Synthetic Methods

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Asymmetric Catalytic Alkynylation of Acetaldehyde: Application to the Synthesis of (+)-Tetrahydropyrenophorol**

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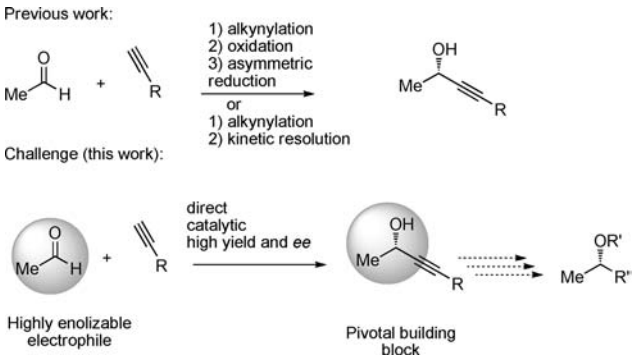
Enantiopure propargylic alcohols are highly potent functionalities present in a wide range of natural products or in pivotal synthetic building blocks. This is especially true for the propargylic alcohols where the substituent is a methyl (Scheme 1). Because of the ability to effect the chemoselective elaboration of the alkyne unit, this process is potentially applicable to the innumerous targets bearing a chiral methyl carbinol subunit. Methods allowing access to these particularly attractive targets are relatively atom and time consuming. They are often based upon alkynylation via the lithiated alkyne and subsequent kinetic resolution or asymmetric reduction (Scheme 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]

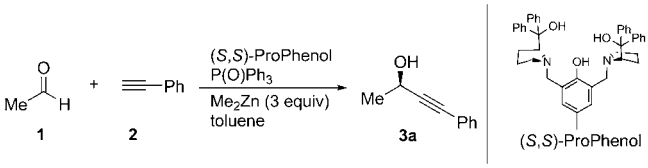


Scheme 1. Challenge of the catalytic asymmetric alkynylation of acetaldehyde.

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 yields and *ee* values, narrow scope, and the 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, thus leading to its rapid consumption by self-aldolization. In addition, the difficulty of controlling the relatively small steric difference between the methyl and hydrogen atom typically results in decreased enantiocontrol. Attracted by this daunting problem during our application of our ProPhenol alkynylation methodology to the synthesis of complex natural products,[3m,n] we wondered if one could solve this problem by favoring the kinetics of alkynylation over the self-aldolization.[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 and the late-stage employment of this process, the alkyne becomes the limiting partner. In preliminary attempts to apply our ProPhenol catalyst and add the aldehyde all at once, a low yield of the alkynylation product was observed (entry 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 and directing it to the desired alkynylation process by modulating the different kinetics. This goal should be attained by playing on the relative concentration of the

Table 1: Screening of reaction conditions for the addition to acetaldehyde.



Entry	Time for addition of **1**	*t* [h]	*T* [°C]	Equiv L*/ $P(O)Ph_3$	Yield [%][a]	*ee* [%][b]
1	0 min	16	4	0.1:0.2	29	53
2	15 min	15	4	0.2:0.4	79	61
3	**30 min**	**1**	**−20**	**0.2:0.4**	**78**	**86**
4	20 min	2	−40	0.2:0.4	47[c]	70
5	30 min	1	−20	0.2:0.2	75	81

[a] Yields of isolated product obtained from 0.2 mmol of the starting alkyne. [b] Determined by HPLC. [c] Only 59% conversion observed.

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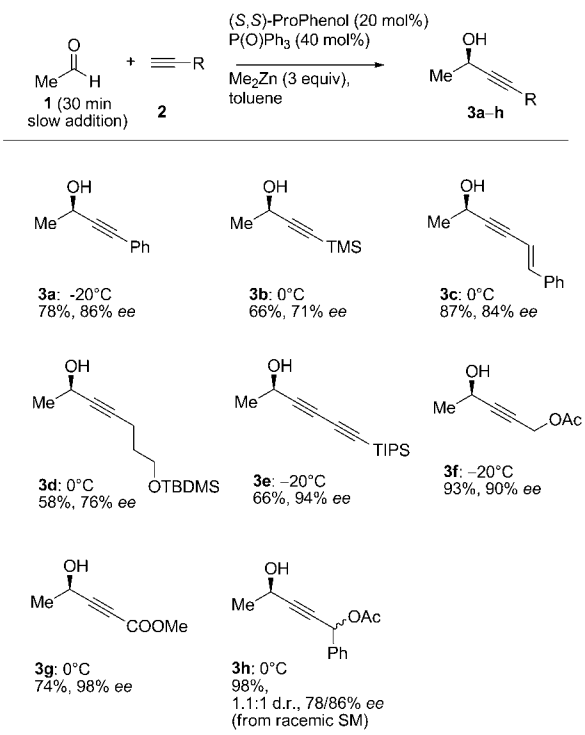
different species. A slow addition of acetaldehyde should keep its concentration low at any given moment in time provided the rate of addition of the alkyne to the aldehyde is faster than the rate of adding the aldehyde, a substantial challenge.[3] Surprisingly, in contradiction to literature indicators where a prolonged reaction time was required, slow addition of the aldehyde over only 15 minutes 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 reaction conditions, the reaction yielded 78% of the desired product with an 86% *ee* (93:7 e.r.). 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/$P(O)Ph_3$ 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 the notion 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 2). 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 had good reactivities, thus forming adducts **3a**–**3d** with enantioselectivities of 71–86% *ee*. The application of electron-poor alkynes led to 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 d.r.). Formation of the new stereocenter of the same configuration in 78–86% *ee*, even when using the racemic propargyl acetate as a 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]

