Organic LETTERS

Letter

pubs.acs.org/OrgLett

Asymmetric Protonation of Cumulenolates: Synthesis of Allenyl Aldehydes Facilitated by an Organomanganese Auxiliary

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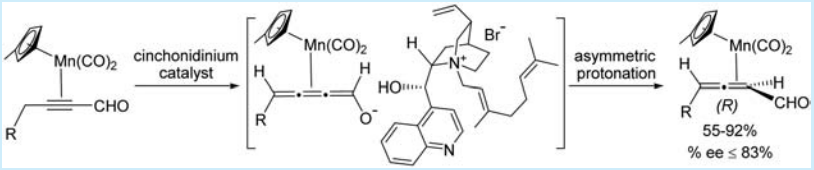
Supporting Information

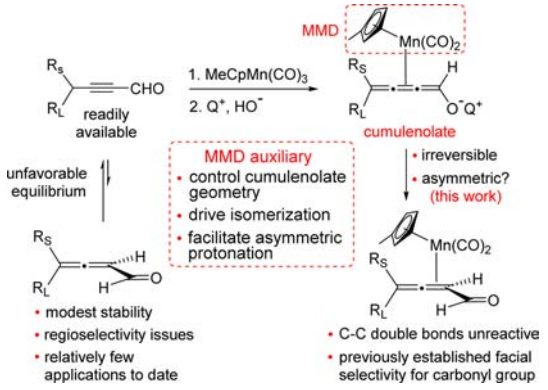


ABSTRACT: Chiral ammonium salts were used to catalyze the isomerization of organomanganese-complexed alkynyl aldehydes to chiral allenal building blocks in moderate to good enantiomeric excesses. Normally, conjugated alkynyl aldehydes do not isomerize to their thermodynamically less stable allene isomers. However, with a manganese auxiliary in place to promote allene formation, asymmetric protonation of cumulenolate intermediates was realized using a variety of cinchonidinium salts in a weakly basic biphasic reaction system. Optimal results were realized using a novel cinchonidinium geranyl derivative with its C-9 hydroxyl group playing a crucial role in enantioselectivity.

Allenyl carbonyl compounds are emerging as useful building blocks in organic synthesis,[1] though, in this class, allenyl aldehydes have found fewer applications probably owing to their modest stability.[2] Nonracemic allenyl aldehydes are generally prepared by oxidation of the corresponding allenol.[3] However, no direct asymmetric methods exist starting from conjugated alkynyl aldehyde precursors, which are usually easily accessible. Indeed, such isomerizations are often thermodynamically disfavored except in specialized substrates where allene formation markedly extends or preserves conjugation.[4] However, we and others have previously noted that complexation of alkynyl carbonyls with methylcyclopentadienyl manganese dicarbonyl (MMD) drives the isomerization reaction toward allene formation.[5] We have also demonstrated that this MMD-auxiliary is useful in diastereoselective addition reactions of the complexed allene product.[6] To further capitalize on the utility of the MMD-auxiliary, we sought to develop an enantioselective route to allenyl aldehydes via an asymmetric isomerization (Scheme 1). This approach would require a face-selective protonation of a cumulenolate derivative, a rather challenging problem though one that has been nicely solved in related enolate systems.[7] In addition, the successful implementation of this approach would also entail the diastereoselective generation of cumulenolates. In the present letter, we report our efforts to accomplish this isomerization to afford nonracemic MMD-allenals using cinchonidine-based chiral phase transfer catalysts (PTCs).

