTM-protected amino aldehydes, we next focused on access to enantiomerically pure substrates. Initial attempts to MTM-protect Cbz-leucine methyl ester resulted in racemization (Scheme 3). However, by switching to the Weinreb amide substrate **5a**, the MTM-protected product (**6a**) could be prepared in excellent yield and, following reduction with Dibal-H, delivered the aldehyde **7a** in 99% yield with an excellent >99:1 enantiomeric ratio. This method was then applied to a variety of amino acid substrates. The aldehydes prepared were typically used without purification, although all of the aldehydes obtained were assayed (HPLC) for enantiopurity and were shown to possess enantiomeric ratios of at least 98:2. The phenylalanine-derived aldehyde (**7f**) was found to be less chemically stable than the other aldehydes and also to be more labile to racemization; however, with care, an er of 99:1 could be achieved.

With a simple and robust synthesis of MTM-protected α -amino aldehydes established, we next examined the use of these molecules in hydroacylation reactions with various alkynes (Table 2). Starting from leucine, the Cbz-, Teoc-, and Boc-

5a $\xrightarrow[\text{DMF}]{\text{NaHMDS, MTM-Cl, NaI}}$ 6a (50:50 er) $\xrightarrow[\text{-78 } ^\circ\text{C, 99\%}]{\text{Dibal-H, toluene}}$ 7a, >99:1 er

7b, >99:1 er 7c, >99:1 er 7d, >99:1 er 7e, >99:1 er
 7f, 99:1 er 7g, 98:2 dr 7h, >99:1 er

In addition to employing amino aldehyde substrates bearing a MTM group, we were also able to exploit the chelating ability of S-methylcysteine and methionine-derived aldehydes, **9** and **10**, respectively (Scheme 4). In both cases, hydroacylation of the MTM-free aldehydes was achieved using the dcpm-derived catalyst in combination with 1-octyne. The methionine-derived substrate required a higher catalyst loading (10 mol %). This reduced reactivity is consistent with our previous report of aliphatic γ -substituted thiomethyl aldehydes and again suggests that the MTM-bearing substrates benefit from a conformational arrangement that promotes chelation.²³ Following on from this, the MTM-protected α -hydroxy aldehyde **11**, derived from phenyllactic acid, delivered the hydroacylation adduct **14** in excellent yield as a single enantiomer.

Reaction scheme showing the synthesis of chiral α,β-unsaturated ketones **8a-n** from chiral amide **7** and alkynes **R²-C≡C-R³** using [Rh(nbd)₂]BF₄ (5 mol%) and dcpm (5 mol%) in acetone at 55 °C for 3 h.

General reaction:

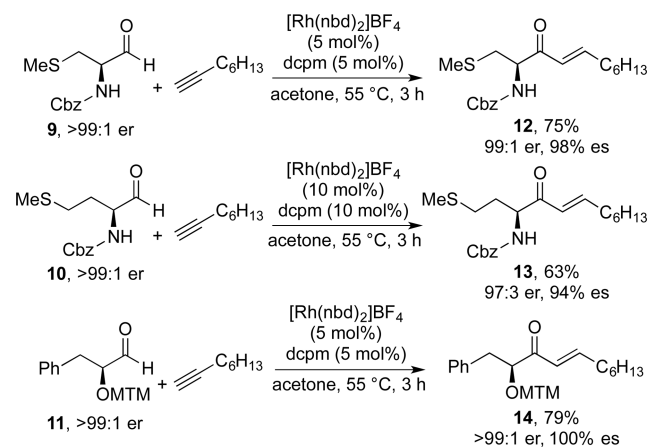
$$\text{PG}-\text{N}(\text{R}^1)-\text{C}(=\text{O})\text{H} + \text{R}^2-\text{C}\equiv\text{C}-\text{R}^3 \xrightarrow[\text{acetone, 55 } ^\circ\text{C, 3 h}]{[\text{Rh}(\text{nbd})_2]\text{BF}_4 (5 \text{ mol\%}), \text{dcpm} (5 \text{ mol\%})} \text{PG}-\text{N}(\text{R}^1)-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{R}^2-\text{R}^3$$

Products **8a-n** are shown with their respective yields and enantiomeric ratios (er).

Products and yields:

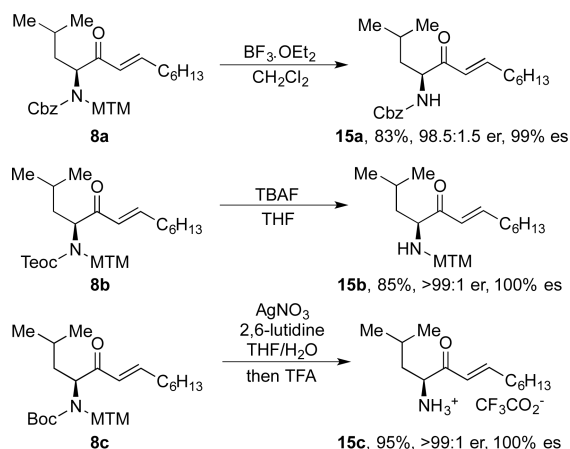
- 8a**, 82% (99:1 er, 98% es)
- 8b**, 96% (>99:1 er, 100% es)
- 8c**, 90% (>99:1 er, 100% es)
- 8d**, 73% (99:1 er, 99% es)
- 8e**, 84% (99:1 er, 99% es)
- 8f**, 87% (>99:1 er, 100% es)
- 8g**, 89% (>99:1 er, 100% es)
- 8h**, 85% (98.5:1.5 er, 99% es)
- 8i**, 84% (98.5:1.5 er, 99% es)
- 8j**, 60% (98:2 er, 97% es)
- 8k**, 79% (97:3 dr, 98% ds)
- 8l**, 67% (98:2 dr, 100% ds)
- 8m**, 86% (>99:1 er, 100% es)
- 8n**, 82% (99:1 er, 99% es)
- 8o**, 92% (98:2 er, 96% es)
- 8p**, 73% (97:3 er, 95% es, >20:1 rr)

