Organocatalysis

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Chiral Allenes via Alkynylogous Mukaiyama Aldol Reaction

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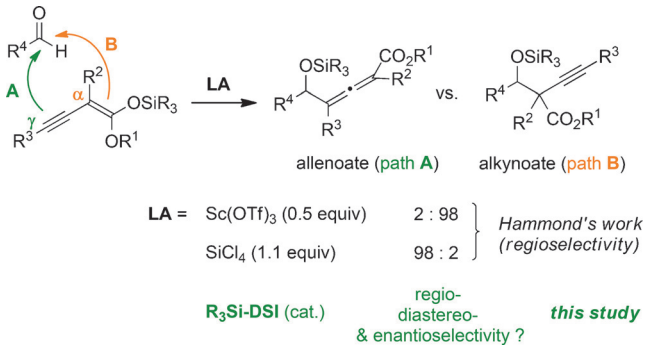
Abstract: *Herein we describe the development of a catalytic enantioselective alkynylogous Mukaiyama aldol reaction. The reaction is catalyzed by a newly designed chiral disulfonimide and delivers chiral allenoates in high yields and with excellent regio-, diastereo-, and enantioselectivity. Our process tolerates a broad range of aldehydes in combination with diverse alkynyl-substituted ketene acetals. The reaction products can be readily derivatized to furnish a variety of highly substituted enantiomerically enriched building blocks.*

Allenes are surprisingly abundant and found in hundreds of natural products with biological activity.[1] They are also attractive motifs for chemical synthesis owing to their unusual properties and reactivity. As cumulated dienes, allenes often display higher reactivity than their noncumulated analogues. Moreover, allenes display a peculiar axial chirality characterized by their elongated tetrahedral geometry. Over the past years, the allene scaffold has been exploited in different ways including to create versatile synthetic intermediates and chiral ligands for asymmetric catalysis.[2,3] Despite the demand for chiral allenes though, enantioselective methods for their synthesis are limited. Indeed, they are most commonly prepared by the resolution of racemic allenes and reactions involving chirality transfer from enantiomerically enriched propargyl alcohols or amines.[4–6] More recently, metal-catalyzed asymmetric allene syntheses have also been reported.[7] In contrast, organocatalytic approaches still remain underexplored and are largely limited to di- or trisubstituted allenes.[8] A significant breakthrough in this area was made in 2013 by Maruoka and co-workers, who reported the asymmetric functionalization of cumulenolates under phase-transfer catalysis. This methodology gave access to chiral tetrasubstituted allenes through alleno-Mannich and alkylation reactions.[9] However, the corresponding asymmetric aldol reaction remained challenging. Recently, Feng and co-workers reported a gold-catalyzed nucleophilic addition of racemic allenoates to isatins with high diastereo- and enantioselectivity.[10] We now report an unprecedented alkynylogous Mukaiyama aldol reaction, which is catalyzed by a newly designed chiral disulfonimide and provides tetrasubstituted allenoates with excellent diastereo- and enantioselectivity.

Several challenges had to be considered in the design of an asymmetric alkynylogous Mukaiyama aldol reaction. In addition to the enantioselectivity issue, two different regioisomers can be produced, the carbinol allenoate through γ-addition of the alkynyl ketene acetal, and the hydroxy alkynoate product through α-addition. Moreover, as a result of the generation of two stereogenic elements, four stereoisomers can be generated in both cases. In 2008,[11] Hammond et al. reported a Lewis acid mediated non-enantioselective alkynylogous Mukaiyama aldol reaction that provided a solution to the α/γ-selectivity problem (Scheme 1). Depending on



Scheme 1. α versus γ selectivity in the alkynylogous Mukaiyama aldol reaction. Tf = trifluoromethanesulfonyl.

the Lewis acid (LA), the reaction gave access either to the alkyne (LA = $Sc(OTf)_3$) or to the allene product (LA = $SiCl_4$). High regioselectivity but no diastereoselectivity was observed.[11–13] On the basis of our previous studies on silylated disulfonimide (DSI)-catalyzed Mukaiyama aldol reactions and vinylogous and bisvinylogous variants, we became interested in also exploring silyl alkynyl ketene acetals as nucleophiles.[14] We hypothesized that our silylated disulfonimide Lewis acid could potentially catalyze such an alkynylogous aldol reaction and thus offer a regio-, diastereo-, and enantioselective approach to the synthesis of chiral tetrasubstituted allenes.