Following our previously reported procedure,[5a] complex **1** was conveniently prepared under low power irradiation in the presence of methylcyclopentadienyl manganese tricarbonyl (MMT).[8] The resulting MMD-complex was then purified using silica chromatography and stored as a toluene stock solution. This solution of complex **1** was then treated with

Scheme 1. MMD-Allenyl Aldehyde via Asymmetric Protonation of Cumulenolate



commercially available phase transfer catalysts **Q1a** and **Q3** (Figure 1) in the presence of aqueous KOH (1 M). We were pleased to notice a modest enantiomeric excess (58%) with the cinchona-based PTC (Table 1, entry 1). Encouraged by these results, we next surveyed other known and new cinchona-based PTCs as well as explored a variety of reaction conditions by analogy with several related studies.[9] We first prepared a series of *N*-benzyl cinchonidinium derivatives (**Q1a**−**Q1f**). The isomerization reaction appeared to improve with electron-withdrawing substituents on the aryl ring.

Others have argued that these electron-poor catalysts are known to favor tighter ion pairing with consequent strengthen-

Received: December 28, 2015
Published: February 29, 2016

DOI: 10.1021/acs.orglett.5b03681
Org. Lett. 2016, 18, 1230−1233

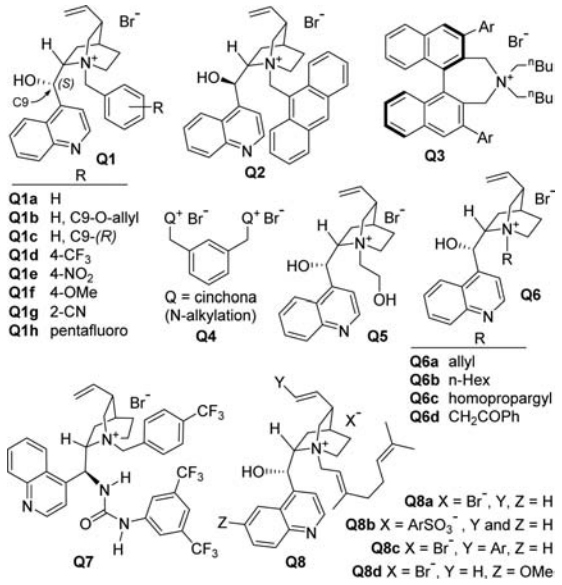
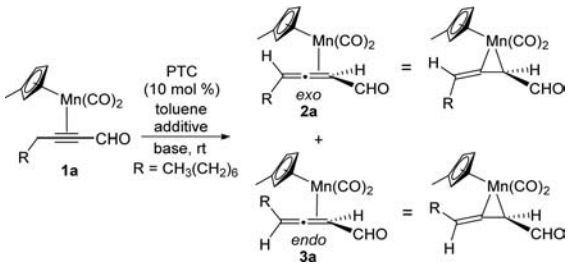


Figure 1. Chiral phase-transfer catalysts surveyed.

Table 1. Optimization of Isomerization Conditions



entry	cat.	base	additive[a]	2a:3a	ee (%)[b] of 2a
1	**Q1a**	1 M KOH		4:1	58
2	**Q1c**	1 M KOH		4:1	55[c]
3	**Q1d**	0.1 M KOH	Et_2O	4:1	79
4	**Q1e**	10 M KOH	Et_2O	4:1	80
5	**Q1f**	0.1 M KOH	Et_2O	5:1	64
6	**Q1g**	0.1 M KOH	Et_2O	5:1	79
7	**Q1h**	0.1 M KOH	Et_2O	3:1	79
8	**Q1b**	0.1 M KOH	Et_2O	2:1	rac
9	**Q2**	1 M KOH		2:1	40
10	**Q3**	1 M KOH		4:1	rac
11	**Q4**	K_2CO_3		5:1	78
12	**Q6a**	0.1 M KOH	Et_2O	6.5:1	70
13	**Q6b**	10 M KOH	Et_2O	5:1	71
14	**Q6c**	10 M KOH	Et_2O	7:1	69
15	**Q6d**	10 M KOH	Et_2O	7:1	65
16	**Q7**	10 M KOH	Et_2O	4:1	rac
17	**Q8a**	0.1 M KOH	Et_2O	6.4:1	77
18	**Q8a**	aq K_2CO_3		7:1	80
19	**Q8a**	K_2CO_3		–	–
20[d]	**Q8a**	K_2CO_3	$CHCl_3$/EtOH	7:1	83

