Asymmetric Catalysis

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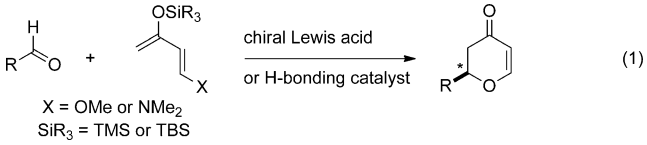
Highly Enantioselective Hetero-Diels–Alder Reaction of 1,3-Bis-(silyloxy)-1,3-dienes with Aldehydes Catalyzed by Chiral Disulfonimide**

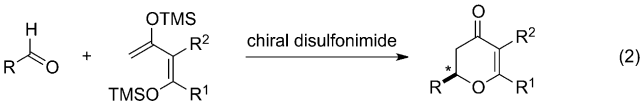
*Joyram Guin, Constantinos Rabalakos, and Benjamin List**

Originating from observation by Danishefsky et al. that hetero-Diels–Alder (HDA) reactions of 1-methoxy-3-(trimethylsilyloxy)butadiene (Danishefsky's diene) with aldehydes are accelerated by Lewis acids [Eq. (1); TMS = trimethylsilyl],[1] asymmetric variants became extensively studied and utilized in the synthesis of enantioenriched six-membered oxygen-containing heterocycles.[2] Indeed, several efficient metal-based chiral Lewis acids have been developed for this reaction.[3] Recently, Rawal and co-workers introduced a metal-free, hydrogen-bonding catalyst for asymmetric HDA reactions of 1-dimethylamino-3-*tert*-butyldimethylsilyloxy-1,3-butadiene (Rawal's diene) with aldehydes [Eq. (1), TBS = *tert*-butyldimethylsilyl].[4] Despite all this progress however, the present catalytic systems for asymmetric HDA reactions are largely limited to the originally introduced dienes, and substituted and functionalized dienes have proven to be highly challenging substrates.[3c,e,g,5] As a consequence, only few catalytic asymmetric syntheses of 2,6-disubstituted dihydropyrones have been reported and the catalytic enantioselective synthesis of 2,5,6-trisubstituted dihydropyrones is entirely unknown.[6,7] Herein, we report a highly enantioselective HDA reaction of aldehydes with substituted 1,3-bis(silyloxy)-1,3-dienes catalyzed by a novel, highly fluorinated, chiral disulfonimide [Eq. (2)].



(1)

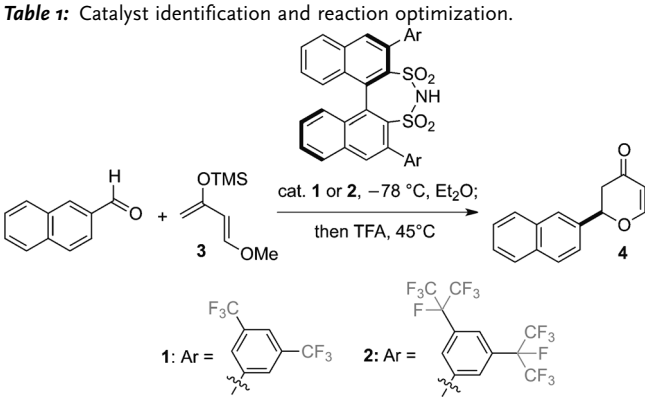
Recently our group has introduced chiral disulfonimides (DSI) as effective catalysts of asymmetric Mukaiyama and vinylogous Mukaiyama aldol reactions with aldehydes.[8,9] We hypothesized that such a catalyst could also promote the mechanistically related HDA reactions of 1,3-bis(silyloxy)-1,3-dienes, which surprisingly have previously been utilized only in non-asymmetric catalysis.[10–12] Our interest in this particular transformation was further stimulated by speculating that the lack of established catalytic asymmetric HDA reactions might stem from a competing silylium-catalyzed background reaction.[13] We had previously shown that disulfonimide-based catalysis offers an efficient solution to this problem in Mukaiyama aldolizations.



(2)

To explore the principal utility of our DSI catalysts in HDA reactions, we initially studied our previously used chiral disulfonimide catalyst **1** in the reaction of 2-naphthaldehyde with the commercially available diene **3**. These experiments showed that the product **4** could indeed be obtained in the presence of 5 mol% of catalyst **1** at −78 °C in Et_2O in good yield and reasonable enantioselectivity (Table 1, entry 1). We reasoned that improving the steric and electronic properties of the catalyst by incorporating large perfluorinated substitu-

Table 1: Catalyst identification and reaction optimization.