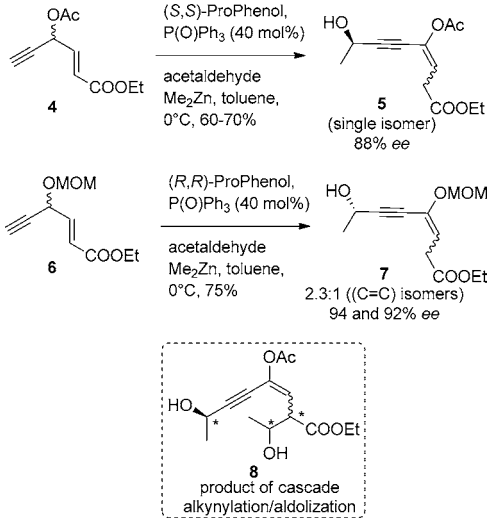
It is interesting to note that adducts such as **3c** or **3g**, which are rapidly obtained by this approach, have already found applications in complex natural product synthesis but previously required lengthy preparations.[9]

Surprisingly, when applying the optimized alkynylation conditions to the highly functionalized product **4**, the complex structure **8** arising from an unexpected alkynylation/aldolization cascade was formed predominantly (Scheme 3). Gratifyingly, optimizing the reaction conditions by decreasing the amount of aldehyde and directly quenching the reaction at the end of the addition allowed isolation of the isomerized product **5**, as well as **7** (from **6**) with good enantiocontrol (88–94% *ee*). Interestingly, this enantiocontrol is independent of the preexisting stereocenter of the starting material which is 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



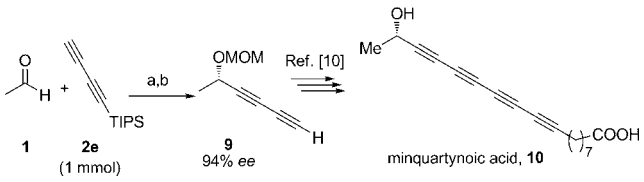
Scheme 2. Scope of the prophenol catalyzed alkynylation of acetaldehyde. TIPS = triisopropylsilyl.



Scheme 3. Addition of highly functionalized alkyne **4** and **6** to acetaldehyde.

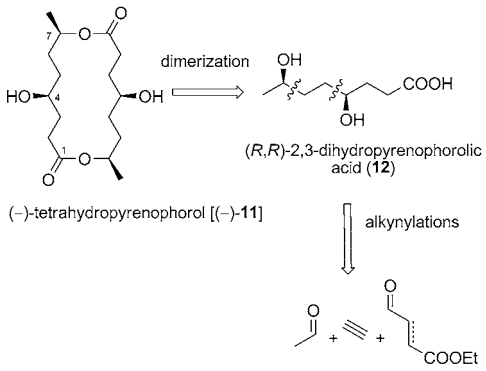
polyacetylenic molecule with anti-HIV and cytotoxic properties (Scheme 4).[10]

To highlight the potential of this process, notably in terms of its tolerance, we envisioned its application for the synthesis



Scheme 4. Formal synthesis of minquartynoic acid. a) (*R*,*R*)-ProPhenol (20 mol%), $P(O)Ph_3$ (40 mol%), acetaldehyde, Me_2Zn, toluene, −20°C, 78%, 94% *ee*. b) 1. MOMCl, DIPEA, CH_2Cl_2; 2. nBu_4NF, AcOH, THF, 65% over two steps. DIPEA = diisopropylethylamine, MOM = methoxymethyl, THF = tetrahydrofuran.

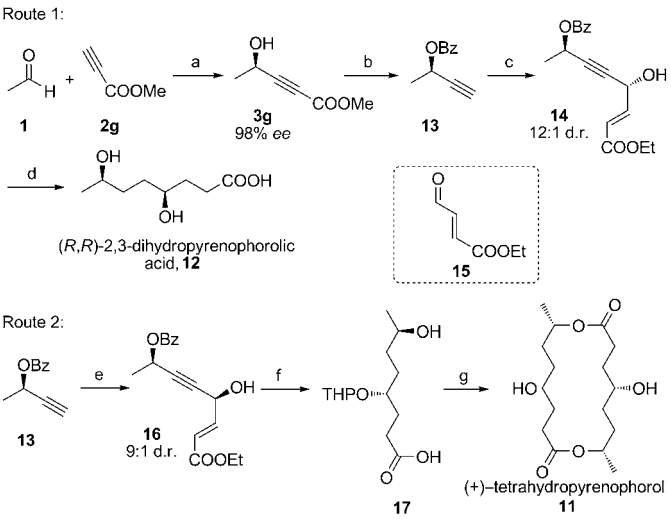
of a more complex structure, namely the natural diolide macrocycle (−)-tetrahydropyrenophorol **11** (Scheme 5).[11] The synthetic challenge of pyrenophorol derivatives arises



Scheme 5. Retrosynthesic analysis of tetrahydropyrenophorol.

from the difficulty in controlling the two stereocenters at remote positions (1,4-diols). This issue 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, thus considerably shortening the synthesis.

