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

Joel F. Hooper, Sangwon Seo, Fiona R. Truscott, James D. Neuhaus, and Michael C. Willis*

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.

*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, 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. 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. Reactions that achieve high levels of regio- and enantioselectivity have been developed, and applications to target synthesis are being reported. Despite the advent of a number of non-chelation-controlled hydroacylation processes, 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 or alkene. 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 someway to addressing these limitations. 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 and others, 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.

The α-amino carbonyl motif is present in a number of medicinal agents and natural products (Scheme 1) and features in intermediates for the synthesis of heterocycles and, in particular, enantiomerically enriched amino alcohols. 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)**

Received: November 13, 2015
Published: January 15, 2016

DOI: 10.1021/jacs.5b11892
J. Am. Chem. Soc. 2016, 138, 1630–1634

This is an open access article published under an ACS AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes.
been reported, examples of enantioenriched aldehydes being employed as substrates in intermolecular reactions are scarce. \(^\text{5a,21}\) Given the mild reaction conditions employed with our recently reported, highly active small-bite-angle catalysts, \(^\text{22}\) 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 \(\alpha\)-amino-substituted aldehydes in HA reactions and describe the application of chiral \(\alpha\)-amino aldehydes as effective substrates for the synthesis of synthetically appealing chiral \(\alpha\)-amino enones.

### RESULTS AND DISCUSSION

We have previously shown that nonchiral \(\alpha\)-hydroxy aldehydes could be effectively employed in HA reactions provided that the alcohol was protected as a methylthiomethyl (MTM) ether. \(^\text{23}\) 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).

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

![Scheme 2](image)

Aldehyde 1a, featuring only a Cbz protecting group on the amine, was essentially inert in a reaction with 1-octyne and a Rh(1)/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.\(^\text{22a,b}\) 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 \([\text{Rh(nbd)}_2]BF_4\) and the bis-phosphine ligand dcpm was employed. Both linear and branched aliphatic alkenes (entries 1–3) as well as carbocyclic alkenes (entries 4 and 5) could be employed. Aromatic alkenes, 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 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.

| entry | alkyne | yield | entry | alkyne | yield |
|---|---|---|---|---|---|
| 1 | Me | 94% | 7 | MeO | 99% |
| 2 | Ph | 73% | 8 | PhMe | 76% |
| 3 | Me | 80% | 9 | Fe | 93% |
| 4 | 87% | 10 | 75% |
| 5 | 75% | 11 | 86% |
| 6 | 99% | 12 | 71% |

Through 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.

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 \(\alpha\)-amino aldehydes established, we next examined the use of these molecules in hydroacylation reactions with various alkenes (Table 2). Starting from leucine, the Cbz-, Teoc-, and Boc-
protected aldehydes were combined with 1-octyne to give the hydroacylation products in excellent yields and with enantio-meric ratios of 99:1 or higher (8a–c). These high er values correlate with enantiospecificities (es) in the range of 95–100%.24 The Cbz-leucine substrate was effectively combined with phenylacetylene and a cyclopropylalkyne (8d,e). The alanine-, valine-, and phenylalanine-derived aldehydes were all combined with 1-octyne without incident (8f–h). In addition, the phenylalanine substrate was also partnered with the bulky tBu-substituted alkyne, as well as propargyl alcohol, while high er values were maintained (8i,j). The hydroxyl-substituted enone 8j, derived from phenylalanine and propargyl alcohol, has the connectivity and carbon backbone featured in KetoACE (Scheme 1). Employing an isoleucine-derived aldehyde, hydroacylation was achieved with 1-octyne, as well as a 3-thiophene-substituted alkyne (8k,l). The functional group tolerance of this reaction was further demonstrated by the use of the N-methyltryptophan aldehyde, giving the enantio-pure hydroacylation products with alkyl- and TMS-substituted alkenes (8m,n). Pleasingly, the reaction was also compatible with internal alkynes, furnishing the expected products in good yields and as single regioisomers (8o,p). Unfortunately, alkenes and allenes show only poor reactivity with this class of aldehyde.

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.

Scheme 3. Synthesis of the Enantiomerically Enriched α-Amino Aldehydes

Table 2. Hydroacylation Reactions of Amino Acid Derived Enantiomerically Enriched Aldehydes

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

**Reaction conditions:** aldehyde (1.0 equiv), alkyne (1.5 equiv), [Rh(nbd)2]BF4 (5 mol %), dcpm (5 mol %), acetone, 55 °C, 3 h. The es values were calculated using raw HPLC data, rather than the rounded er values reported above.
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 the Cbz-protected hydroacylation product 8a with BF₃·OEt₂ 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 → 15b). The use of a Boc group allowed for a double deprotection; treatment with AgNO₃ and then TFA delivered the ammonium trifluoroacetate salt (8c → 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 (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 (AgNO₃, 2,6-lutidine, THF/H₂O, rt) and its subsequent thermal decomposition (reflux in toluene) to provide carbamate 18 (98:2 er). Literature precedent 25 using LiAl(OtBu)₃H allowed excellent anti-diastereoselective reduction of ketone 18 to alcohol 19 in good yield. Finally, treating 19 with NaOH and heating in MeOH/H₂O 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,26c electrochemically active organometallic 21b,26b and alkyn 21c (suitable for Huisgen cycloaddition chemistry),26c in good yields.

