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Iminium-Ion Activation as an Efficient Strategy for Divergent Synthesis of Optically Active Propargylic, Homopropargylic, and Allenic Compounds

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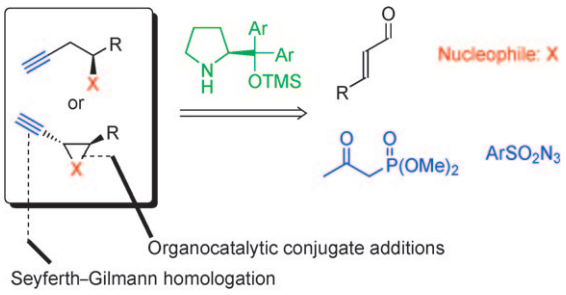
The acetylenic motif serves as a common synthon in many C–X and C–C bond disconnections.[1] Propargylic and homopropargylic compounds in particular are important as chiral building blocks in the course of stereoselective synthesis,[2] not at least owing to their transformational diversity and condition tolerance.[3] The synthesis of propargylic and homopropargylic compounds remains an attractive yet challenging task, pursued by many research groups. Nowadays, modern synthesis and synthetic methods oftentimes include new and important aspects such as time-cost control and sustainability.[4] One of the methods to reduce time costs is the invention of more chemospecific reactions, thereby avoiding the use of protective groups and superfluous redox manipulations.[5] An alternative, but equally efficient solution to the problem is the incorporation of one-pot procedures[6] and entrapment of intermediates when formed, making product isolation unnecessary. Moreover, other issues such as structural lability, a frequent cause for product oxidation/reduction/protections, can also be successfully prevented by the use of one-pot strategies.

Organocatalysis[7] is a highly robust and reliable synthetic tactic, impervious to air or water; therefore, being exceedingly suitable for this type of "assemble and build strategy", in which simple and available components are assembled to form a chiral structural skeleton, upon which molecular complexity can be built in a one-pot fashion. Recently, we merged the enamine-catalyzed enantioselective electrophilic fluorination of aldehydes and Seyferth–Gilmann homologation to form highly enantioenriched propargylic fluorides in a one-pot reaction from commercially available reagents.[8] Given the interests in optically active acetylenes, conceptual generalization leading to diversity-oriented synthesis of optically active propargylic compounds is a highly desirable and important synthetic methodology. However, this seemingly intuitive approach encountered unavoidable difficulties, such as product decomposition and racemization, when substituting the α-fluorination reaction with other organocatalytic α-functionalizations. We then turned our attention toward the use of iminium-ion activation assuming better stability of the reaction intermediates and products. Herein, we wish to report a series of chiral iminium-ion-activated conjugate addition–homologation sequences, forming highly enantioenriched propargylic and homopropargylic compounds in a simple and benign way (Scheme 1).



Scheme 1. Organocatalytic synthesis of optically active propargylic and homopropargylic compounds.

Terminal propargylic epoxides[9] represent a highly privileged class of synthetic intermediate, incorporated innumerable times in natural product synthesis or construction of other intricate molecular structures.[9f,g] Despite the relevance, routes by which they are obtained are relatively few and often very time-consuming. The traditional strategy proceeds through the ring-closure reaction of chiral halohydrins,[9a,b] or by enantioselective epoxidation of enynes[9c,d] providing the desired products. Recently, Martín et al.[9e] also reported a three-step procedure to the same class of compound starting from pure epoxyaldehydes. We envi-

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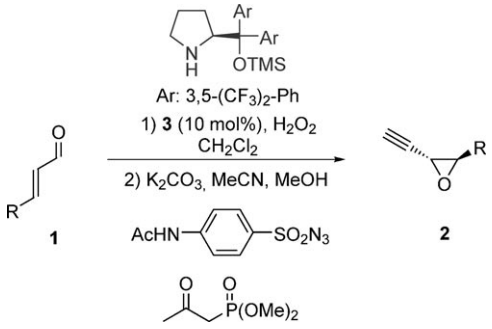
sioned that a more simple approach can be devised by combining the organocatalyzed epoxidation reaction[7l] of α,β-unsaturated aldehydes with the Ohira modification[10] of the Seyfert–Gilmann homologation and the results are as outlined in Table 1.

Table 1. The organocatalytic synthesis of chiral propargylic epoxides.[a]

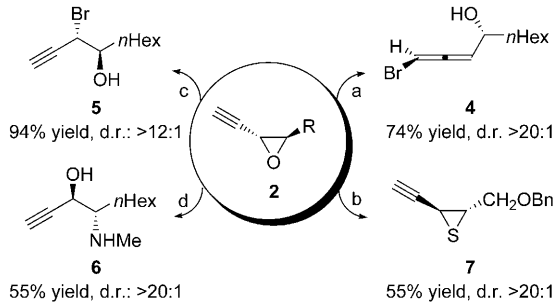


	R (**1**)	d.r.[d]	Product	Yield [%][b]	*ee* [%][c]
1	*n*Butyl (**1a**)	>20:1	**2a**	83	99
2[e]	*i*Propyl (**1b**)	>20:1	**2b**	63	99
3	*n*-Hexyl (**1c**)	>20:1	**2c**	81	98
4	Ph (**1d**)	>20:1	**2d**	66	98
5	*o*-NO_2-Ph (**1e**)	>20:1	**2e**	86	99
6	CH_2OBn (**1f**)	>20:1	**2f**	73	91
7[f]	CO_2Et (**1g**)	>20:1	**2g**	58	97