Entry[a]	Cat. (mol%)	**3** (equiv)	*t* [d]	Yield [%][b]	e.r.[c]
1	**1** (5.0)	1.5	0.5	77	87:13
2	**2** (5.0)	1.5	0.5	83	96:4
3	**2** (1.0)	2.0	3.0	89	96:4
4	**2** (0.5)	2.0	4.0	60	97:3
5[d]	**2** (1.0)	2.0	4.0	89	97:3

[a] Reaction conditions: 0.125 mmol of aldehyde and 0.25 mmol of diene were stirred in the presence of catalyst in Et_2O [0.16 M] at −78 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 0.12 M. TFA = trifluoroacetic acid.

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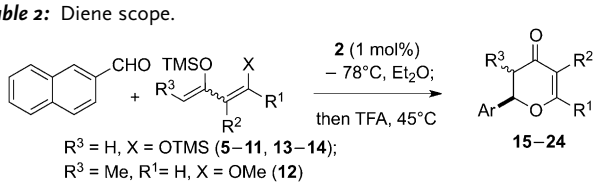
ents at the 3,5-positions of the 3,3′-aryl moieties in the disulfonimide backbone could have a beneficial effect on the enantioselectivity and at the same time may also enhance the catalytic activity. To test our hypothesis, we synthesized the new disulfonimide **2** in which the CF_3 groups have been replaced by the larger perfluoroisopropyl substituent (for the synthesis of catalyst **2** see the Supporting Information). As hoped, the newly synthesized catalyst **2** was found to be significantly more enantioselective than **1**. With 5 mol% of **2**, the desired product was obtained in good yield and with an enantiomeric ratio of 96:4 (Table 1, entry 2). Importantly, the catalyst loading could be reduced to only 1 mol% without diminishing the reaction efficiency, but also requiring a slightly higher diene concentration and longer reaction time (Table 1, entry 3). A small improvement on the enantioselectivity was further noticed upon lowering the amount of catalyst to 0.5 mol%, but then full conversion of the aldehyde could not be achieved (Table 1, entry 4). The best reaction outcome was obtained upon using 1 mol% of **2** at a 0.12 M substrate concentration (Table 1, entry 5).

After establishing the optimal reaction conditions with the diene **3**, we began exploring the scope of this transformation with various densely substituted 1,3-bis(silyloxy)-1,3-dienes. Importantly, these dienes are readily synthesized in one step by the reaction of commercially available and inexpensive 1,3-diketones with TMSOTf and Et_3N or with LDA and TMSCl.[10c,11,12] Dienes were obtained as a *E*/*Z* mixture and used as such. We were pleased to find that linear 1,3-bis(silyloxy)-1,3-dienes **5**–**11** underwent smooth reaction with 2-naphthaldehyde in the presence of 1 mol% of **2**. Essentially all dienes delivered the corresponding products in good to excellent enantiomeric ratio (Table 2). The nature of the diene substituents has a significant influence on the chemical reactivity and the enantioselectivity. Substantial improvement of the enantioselectivity was realized by increasing the steric bias of the diene (Table 2, entries 1–3), that is, when dienes **5**–**7** were employed with 2-naphthaldehyde under the optimized reaction conditions, the corresponding 2,6-disubstituted dihydropyrones **15**–**17** were obtained in good yields and enantioselectivity. The tetrasubstituted dienes **8**–**11** were particularly useful and all of them provided the corresponding 2,5,6-trisubstituted dihydropyrones **18**–**21** in good yields with excellent enantioselectivity (Table 2, entries 4–7). It is noteworthy to mention that the catalytic enantioselective synthesis of products **18**–**21** has not been achieved previously. Furthermore, the diene **12**, bearing a terminal substituent, could also be utilized, thus furnishing product **22** with two contiguous stereocenters in good yield with moderate diastereoselectivity and good enantioselectivity (Table 2, entry 8).

We further expanded the utility of the asymmetric catalytic HDA reaction towards the synthesis of enantioenriched polycyclic skeletons by making use, for the first time, of the so-called inner-outer-ring 1,3-bis(silyloxy)-1,3-dienes **13** and **14**.[11] The diene **13** was found to be somewhat less reactive, and the reaction proceeded only at −15 °C, thus furnishing the bicyclic product **23** in reasonable yield with excellent enantioselectivity (Table 2, entry 9), while **14**, the benzene-fused analogue of **13**, proved to be more reactive and provided the tricyclic dihydropyrone **24** with even higher enantioselectivity and yield (Table 2, entry 10). The absolute configuration of compound **21** was determined to be *R* by single-crystal X-ray structure analysis (see the Supporting Information).

