Published in final edited form as:

Angew Chem Int Ed Engl. 2012 July 2; 51(27): 6704–6708. doi:10.1002/anie.201203035.

Asymmetric catalytic alkynylation of acetaldehyde and its application to the synthesis of (+)-tetrahydropyrenophorol

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Abstract

By controlling the kinetics of alkynylation over aldolisation (by slowing adding the acceptor), the challenging asymmetric catalytic alkynylation of acetaldehyde has been realized. This protocol yields the corresponding attractive synthons in good to excellent enantiocontrol and shows broad tolerance and applicability. This was highlighted by its application to the synthesis of several natural products such as the rapid construction of the macrocyclic diolide (+)-tetrahydropyrenophorol.

Keywords

multicatalysis; alkynylation; asymmetric catalysis; natural product synthesis; acetaldehyde

Enantiopure propargylic alcohols are highly potent functionalities present in a wide range of natural products or in pivotal synthetic building blocks. This is especially true for the propargylic alcohols where the substituent is a methyl (Figure 1). Because of the ability to effect the chemoselective elaboration of the alkyne unit, this process is potentially applicable to the innumerable targets bearing a chiral methyl carbinol subunit. Methods allowing the access to these particularly attractive targets are relatively atom and time consuming. They are often based upon alkynylation via the lithiated alkyne followed by kinetic resolution or asymmetric reduction (Figure 1).¹ In addition, the use of the lithiated alkyne suffers from substrate compatibility. Alternatively, direct catalytic asymmetric alkynylation of aldehydes has recently appeared as a direct method of choice to access propargylic alcohols.²

Unfortunately, despite recent progress, the alkynylation of enolizable aldehydes (aliphatic aldehydes) remains limited.³ This is especially true for the asymmetric alkynylation of acetaldehyde. The rare examples on this problematic reaction report low yield / *ee*, narrow scope and requirement of a stoichiometric amount of ligand.⁴ This unmet challenge arises from the propensity of acetaldehyde to serve at the same time as an excellent nucleophile and electrophile leading to its rapid consumption by self-aldolisation. In addition, the difficulty of controlling the relatively small steric difference between the methyl and hydrogen typically results in decreased enantiocontrol. Attracted by this daunting problem

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during our application of our ProPhenol alkynylation methodology to the synthesis of complex natural products,^{3m,3n} we wondered if one could solve this problem by favoring the kinetics of alkynylation over the self-aldolisation.⁵ Herein we disclose our discovery of such a process and its implementation to natural products synthesis.

Optimization of the asymmetric catalytic alkynylation of acetaldehyde is summarized in Table 1. Given the low price and ready availability of acetaldehyde, in a late stage employment of this process, the alkyne becomes the limiting partner. In preliminary attempts applying our ProPhenol catalyst and adding the aldehyde all at once, a low yield of the alkynylation product could be observed (entry 1, Table 1). Instead, the product arising from self aldol condensation of the acetaldehyde was recovered as the major one. This aldol process, also catalyzed by the zinc-ProPhenol system, is due to the high propensity of the aldehyde to serve both as a powerful electrophile and nucleophile.^{5a} Understanding that this side reaction was due to the relatively high concentration of aldehyde, we envisaged distracting the aldehyde from its self condensation to the desired alkynylation process by modulating the different kinetics. This goal should be attained by playing on the relative concentration of the different species. A slow addition of acetaldehyde should keep its concentration low at any given moment in time provided the rate of addition of the alkyne to the aldehyde is faster than the rate of adding the aldehyde, a substantial challenge.³ Surprisingly, in contradiction to literature indicators where a prolonged reaction time was required, slow addition of the aldehyde over only 15 min gave a 79% yield together with a promising 61% *ee* using the ProPhenol based catalyst (entry 2). A temperature of -20°C and addition time of 30 minutes was found to be optimal in terms of enantiocontrol (entry 3). Under these conditions, the reaction yielded 78% of the desired product with an 86% *ee* (93:7 *er*). Further decrease in temperature did not improve the enantioselectivity (entry 4). Interestingly, compared to previous alkynylations,³ the reaction was impressively fast and was over at the end of the aldehyde addition. Finally, changing the ProPhenol:P(O)Ph₃ ratio from 1:2 to 1:1 only slightly decreased the selectivity of the reaction (81% *ee*, entry 5). While the X-Ray structure of the zinc ProPhenol catalyst shows that two Lewis basic THF molecules bind to the dinuclear complex, the small impact of reducing the ratio of phosphine oxide to catalyst supports that two phosphine oxides may not be coordinated in the transition state.⁶