[a] Reaction performed on 0.20 mmol scale (see Supporting Information). [b] Yields of isolated products after column chromatography. [c] *ee* determined by chiral stationary phase HPLC or GC. [d] Determined by NMR spectroscopy. [e] Yield determined by NMR spectroscopy with internal standard due to product volatility. [f] Complete trans-esterification to the methyl ester.

The direct, one-pot formation of optically active propargylic epoxides **2** is initiated by reaction of aldehydes **1** with H_2O_2 catalyzed by (*S*)-2-[bis(3,5-bis-trifluoromethylphenyl)-trimethylsilyloxymethyl]pyrrolidine (**3**)[7m] in CH_2Cl_2. The intermediate *trans*-epoxyaldehydes were subsequently trapped by the Ohira–Bestmann reagent, in situ generated from dimethyl 2-oxopropylphosphonate and 4-acetamidobenzenesulfonyl azide, furnishing the homologated products **2** in high yields and excellent enantioselectivities. Both simple or substituted alkyl and aryl side chains are allowed, furnishing the desired *trans*-propargylic epoxides in 63–86% yield and 91–99% *ee* (Table 1, entries 1–5). When employing substrates carrying other functional groups, for example, ester (Table 1, entry 7) or hydroxybenzyl group (Table 1, entry 6), the same levels of yield and optical purity were obtained; however, for compound **2g**, complete transesterification to the methyl ester was accomplished. It should be noted that the reported reaction is almost complete diastereoselective (d.r. 20:1), and easily up-scaled to 5 mmol without affecting the obtained yield and enantioselectivity. The absolute configuration of product **2a** was determined by chemical correlation,[9a] confirming the (2*R*,3*R*) configuration, as expected by comparison to the epoxyaldehyde intermediates. The remaining configurations are assumed by analogy.

Rivaling the intriguing demands for easy access to molecular complexity, we aim to demonstrate the simplicity and diversity with which our product can be transformed (Scheme 2). Enantiomerically enriched allenes[11] are



Scheme 2. Transformations of the propargylic epoxides. a) NH_4Br, CuBr, Cu, HBr, Et_2O, −50°C to −10°C, 2 h; b) $CS(NH_2)_2$, MeOH, RT, 1 d; c) PPh_3, Br_2, RT, 15 min; d) $MeNH_2$, H_2O, 60°C, 3 d.

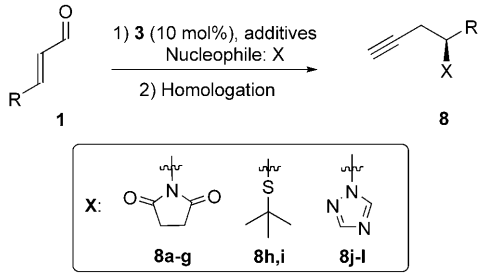
valuable chiral building blocks in contemporary organic synthesis. Following the procedure reported by Chemla et al.,[11c] the allenic alcohol **4** was obtained in 74% yield as a single diastereomer. It is also known that by the addition of a Grignard reagent, this type of bromoallenol product can be transformed into *anti*-homopropargylic alcohols, a structural motif found in ubiquitous total synthesis endeavors.

To demonstrate further utility of the propargylic epoxides, ring-opening reactions with heteroatom-centered nucleophiles, such as a halide or nitrogen, were conducted, providing the optically active halohydrin **5** and 1,2-aminoalcohol **6** in 94 and 55% yield, respectively. Moreover, the chiral synthesis of propargylic thiiranes[12] **7** was accomplished by a double S_N2 type mechanism, giving the desired product in 55% yield based on recovered starting material and with no loss of optical purity.

Encouraged by these results, we decided to exploit the possibility of combining other β-heterofunctionalizations with the in situ homologation strategy. Gratifyingly, the predicted versatility and robustness of this "assemble and build" type tactic for synthesis of homopropargylic compounds could be realized for nucleophiles such as amines, sulfides and triazoles as described in Table 2.