We began our investigations by using the silyl alkynyl ketene acetal **2** in combination with 2-naphthaldehyde (**1**) as a model electrophile (Table 1). The initial objective was to study the regioselectivity of the transformation to give carbinol allenoate **4**. By using (*R*)-DSI **3a**, we explored the nature of the silicon group on the nucleophile. As expected, a strong impact of the size of the silicon group on the regioselectivity was observed. The TES group gave a 1:1 mixture of product **4** and hydroxy alkynoate **5**. A significant improvement was noted with the TBS group, which led to a 9:1 ratio in favor of the allene, formed with 6:1 d.r. and a promising enantiomeric ratio of 88:12 (Table 1, entries 1 and 2). The TIPS-substituted nucleophile led to a further increase in regio- and diastereoselectivity but also to a lower enantiomeric ratio (Table 1, entry 3). Several DSI catalysts

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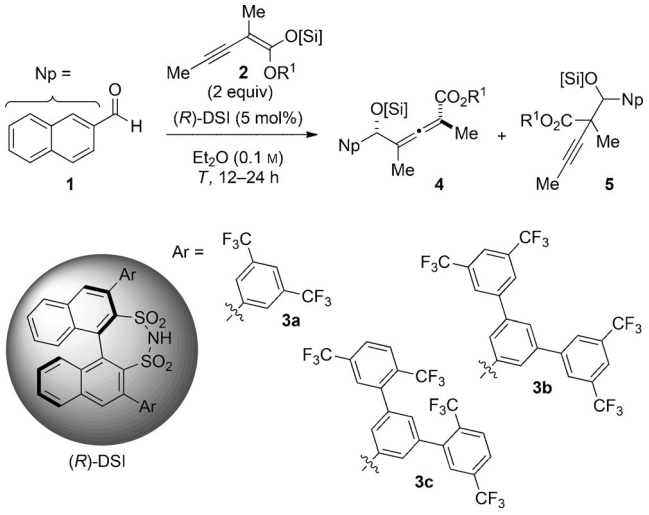
Table 1: Reaction development.[a]



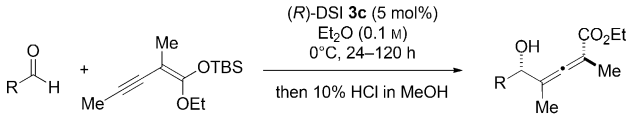
Entry	(*R*)-DSI	[Si]	R^1	Conv. [%][b]	**4**/**5**	d.r.[b]	e.r.[c]
1	**3a**	TES	Et	>95	1:1	2:1	80:20[d]
2	**3a**	TBS	Et	>95	9:1	6:1	88:12[d]
3	**3a**	TIPS	Et	>95	>20:1	9:1	78:22[e]
4	**3b**	TBS	Et	>95	10:1	8:1	90:10[d]
5	**3c**	TBS	Et	>95	16:1	16:1	97.5:2.5[d]
6	**3c**	TBS	Me	>95	9:1	9:1	96.5:3.5[e]
7	**3c**	TBS	*i*Pr	>95	>20:1	20:1	96:4[e]
8	**3c**	TBS	*t*Bu	<5	–	–	–
9[f]	**3c**	TBS	Et	>95	>20:1	19:1	98:2[d]

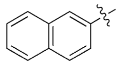
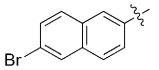
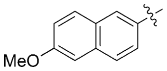
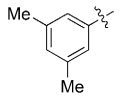
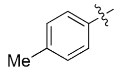
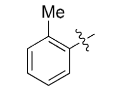
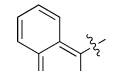
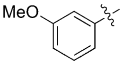
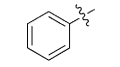
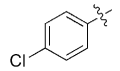
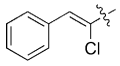
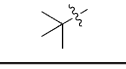
[a] Reactions were carried out at room temperature on a 0.05 mmol scale and quenched after 12 h. [b] The conversion and diastereomeric ratio were determined by ^{1}H NMR analysis. [c] The enantiomeric ratio was determined by HPLC on a chiral stationary phase. [d] The enantiomeric ratio was determined after cleavage of the silicon group with 10% HCl in MeOH. [e] The enantiomeric ratio was determined after saponification with LiOH in MeOH. [f] The reaction was carried out at 0°C and quenched after 24 h. TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl.

were then screened. The use of catalyst **3b** with 3,5-di(trifluoromethyl)benzene substitution in the 3,3′-position of the backbone gave us a hint about the nature of the "ideal" catalyst for this reaction, since all selectivity parameters were increased (Table 1, entry 4).[14c] In fact, by simply modulating the CF_3 substitution on those aromatic moieties, we obtained catalyst **3c** with 2,5-di(trifluoromethyl)benzene substitution, which afforded excellent enantioselectivity (97.5:2.5 e.r.) and high regio- and diasteroselectivity (16:1 ratio in both cases; Table 1, entry 5). Variation of the ester group (R^1) revealed that the ethyl moiety represented the best compromise in terms of diastereo- and enantioselectivity as compared to methyl and isopropyl groups (Table 1, entries 5–7). Use of the corresponding *tert*-butyl ester derived ketene acetal did not lead to any conversion (Table 1, entry 8). Optimized conditions were finally established with Et_2O (see the Supporting Information for solvent screening) at 0°C. Under these conditions, the desired allene **4** was obtained with excellent regioselectivity (>20:1), 19:1 d.r., and 98:2 e.r. (Table 1, entry 9).