This promising reactivity was further confirmed when applying electronically different alkynes (Scheme 1). As already observed for related systems, the reaction was dependent on the nature of the donor alkyne. As a result, the temperature had to be adjusted to obtain an optimal reactivity. In a general trend, electron rich alkynes gave good reactivities forming adducts **3a–3d** with enantioselectivities of 71–86% *ee*. The application of electron poor alkynes gave adducts **3e–3g** with enhanced enantioselectivities ranging from 90–98% *ee*. Equally important, the reaction tolerated a more complex structure bearing an extra stereocenter to give the adduct **3h** in excellent yield (98% yield, 1.1:1 *dr*). Formation of the new stereocenter of the same configuration in 78–86% *ee* even when using the racemic propargyl acetate as donor demonstrates the preference for catalyst control over substrate control and is promising for the application of this highly tolerant system at a late stage in a total synthesis.⁷

It is interesting to note that adducts such as **3c** or **3g**, rapidly obtained by this approach, have already found applications in complex natural product synthesis but previously required lengthy preparations.⁹

Surprisingly, when applying the optimized alkynylation conditions to the highly functionalised product **4**, the complex structure **8** arising from an unexpected alkynylation-aldolisation cascade was formed predominantly (Scheme 2). Gratifyingly, optimizing the

conditions by decreasing the amount of aldehyde and directly quenching the reaction at the end of the addition, allowed the isolation of the isomerized products **5** and **7** in good enantiocontrol (88–94% *ee*). Interestingly, this enantiocontrol is independent of the preexisting stereocenter of the starting material destroyed during the reaction (both enantiomers of **5** could be obtained in equal stereocontrol simply by changing the absolute configuration of the ProPhenol).⁸

It should be pointed out that the resultant elaborated products, readily obtained in two steps from commercially available starting materials, are the equivalent of an asymmetric addition of an acylalkyne to acetaldehyde (i.e. by hydrolysis of the enol ether liberating the free corresponding ketone).

In addition, the enantiomer of **3e**, prepared in 78% yield from 1 mmol of starting alkyne could lead in two steps to a known precursor of minquartynoic acid **10**, a natural polyacetylenic molecule with anti-HIV and cytotoxic properties (Scheme 3).¹⁰

In order to highlight the potential of this process, notably in terms of its tolerance, we envisioned its application for the synthesis of a more complex structure, namely natural diolide macrocycle tetrahydropyrenophorol **11** (Figure 2).¹¹ The synthetic challenge of pyrenophorol derivatives arises from the difficulty of controlling the two stereocenters at remote positions (1,4 diols). This has led the literature syntheses to be relatively lengthy.¹² Retrosynthetic disconnection of this structure by iterative alkynylation, should control in an independent manner the rapid introduction of both stereocenters, considerably shortening the synthesis.

Preliminary attempts at controlling the stereochemistry at C-4 first failed due to its particular instability.¹³ This led us to reverse our synthetic strategy by controlling the stereochemistry at C-7 first (Scheme 4). Applying the alkynylation of acetaldehyde, ester removal and alcohol protection led to **13** (98% *ee*). This product underwent a highly efficient second asymmetric alkynylation yielding **14** with good diastereocontrol. Hydrogenation and subsequent protection of the alcohol with a TBDMS was then performed in the hope of applying our recently disclosed acid catalyzed macrocyclisation strategy.¹⁴ Unfortunately, this failed due to the silyl group lability. Indeed, deprotection of the two esters proved infeasible and instead, only the dihydropyrenophorolic acid **12** could be isolated from the corresponding mixture (**12** is another natural metabolite related to tetrahydropyrenophorol isolated from the same endophytic *Phoma* sp).¹¹

This failure led us to turn to a Mitsunobu based cyclisation to form the cyclic diolide.¹⁵ The flexibility of this alkyne strategy allowed us to invert the stereochemistry at C-4 from the same precursor **13** by using the (*R,R*)-ProPhenol ligand. Successive mild protection followed by hydrogenation and basic treatment successfully provided access to the cyclisation precursor **17**. Applying a Mitsunobu based cyclisation followed by THP removal gratifyingly led to an efficient synthesis of (+)-tetrahydropyrenophorol **11**.¹⁶

Mechanistically, this study has revealed several interesting features of the ProPhenol catalyzed alkynylation. First, the multicatalytic nature of the ProPhenol ligand allows for an impressively fast alkynylation, thus limiting side reactions. Most importantly, the rate of addition seems to play an important role on the enantioselectivity of the reactions; the slower addition improving the stereoselectivity as well as the yield.¹⁷ This crucial mechanistic aspect suggests that when a slow addition is performed, the concentration in aldehyde being lower, only one molecule of aldehyde coordinates to the Lewis acidic zinc atoms of the ProPhenol. Restricting the number of bound acetaldehyde molecules limits the number of possible diastereoisomeric transition states also resulting in higher *ee*.

In summary, thanks to the control of the relative rates of aldolization vs alkynylation, we have been able to address the challenge of asymmetric acetaldehyde alkynylation. This simple process was further applied to the rapid and efficient synthesis of a natural product, (+)-tetrahydropyrenophorol. Due to its high practicality, the chemoselectivity of alkynylzinc intermediates, the catalyst rather than substrate control and the range of accessible molecules, we believe that this methodology will find applications in the late stages of synthesis of other complex natural products where catalyst rather than substrate control becomes crucial. The novel use of substrates **5** or **7** as acylalkyne equivalents is also noteworthy. The combination of the unexpected mechanistic implications with the synthetic utility makes the observations of particular importance.