[a]Reactions were performed with base (3 equiv) in toluene/additive (3:1) (0.10 M with respect to substrate) at rt (unless indicated otherwise). [b]The enantiomeric excess was determined by chiral HPLC analysis of MMD-allene **2a**; all products gave levorotatory optical rotations. [c]This product gave a dextrorotatory optical rotation. [d]Reaction conducted at −5 °C in toluene/$CHCl_3$ (3:1) with EtOH (0.12 equiv).

ing of the substrate−catalyst interactions.[10] In particular, while a *para*-methoxy group (in **Q1f**) causes a marked drop in enantioselectivity (64% ee; Table 1, entry 5), the introduction of *para*-CF_3, *para*-nitro substituents (in **Q1d** and **Q1e**) and the pentafluoro phenyl group (in **Q1h**) afforded product **2a** with ee values up to 80%. Similar selectivity was observed with **Q1g** containing a cyano group (entry 6) at the ortho position of the phenyl ring; this catalyst is thought to favor a more rigid conformation by hydrogen bonding with the cinchona 9-OH group.[11] Previously reported dimer cinchonine catalyst **Q4**[12] provided a 78% ee (entry 11) using solid K_2CO_3 as base. Interestingly, the free hydroxyl group at the C9 position proved crucial to asymmetric induction with this catalyst platform since C9−O-allyl catalyst **Q1b** gave **2a** as the racemate (entry 8). Using a C9-OH inverted catalyst (**Q1c**), product **2a** was obtained as the opposite enantiomer (entry 2). This result also points to the critical role of the 9-OH group during the enantio-induction step of the isomerization process.[13] To further probe its mode of action, we next attempted the reaction using catalyst **Q7** possessing a better H-bond donor urea group.[12b] However, in this reaction, allenal **2a** was obtained in racemic form (entry 16).

One of the challenges of this project was to produce MMD-complexed allene product in high diastereomeric purity. Upon isomerization, the larger group at the γ-position generally favors a position *anti* to the MMD auxiliary; this is referred to as the *exo*-product.[5b] We noticed that the *exo*/*endo* ratio was negatively affected by the steric bulk of the *N*-quinuclidinium group. In general, most aryl methylene substituted cinchona catalysts afforded an *exo*/*endo* ratio up to 5:1. However, when the larger anthracenyl methylene group was incorporated (catalyst **Q2**), both enantiomeric excess (40%) and *exo*/*endo* selectivity (2:1) were diminished (entry 9). We then prepared catalysts with smaller N-substituents (**Q5**, **Q6a**−**Q6d**); however, these smaller linear groups only slightly improved the *exo*/*endo* ratio (up to 7:1).

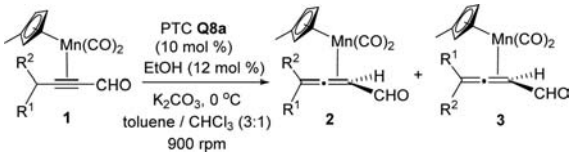
Continuing to explore linear N-substituents, we prepared geranyl substituted cinchonine catalyst **Q8a**, which has not been previously reported. This catalyst appeared to give an improved combination of *exo*/*endo* selectivity and enantiomeric excess (6.4:1 and 77% ee, entry 17).