The scope of the enantioselective alkynylogous Mukaiyama aldol reaction with respect to the electrophile was then investigated under these optimal conditions (Table 2). When 2-naphthaldehyde was employed, the transformation afforded product **6a** in 85% yield with 19:1 d.r. and 98:2 e.r. after cleavage of the TBS group under acidic conditions (Table 2, entry 1). Substrates with a naphthyl core bearing a bromine or methoxy substituent at the 6-position gave access to the corresponding carbinol allenoates **6b** and **6c** in high yields with comparable diastereo- and enantioselectivity (Table 2, entries 2 and 3). The influence of substitution at different positions of the phenyl group was then studied. A *meta*,*meta*-dimethyl-substituted substrate provided the expected product **6d** in 78% yield with excellent 96:4 e.r. and 27:1 d.r. (Table 2, entry 4). Product **6e** was obtained from a *para*-methyl-substituted substrate with much

Table 2: Scope of the asymmetric alkynylogous Mukaiyama aldol reaction with respect to the aldehyde substrate.[a]



Entry	Product		Yield [%][b]	d.r.[c]	e.r.[d]
1[e]		**6a**	85	19:1	98:2
2		**6b**	78	18:1	98:2
3		**6c**	92	17:1	97:3
4		**6d**	78	27:1	96:4
5		**6e**	82	10.6:1	92:8
6		**6f**	69[f]	3.7:1	75.5:24.5
7		**6g**	72	7.6:1	95:5
8		**6h**	75	15:1	96:4
9		**6i**	92	12.5:1	93:7
10		**6j**	68[f]	12.3:1	92.5:7.5
11		**6k**	52	4.5:1	95:5
12		**6l**	<5	–	–

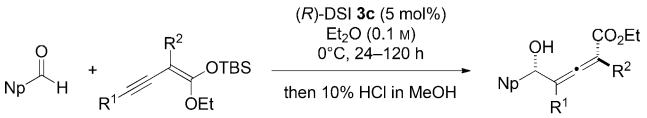
[a] Reactions were carried out on a 0.15 mmol scale. All regioisomeric ratios were above 20:1. [b] The yield was determined for the mixture of the two diastereoisomers. [c] The diastereomeric ratio was determined by ^{1}H NMR analysis. [d] The enantiomeric ratio was determined by HPLC on a chiral stationary phase. [e] The reaction was carried out on a 1.5 mmol scale. [f] The starting material was recovered.

lower diastereoselectivity and a slight decrease in enantioselectivity (Table 2, entry 5). In comparison, *ortho* substitution had a dramatic effect on both the diastereo- and enantioselectivity: product **6f** was isolated with 3.7:1 d.r. and 75.5:24.5 e.r. (Table 2, entry 6). 1-Naphthaldehyde and *meta*-methoxybenzaldehyde proved to be good substrates for the reaction, which afforded **6g** and **6h** with enantiomeric ratios of 95:5 and 96:4, respectively. Interestingly, *para*-chloro-substitution on the starting material had no effect in terms of diastereo- and enantioselectivity (product **6j**), since very similar results were obtained for product **6i** when benzaldehyde was used (Table 2, entry 9 vs. 10). The transformation also proceeded well with α-chlorocinnamaldehyde to give product **6k** with 95:5 e.r. but with moderate yield and diastereoselectivity. Finally, the use of aliphatic aldehydes in this reaction is currently a challenge, and no reactivity was observed with pivalaldehyde (Table 2, entry 12). Enolizable aliphatic aldehydes led to the formation of the corresponding enol silanes (see the Supporting Information). The absolute configuration of allenoate **6j** was determined to be 3*R*,5*S* by single-crystal X-ray analysis of a derivative (see the Supporting Information).[15] The configurations of the other products were assigned by analogy.

The scope of the reaction with respect to the nucleophile was also explored (Table 3). A terminally phenyl substituted nucleophile, **2m**, reacted with naphthaldehyde (**1**) in the presence of (*R*)-DSI **3c** (5 mol%) to give product **6m** with somewhat lower reactivity and selectivity as compared to the methyl-substituted substrate (Table 3, entry 2 vs. 1). A substrate with a longer aliphatic linear chain at the same position was also tested, and product **6n** was obtained in 68% yield with excellent selectivity (96.5:3.5 e.r. and 13:1 d.r.). The R^2 group was investigated next. Product **6o** with an *n*-butyl substituent was obtained in 68% yield with very high diastereoselectivity (20:1 d.r.) and enantioselectivity (98.5:1.5; Table 3, entry 4). The benzyl group proved to be a suitable substituent as well, giving access to the tetrasubstituted allene **6p** in a 50% yield with d.r. 11:1 and an excellent enantiomeric ratio (98.5:1.5; Table 3, entry 5).