Scheme 4. Hydroacylation of Cysteine-, Methionine-, and Phenyllactate-Derived Aldehydes



The variation possible in the identity of the electron-withdrawing groups on the nitrogen atom of the amino aldehydes allows flexibility with regard to N-deprotection strategies and corresponding reagent choice; three example transformations are shown below (Scheme 5). Treatment of

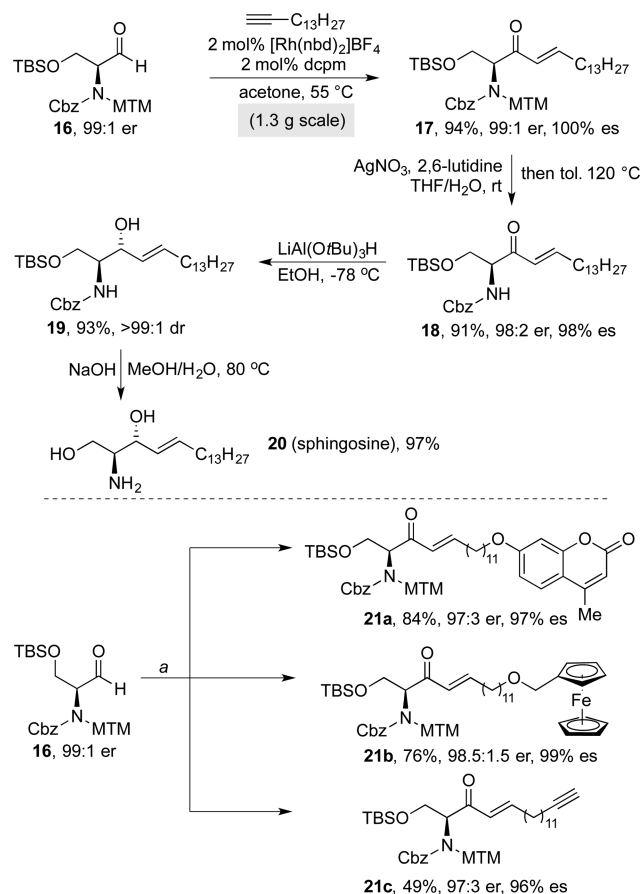
Scheme 5. Example Deprotection Possibilities for Hydroacylation Products



the Cbz-protected hydroacylation product **8a** with $\text{BF}_3 \cdot \text{OEt}_2$ allowed for the selective removal of the MTM group (**15a**). Alternatively, the carbamate could be removed in the presence of the MTM group by treating the Teoc derivative with TBAF (**8b** \rightarrow **15b**). The use of a Boc group allowed for a double deprotection; treatment with AgNO_3 and then TFA delivered the ammonium trifluoroacetate salt (**8c** \rightarrow **15c**). Importantly, enantiomeric ratios were conserved throughout these protecting group manipulations.

As a demonstration of the utility of the MTM-directed hydroacylation reactions of enantiomerically enriched α -amino aldehydes, we applied this method to a short enantio- and diastereoselective synthesis of the natural product sphingosine (**20**) (Scheme 6). The key MTM/Cbz-protected, serine-derived amino aldehyde **16** was available as before, by Dibal-H reduction of the corresponding Weinreb amide in good yield and with a 99:1 er. Hydroacylation of **16** proceeded smoothly on a gram scale using only 2 mol % catalyst loading, affording enone **17** in 94% yield with no loss in the enantiopurity (99:1). Selective MTM deprotection was achieved by first converting to the hydroxymethyl group (AgNO_3 , 2,6-lutidine, THF/ H_2O , rt) and its subsequent thermal decomposition (reflux in toluene) to provide carbamate **18** (98:2 er). Literature precedent²⁵ using $\text{LiAl}(\text{O}t\text{Bu})_3\text{H}$ allowed excellent anti-diastereoselective reduction of ketone **18** to alcohol **19** in good yield. Finally, treating **19** with NaOH and heating in MeOH/ H_2O led to one-pot TBS and Cbz deprotection and afforded sphingosine **20**. The MTM-directed hydroacylation not only established an efficient and competitive route to this natural product but the mild reaction conditions also allowed the straightforward preparation of several tagged derivatives. For example, hydroacylation of aldehyde **16** with functionalized alkynes afforded fluorophore **21a**,^{26a} electrochemically active organometallic **21b**,^{26b} and alkyne **21c** (suitable for Huisgen cycloaddition chemistry),^{26c} in good yields.

Scheme 6. Application to the Synthesis of Sphingosine (20), Together with the Preparation of Example Tagged Derivatives (21a–c)^a



^aReagents: $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ (2 mol %), dcpm (2 mol %), and appropriately tagged terminal alkyne (1.5 equiv).

CONCLUSIONS

In conclusion, we have developed a Rh(I)-catalyzed MTM-directed hydroacylation of alkynes using enantiomerically enriched α -amino aldehydes. The reaction is highly functional group tolerant, delivering a wide range of α -amino enones in excellent yields and with almost complete retention of enantiopurities. This transformation has been used for the crucial C–C bond-forming step in a concise synthesis of the natural product sphingosine. MTM-free aldehydes derived from S-methylcysteine and methionine could also be employed in efficient intermolecular alkyne HA reactions. The demonstration of N-MTM groups functioning as efficient chelating units provides an additional synthetically useful motif to exploit in intermolecular HA reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11892.

Experimental procedures and supporting characterization data and spectra (PDF)

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Author Contributions

J.F.H. and S.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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