Homopropargylic amines are typically prepared by a Barbier-type reaction of propargylic bromides and aldimines.[13] However, this usually requires stoichometric use of metals such as indium. Recently, Soderquist et al. reported an asymmetric allenylboration leading to optically active homopropargylic amines.[13b] Our approach, by merging the organocatalyzed β-amination reaction[7n,o] of α,β-unsaturated aldehydes with the Ohira–Bestmann homologation by using succinimide as the nucleophilic nitrogen source, allowed a more convenient method for preparation of optically active homopropargylic amines. Evaluating a plethora of readily available aliphatic α,β-unsaturated aldehydes, we found the

Table 2. Scope of the organocatalytic synthesis of diverse homopropargylic compounds.[a]

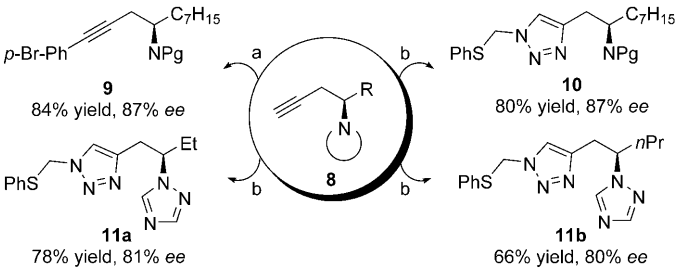


	R (**1**)	X	Product	Yield [%][b]	*ee* [%][c]
1	*n*-butyl (**1a**)	suc	**8a**	43	87
2	*n*-propyl (**1i**)	suc	**8b**	41	87
3	CH_2OBn (**1f**)	suc	**8c**	40	85
4	ethyl (**1h**)	suc	**8d**	44	85
5[d]	ethyl (**1h**)	suc	*ent*-**8d**	42	−85
6	*n*-heptyl (**1j**)	suc	**8e**	43	88
7	*cis*-$(CH_2)_2CH{=}CHC_2H_5$ (**1k**)	suc	**8f**	48	85
8	$(CH_2)_2Ph$ (**1L**)	suc	**8g**	30	88
9	*i*-propyl (**1b**)	*t*BuSH	**8h**	34	89
10	Ph (**1d**)	*t*BuSH	**8i**	48	85
11	*i*-propyl (**1b**)	triaz	**8j**	44	79
12	ethyl (**1h**)	triaz	**8k**	47	81
13	*n*-propyl (**1i**)	triaz	**8l**	49	80

[a] Reaction performed on 0.20 mmol scale, for each specific reaction condition, see the Supporting Information; Nuc = nucleophile, suc = succinimide; triaz = 1,2,4-triazole. [b] Yields of isolated products after column chromatography. [c] *ee* determined by chiral stationary phase HPLC. [d] The enantiomer of catalyst **3** was used.

reaction to be unbiased to chain size (Table 2, entries 1, 2, and 4–6) or saturation (Table 2, entry 7) providing the desired optically active products **8a**, **8b**, and **8d–8f** in moderate to good yields and high enantioselectivities. For substrates carrying functionalities such as a hydroxybenzyl (Table 2, entry 3) or a phenyl group (Table 2, entry 8), the reaction also proceeded smoothly and in 85–88% *ee*. The preparation of homopropargylic sulfides was achieved using *tert*-butyl sulfide as nucleophile. Significantly, in this case both aliphatic (Table 2, entry 9) and aromatic (entry 10) substituents were tolerated affording the products **8h** and **8i** in 34–48% yield and 85–89% *ee*. The low yield in the case of (*E*)-4-methylpent-2-enal results mainly from the highly volatile nature of the product. Finally, 1,2,4-triazole could also be included as reaction partner giving rise to the synthesis of homopropargylic N-heterocycles **8j–8l**. However, in this case, pre-prepared Ohira–Bestmann reagent was used to combat the diminishing yields obtained from the typical in situ generation method. As a proof of concept, three aldehydes with linear or branched side chains were transformed into the requisite products **8j–8l** in 44–49% yield and 79–81% *ee*.

Having remarked the transformational diversity of the homopropargylic adducts, we next employed the obtained protected optically active amine[14] **8e** in several general and reliable transformations. In doing so, compound **8e** was coupled with an aryl iodide under standard Sonogashira conditions[15] providing the internal homopropargylic amine **9** in 84% yield and with full conservation of the optical integrity. Given the importance of the N-heterocyclic structure in life science,[16] we demonstrate that enantiomerically enriched triazoles can be obtained by "clicking" the same starting alkyne with organic azides, as exemplified by the formation of **10** in 80% yield and 87% *ee*. Alternatively, by starting from the homopropargylic triazoles **8k** and **8l**, optically active 1,2-ditriazoles (**11a** and **11b**) with differentiated substitution pattern were obtained (Scheme 3).



Scheme 3. Transformations of the homopropargylic compounds. NHPg = succinimide. a) CuI, $[Pd(PPh_3)_4]$, *p*-Br-PhI, Et_3N, 60 °C, 4 h; b) sodium ascorbate, $CuSO_4$, $PhSCH_2N_3$, H_2O/*t*BuOH, RT, overnight.

In summary, we have demonstrated that the iminium-ion activation mode can be conceptually extended to a highly efficient "assemble and build strategy" for divergent synthesis of chiral propargylic, homopropargylic, and allenic compounds. The structural types produced by the reactions described in this communication include propargylic epoxides and thiiranes; homopropargylic amines, sulfides, and triazoles; allenic alcohols, click and Sonogashira adducts, all derived entirely from readily available starting materials. The flexibility with which organocatalyzed functionalizations can be joined with the Ohira–Bestmann homologation reaction should certainly facilitate new reaction development leading to generation of other synthetically relevant compounds.

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