**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 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)

* AUTHOR INFORMATION

Corresponding Author
* michael.willis@chem.ox.ac.uk
REFERENCES

(1) (a) Willis, M. C. Chem. Rev. 2010, 110, 725. (b) Jun, C.-H.; Jo, E.-A.; Park, J.-W. Eur. J. Org. Chem. 2007, 2027, 1869.
(2) Selected examples: (a) Schedler, M.; Wang, D.-S.; Glorius, F. Angew. Chem., Int. Ed. 2013, 52, 2585. (b) Bugaut, X.; Liu, F.; Glorius, F. J. Am. Chem. Soc. 2011, 133, 8130.
(3) Intermolecular examples: (a) Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B.-I. Angew. Chem., Int. Ed. 2002, 41, 2146. (b) González-Rodríguez, C.; Pawley, R. J.; Chaplin, A. B.; Thompson, A. L.; Weller, A. S.; Willis, M. C. Angew. Chem., Int. Ed. 2011, 50, S134. (c) Zhang, H.-J.; Bolm, C. Org. Lett. 2011, 13, 3900. (d) Chen, Q.-A.; Cruz, F. A.; Dong, V. M. J. Am. Chem. Soc. 2015, 137, 5157.
(4) Intermolecular examples: (a) Stemmler, R. T.; Bolm, C. Adv. Synth. Catal. 2007, 349, 1185. (b) Osborne, J. D.; Randell-Sly, H. E.; Currie, G. S.; Cowley, A. R.; Willis, M. C. J. Am. Chem. Soc. 2008, 130, 17232. (c) Shibata, Y.; Tanaka, K. J. Am. Chem. Soc. 2009, 131, 12552. (d) Inui, Y.; Tanaka, M.; Imai, M.; Tanaka, K.; Suemune, H. Chem. Pharm. Bull. 2009, 57, 1158. (e) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. J. Am. Chem. Soc. 2010, 132, 16330. (f) Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. J. Am. Chem. Soc. 2010, 132, 16354. (g) von Delius, M.; Le, C. M.; Dong, V. M. J. Am. Chem. Soc. 2012, 134, 15022.
(5) For a review, see the following: Leung, J. C.; Krische, M. J. Chem. Soc. 2012, 3, 2202.
(7) Rh-catalysis: (a) Marder, T. B.; Roe, D. C.; Milstein, D. Organometallics 1988, 7, 1451. (b) Roy, A. H.; Lenges, C. P.; Brookhart, M. J. Am. Chem. Soc. 2007, 129, 2082.
(8) Ru-catalysis: (a) Kondo, A.; Akazome, M.; Tsuji, Y.; Watanabe, Y. J. Org. Chem. 1990, 55, 1286. (b) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. J. Am. Chem. Soc. 2008, 130, 14094. (c) Shibahara, F.; Bower, J. F.; Krisciene, M. J. J. Am. Chem. Soc. 2008, 130, 14120. (d) Williams, V. M.; Leung, J. C.; Fatman, R. L.; Krische, M. J. Tetrahedron 2009, 65, 5024 (see also ref 3e).
(9) Co-catalysis: (a) Lenges, C. P.; White, P. S.; Brookhart, M. J. Am. Chem. Soc. 1998, 120, 6965. (b) Chen, Q.-A.; Kim, D. K.; Dong, V. M. J. Am. Chem. Soc. 2014, 136, 3772.
(10) O-Chelation: (a) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. J. Org. Chem. 1997, 62, 4564. (b) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. J. Org. Chem. 2004, 69, 1144. (c) Murphy, S. K.; Petrone, D. A.; Coulter, M. M.; Dong, V. M. Org. Lett. 2011, 13, 6216.
(11) N-Chelation: (a) Willis, M. C.; McNally, S. J.; Beswick, P. J. Angew. Chem., Int. Ed. 2004, 43, 340. (b) Willis, M. C.; Woodward, R. L. J. Am. Chem. Soc. 2005, 127, 18012. (c) Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; McNally, S. J.; Currie, G. S. J. Org. Chem. 2006, 71, 5291. (d) Lenden, P.; Entwistle, D. A.; Willis, M. C. Angew. Chem., Int. Ed. 2011, 50, 10657. For an intramolecular example, see the following: (e) Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matsuokis, A. N.; Musselman, J. D.; Tiley, T. A. Tetrahedron Lett. 2002, 43, 7031.
(12) N-Chelation: (a) Suggs, J. W. J. Am. Chem. Soc. 1978, 100, 640. For all other generated N-chelation, see the following: (b) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. Angew. Chem., Int. Ed. 2000, 39, 3070 and ref 3a.
(13) P-Chelation: Lee, H.; Jun, C.-H. Bull. Korean Chem. Soc. 1995, 16, 66.
(14) C-Chelation: Lochow, C. F.; Miller, R. G. J. Am. Chem. Soc. 1976, 98, 1281.