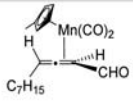
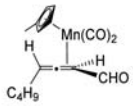
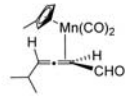
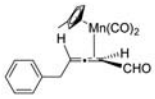
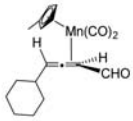
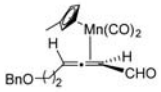
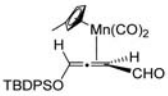
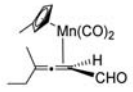
With promising catalyst **Q8a** in hand, we proceeded to optimize the reaction conditions. In the foregoing experiments, chemical yields were generally in the range of 60−80% (see Supporting Information). We noticed that the use of aqueous hydroxide salts (even degassed) often degraded the MMD auxiliary over long reaction times resulting in lower yields of allene product. On the other hand, reactions without water, such as K_2CO_3/toluene, gave no product. However, the K_2CO_3/toluene/$CHCl_3$/**Q8a** system afforded good yields (85%) of **2a** after stirring for 10 h at 900 rpm[14] at −5 °C in the presence of a catalytic amount of EtOH (12%).[15] Importantly, these conditions also led to the highest enantioselectivity (83% ee) and *exo*/*endo* ratio (7:1) of allene **2a** (entry 20) observed in this study.[16]

We next investigated the substrate scope using our optimized isomerization conditions (Table 2). In general, nonracemic MMD-complexed allene aldehydes were prepared in good yields (55−92%) and in enantiomeric excesses ranging from 54% to 83%. The space-filling properties of the γ-groups of alkyne substrates **1** only modestly influenced the enantioselectivity of product **2** formation. Thus, alkynes substituted with linear alkyl groups (**1a** and **1b**) and the more bulky isopropyl group (**1c**)

DOI: 10.1021/acs.orglett.5b03681
Org. Lett. 2016, 18, 1230−1233

Table 2. Phase Transfer Catalyzed Isomerization Reaction Generality



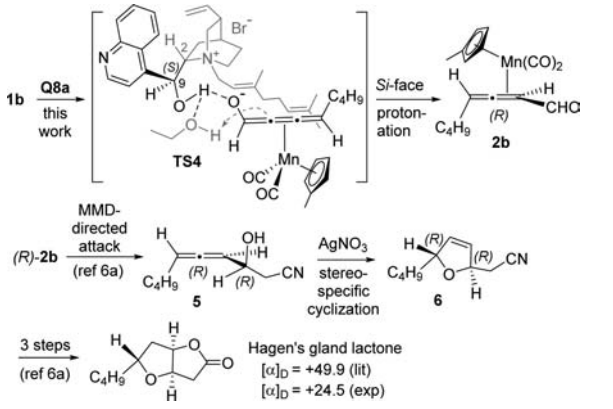
entry		allene isomer **2**	% yield of **2**[a]	**2**:**3**	ee (%)
1	**2a**		82	7:1	83
2	**2b**		82	6:1	79
3	**2c**		92	35:1	83
4	**2d**		86	12:1	66
5	**2e**		91	exo only	75
6[b]	**2f**		77	22:1	58
7	**2g**		65	exo only	60[c]
8	**2h**		55	5:1	54[c,d]

[a]Yield of *exo* isomer; in most cases reaction complete in 16 h. [b]Gives −37% ee with catalyst **Q8a** and 1 M KOH and −30% ee with **Q1d** and 1 M KOH. [c]This product gave a dextrorotatory optical rotation. [d]This is an approximate measurement since the enantiomer peaks were not well resolved using chiral HPLC.

(Table 2, entries 1−3) afforded allenes with similar enantiomeric excesses (79−83%). By contrast, steric bulk at the γ-position appeared to correlate well with a high *exo*/*endo* ratio (entries 3−5). Substrate **1f** containing a benzyloxy group led to a surprisingly lower enantioselectivity (58%) than expected (entry 6). Though the reason for this diminution is not clear, it is possible that the ether oxygen of the benzyloxy group coordinates with the C9-OH of catalyst **Q8a** and thereby reduces selectivity in the cumulenolate protonation step (37% ee). Switching from K_2CO_3 to KOH further deteriorated the enantioselectivity. For this substrate, we also attempted isomerization with catalyst **Q1d** which led to both a diminished enantioselectivity (30% ee) and *exo*/*endo* ratio (9:1). From these and other experiments, it is clear that geranyl cinchonidinium **Q8a** is the optimal catalyst that we have identified thus far for the present asymmetric isomerization. We were pleased to observe that silyloxy alkyne **1g** was transformed to nonracemic allene **2g** using our optimized PTC conditions with catalyst **Q8a** (entry 7). These silyloxy allenes are emerging as important and versatile building blocks.[17] For this isomerization, the use of K_2CO_3 was critical since other bases such as KOH or DBU were not effective. Finally, trisubstituted allene **2h** (entry 8) was prepared using the present method in 55% yield and 54% ee. This isomerization required a significantly longer time (30 h) but was modestly selective for the *exo*-isomer despite the small difference in size of the γ-substituents (methyl versus ethyl).