The significant interest in chiral allenes is based on their ability to be readily converted into enantiomerically enriched building blocks by chirality transfer.[16] To illustrate the utility of our products, we prepared four different highly substituted scaffolds from the enantiomerically and diastereomerically enriched substrate **6a** (Scheme 2). After saponification of the ester moiety with LiOH in EtOH, the corresponding carboxylic acid reacted by intramolecular lactonization in the presence of $AgNO_3$ (10 mol%).[11] γ-Lactone **7** was obtained in 83% yield over the two steps and with perfect retention of the stereogenic information. The enantiomerically enriched dihydrofuran **8** could be generated directly from allene **6a** in 77% yield by the use of a catalytic amount of a gold complex activated by silver triflate,[11] again with complete preservation of stereochemical purity. $NaBH_4$ was used a reducing agent for the selective formation of *E* olefin **9**.[17] We suspect the intermediate formation of an alkoxyborohydride species, followed by the internal 1,4-addition of a hydride to the Michael acceptor system. Product **9** was obtained in 44% yield with low diastereoselectivity but with high enantiomeric ratios for both diastereomers. Remarkably, the methylation of allenoate **6a** with a mixture of MeLi and CuI in THF proceeded towards the exclusive formation of the *Z* double bond, and subsequent lactonization furnished product **10** in 59% yield with an excellent enantiomeric ratio for each diastereoisomer. We assume that this process involves

Table 3: Scope of the asymmetric alkynylogous Mukaiyama aldol reaction with respect to the nucleophile.[a]



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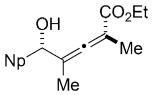
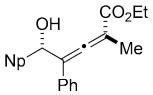
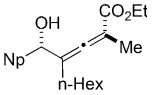
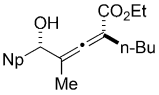
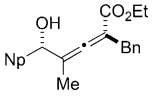
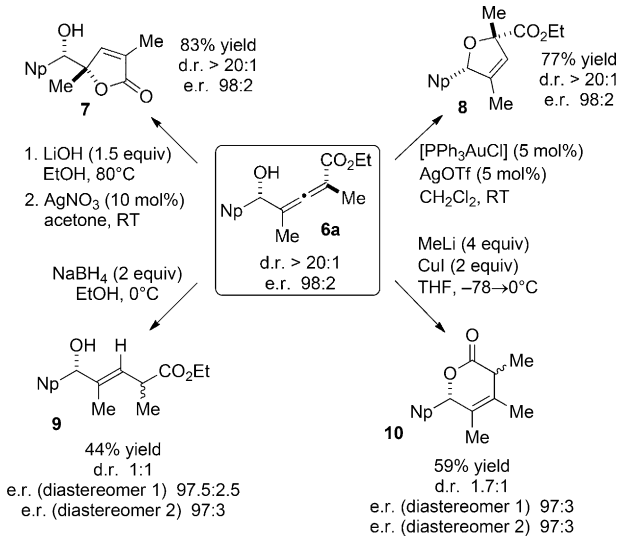
Entry	Product		Yield [%][b]	d.r.[c]	e.r.[d]
1		**6a**	85	19:1	98:2
2[e]		**6m**	33[f]	5:1	93.5:6.5
3		**6n**	68	13:1	96.5:3.5
4		**6o**	68	20:1	98.5:1.5
5		**6p**	50	11:1	98.5:1.5

[a] Reactions were carried out on a 0.15 mmol scale. All regioisomeric ratios were above 20:1. [b] The yield was determined for the mixture of the two diastereoisomers. [c] The diastereomeric ratio was determined by ^{1}H NMR analysis. [d] The enantiomeric ratio was determined by HPLC on a chiral stationary phase. [e] The reaction was carried out at room temperature. [f] The starting material was recovered.



Scheme 2. Derivatization of the enantiomerically enriched carbinol allenoate **6a**.

stereoselective cuprate addition to the less-hindered face of the lithiated alkoxide intermediate.[17]

In summary, we have developed an alkynylogous Mukaiyama aldol reaction for the synthesis of chiral, enantiomerically enriched allenes. Versatile silyl alkynyl ketene acetals in combination with precatalyst disulfonimide **3c** deliver a silylium-ion-based Lewis acid, which is able to activate a broad range of aldehydes. Chiral tetrasubstituted allenes were obtained in high yields with excellent regio-, diastereo-, and enantioselectivity. Finally, various useful transformations of the products gave access to diverse highly substituted enantiomerically enriched building blocks.

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Keywords: aldol reactions · allenes · disulfonimides · Lewis acids · organocatalysis

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