Experimental Section

Typical procedure for the alkynylation of acetaldehyde: A microwave vial equipped with a stir bar was charged with the corresponding alkyne (0.2 mmol, 1 eq), 25.1 mg of (*S,S*)-ProPhenol ligand (0.04 mmol, 20 mol%), 21.9 mg of P(O)Ph₃ (0.08 mmol, 40 mol%). 0.3 ml of dried toluene were then added and the mixture cooled to 0°C under N₂. 0.5 ml of Me₂Zn solution (1.2 M in toluene) were then slowly added over 5 minutes and the mixture stirred at 0°C for 25 minutes. The mixture was then placed at the appropriate bath temperature (−20°C or 0°C) in a cold room (4°C). 50 µl of acetaldehyde (0.8 mmol, 4 eq) was then slowly added by small portions over 30 minutes. The resulting mixture was then stirred at the appropriate temperature for 2 hours before being slowly quenched by slow addition of 3 ml of aqueous NH₄Cl. After stirring for 15 minutes, this solution was extracted by 4 times 3 ml of diethyl ether, dried over MgSO₄, filtered and the solvent evaporated. Purification over silica gel (Hexane / Et₂O) afforded the corresponding alcohol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Science Foundation (CHE-0846427) and the National Institutes of Health (GM-33049) for their generous support of our programs. A.Q. is grateful to the Swiss National foundation for a fellowship.

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 7. Application of the same unprotected starting material considerably decreased both reactivity and enantiocontrol (74% yield by a 1h20 addition, 1:1 *dr*, 39/45% *ee*).
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 17. This higher enantiocontrol when performing a slow addition was also observed when using other aldehydes or when scaling up the reactions (see SI for details). This is in agreement with the role of triphenylphosphine oxide in these alkynylations. See ref 3h).

Previous works: **Challenge (this work):**

Figure 1.
Challenge of the catalytic asymmetric alkynylation of acetaldehyde.

Figure 2.
Retrosynthetic analysis of tetrahydropyrenophorol

Scheme 1.
Scope of the prophenol catalyzed alkynylation of acetaldehyde.

Scheme 2. Addition of highly functionalized alkyne **4** and **6** to acetaldehyde.

a) (*R,R*)-ProPhenol (20 mol%), P(O)Ph₃ (40 mol%), acetaldehyde, Me₂Zn, toluene, -20°C, 78%, 94% ee. b) i) MOMCl, DIPEA, CH₂Cl₂. ii) *n*Bu₄NF, AcOH, THF, 65% over two steps.

Scheme 3.
Formal synthesis of minquartynoic acid.

Route 1: **Route 2:**

a) (*S,S*)-ProPhenol (20 mol%), P(O)Ph₃ (40 mol%), acetaldehyde, Me₂Zn, toluene, 4°C, 77% yield, 98% ee. b) i) LiOH aq, THF then CuCl, CH₃CN. ii) BzCl, DMAP, pyridine. 90% over 2 steps. c) (*S,S*)-ProPhenol (20 mol%), P(O)Ph₃ (40 mol%), **15**, Me₂Zn, toluene, 0°C, 70% yield, 12:1 *dr*. d) i) H₂, Rh/C, *i*PrOH. ii) TBDMSCl, imidazole, CH₂Cl₂. iii) NaOH aq, MeOH. 25% over 3 steps. e) (*R,R*)-ProPhenol (20 mol%), P(O)Ph₃ (40 mol%), **15**, Me₂Zn, toluene, 0°C, 75% yield, 9:1 *dr*. f) i) 3,4-dihydropyran, PPTS, CH₂Cl₂. ii) H₂, Rh/C, *i*PrOH. iii) NaOH aq, MeOH. 40% over 3 steps. g) i) PPh₃, DEAD, Toluene/THF (10:1), -25°C. ii) PPTS, MeOH. 58% over two steps.

Scheme 4.
Synthesis of (+)-tetrahydropyrenophorol.

Table 1

Conditions screening in the addition to acetaldehyde:

Entry	Time addition 1	Reaction time, T °C	eq L*/P(O)Ph ₃	Yield ^[a]	ee (%) ^[b]
1	0 min	16h, 4 °C	0.1:0.2	29%	53%
2	15 min	15h, 4 °C	0.2:0.4	79%	61%
3	30 min	1h, -20 °C	0.2:0.4	78%	86%
4	20 min	2h, -40 °C	0.2:0.4	47% ^[c]	70%
5	30 min	1h, -20 °C	0.2:0.2	75%	81%

^[a] Isolated yields starting from 0.2 mmol starting alkyne.

^[b] Determined by HPLC.

^[c] Only 59% conversion observed.