The absolute configuration of allene **2b** was determined indirectly by converting this nonracemic starting material in several steps to Hagen's gland lactone using our previously established racemic route[6a] and comparing its specific rotation with that of the naturally occurring material.[18] Thus, the anion of acetonitrile was added diastereoselectively to nonracemic allenyl aldehyde **2b** to afford intermediate **5** (Scheme 2). A subsequent

Scheme 2. Asymmetric Total Synthesis of Hagen's Gland Lactone; Determination of Absolute Configuration of Allene 2b



stereospecific silver-mediated cyclization reaction then produced furan **6** in the *trans*-configuration. After three additional steps,[6a] Hagen's gland lactone was produced; its positive specific rotation (dextrorotatory) matched that of the naturally occurring sample. This could only have occurred if our allene starting material was of the (*R*)-configuration. While the main goal of this total synthesis was to establish the configuration of allenyl aldehydes produced using the present method, we note that this is one of the most succinct catalytic asymmetric total syntheses of Hagen's gland lactone published to date.[19]

Our previous experience with MMD-cumulenolate intermediates suggests that the manganese auxiliary promotes *Z*-geometry (i.e., the alkyl and oxy anion in a *cis* relationship).[6b] However, the basis for facial selectivity in the protonation step leading to **2b** is not entirely clear. In an attempt to rationalize the preference for the (*R*)-configuration, we find it useful to follow Dolling's stereochemical model.[20] By analogy with this model, we envision the MMD-complexed cumulenolate to bind with the C9-OH of the cinchonine catalyst as in **TS4** (Scheme 2). In this conception, the large MMD group sits below the quinuclidine ring allowing the cumulenolate to engage in π−π interactions with either the aryl (catalyst **Q1c**−**Q1h**) or geranyl group (catalyst **Q8a**). Interactions with C−H bonds adjacent to the quinuclidine ammonium center are also envisioned.[21] The protonating agent which is either water (with KOH base) or ethanol (with K_2CO_3 base) may also participate in H-bonding

DOI: 10.1021/acs.orglett.5b03681
Org. Lett. 2016, 18, 1230−1233

with C9-OH to deliver a proton to the *Si*-face of the cumulenolate.

In summary, we have developed a catalytic PTC system to prepare nonracemic MMD-complexed allenyl aldehydes from easily accessible conjugated alkynyl aldehydes. We realized optimal results using cinchonidinium derivatives with the hydroxyl group playing a crucial role in enantioselectivity. In particular, we identified a new cinchonidinium-based PTC containing a geranyl group capable of producing MMD-allene products in good yields and enantioselectivities (up to 83% ee). We also determined the absolute configuration produced by the present method by comparing a natural product synthesized from one of our allene products with the naturally occurring material. This latter effort also underscores the value of MMD-complexed nonracemic allenyl aldehydes as building blocks in complex total synthesis, an area of current investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03681.

Characterization data for all new compounds and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We wish to acknowledge Indo-US Science and Technology Forum, India for fellowship support to B.A.B. through the IUSSTF fellowship program. We also thank the NIH (GM110651) and the ACS-PRF (51785) for financial support.

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(16) We also examined several other catalysts (**Q8b**−**Q8d**), alcohol additives, hydroxide metal salts, and a number of other variables; these are summarized in Tables A−C in the Supporting Information.

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DOI: 10.1021/acs.orglett.5b03681
Org. Lett. 2016, 18, 1230−1233