Preliminary attempts at controlling the stereochemistry at C4 first failed because of its particular instability.[13] This issue led us to reverse our synthetic strategy by controlling the stereochemistry at C7 first (Scheme 6). 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 TBDMS was then performed in the hope of applying our recently disclosed acid-catalyzed macrocyclization 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



Scheme 6. Synthesis of (+)-tetrahydropyrenophorol. a) (*S*,*S*)-ProPhenol (20 mol%), $P(O)Ph_3$ (40 mol%), acetaldehyde, Me_2Zn, toluene, 4°C, 77% yield, 98% *ee*. b) 2. LiOH aq, THF then CuCl, CH_3CN; 2. BzCl, DMAP, pyridine, 90% over 2 steps. c) (*S*,*S*)-ProPhenol (20 mol%), $P(O)Ph_3$ (40 mol%), **15**, Me_2Zn, toluene, 0°C, 70% yield, 12:1 d.r. d) 1. H_2, Rh/C, *i*PrOH; 2. TBDMSCl, imidazole, CH_2Cl_2; 3. NaOH aq, MeOH, 25% over 3 steps. e) (*R*,*R*)-ProPhenol (20 mol%), $P(O)Ph_3$ (40 mol%), **15**, Me_2Zn, toluene, 0°C, 75% yield, 9:1 d.r. f) 1. 3,4-dihydropyran, PPTS, CH_2Cl_2; 2. H_2, Rh/C, *i*PrOH; 3. NaOH aq, MeOH, 40% over 3 steps. g) 1. PPh_3, DEAD, toluene/THF (10:1), −25°C; 2. PPTS, MeOH, 58% over two steps. Bz = benzoyl, DMAP = 4-(dimethylamino)pyridine, PPTS = pyridinium *para*-toluenesulfonate, TBDMS = *tert*-butyldimethylsilyl.

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-type cyclization to form the cyclic diolide.[15] The flexibility of this alkyne strategy allowed us to invert the stereochemistry at C4 from the same precursor **13** by using the (*R*,*R*)-ProPhenol ligand. Successive mild protection, subsequent hydrogenation, and treatment with base successfully provided access to the cyclization precursor **17**. A Mitsunobu-type cyclization and subsequent 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 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, that is, the slower addition improves the stereoselectivity as well as the yield.[17] This crucial mechanistic aspect suggests that when a slow addition is performed, the concentration of the aldehyde is lower, and 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, thus resulting in higher *ee* values.

In summary, thanks to the control of the relative rates of aldolization versus alkynylation, we have been able to address

the challenge of asymmetric acetaldehyde alkynylation. This simple process was additionally applied to the rapid and efficient synthesis of a natural product, (+)-tetrahydropyrenophorol. As a result of 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 syntheses 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 equiv), 25.1 mg of (*S*,*S*)-ProPhenol ligand (0.04 mmol, 20 mol%), 21.9 mg of $P(O)Ph_3$ (0.08 mmol, 40 mol%). Dry toluene (0.3 mL) was then added and the mixture cooled to 0°C under N_2. A Me_2Zn solution (0.5 mL; 1.2 M in toluene) was then slowly added over 5 min and the mixture stirred at 0°C for 25 min. The mixture was then placed at the appropriate bath temperature (−20°C or 0°C) in a cold room (4°C). Acetaldehyde (50 μL; 0.8 mmol; 4 equiv) was then slowly added in small portions (4 μL) over 30 min. The resulting mixture was then stirred at the appropriate temperature for 2 h before being slowly quenched by slow addition of 3 mL of aqueous NH_4Cl. After stirring for 15 min, this solution was extracted four times each with 3 mL of diethyl ether, dried over $MgSO_4$, filtered, and the solvent evaporated. Purification by silica gel chromatography (*n*-hexane/Et_2O) afforded the corresponding alcohol.

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[7] Application of the same unprotected starting material considerably decreased both reactivity and enantiocontrol (74% yield by a 1 h20 addition, 1:1 d.r., 39/45% *ee*).

[8] It must be pointed out that NMR analysis did not allow us to determine the geometry of the enol ether.

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[13] See the Supporting Information for details. Derivatization of **7** also led to an advanced precursor of tetrahydropyrenophorol. Unfortunately, the difficulty at separating the obtained diastereoisomers prevented us from accomplishing the particularly short six-step route to the natural diolide (see the Supporting Information).
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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 the Supporting Information for details). This is in agreement with the role of triphenylphosphine oxide in these alkynylations. See Ref. [3h]).