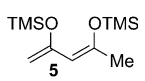
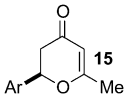
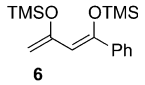
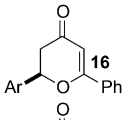
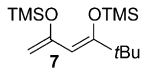
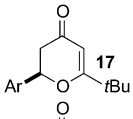
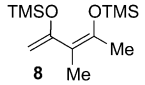
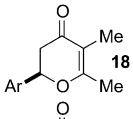
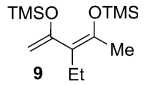
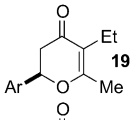
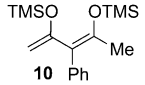
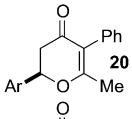
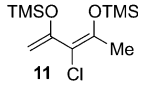
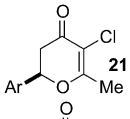
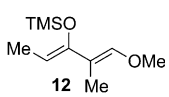
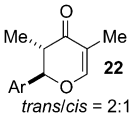
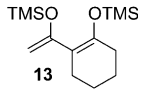
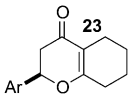
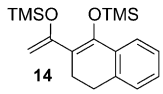
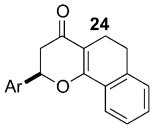
Encouraged by our exploration of the diene scope, we next investigated the utility of various aldehydes. The dienes **3**, **7**, and **8** were used in this study (Table 3). The diene **3** reacted with 6-methoxy-2-naphthaldehyde and *meta*-substi-

Table 2: Diene scope.



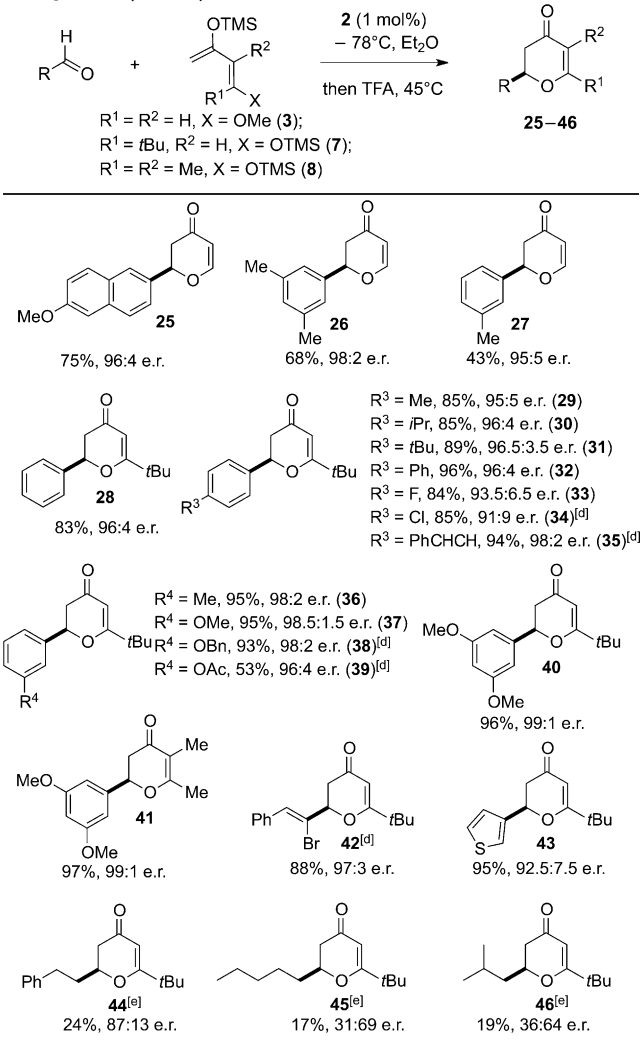
R^3 = H, X = OTMS (**5**–**11**, **13**–**14**);
R^3 = Me, R^1= H, X = OMe (**12**)

15–**24**

Entry[a]	Diene[b]	Product	Yield [%][c]	e.r.[d]
1	 **5**	 **15**	91	96:4
2[e]	 **6**	 **16**	56	96:4
3	 **7**	 **17**	97	99:1
4	 **8**	 **18**	95	99:1
5	 **9**	 **19**	75	98:2
6	 **10**	 **20**	87	98:2
7	 **11**	 **21**	88	96:4
8[f]	 **12**	 **22** *trans*/*cis* = 2:1	93	86:14 (*trans*), 7:93 (*cis*)
9[g]	 **13**	 **23**	64	97:3
10	 **14**	 **24**	95	>99:1

[a] Reaction conditions: 0.125 mmol of aldehyde, 0.25 mmol of diene, and 1 mol% of catalyst **2** were stirred in Et_2O [0.12 M] for 4 days at −78 °C. [b] Used as *E*/*Z* mixture. [c] Yield of isolated product. [d] Determined by HPLC analysis on a chiral stationary phase. [e] At −30 °C, 5 d. [f] At −50 °C, a 2:1 diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [g] At −15 °C, 5 d. Ar = 2-naphthyl.

Table 3: Aldehyde scope.[a,b,c]

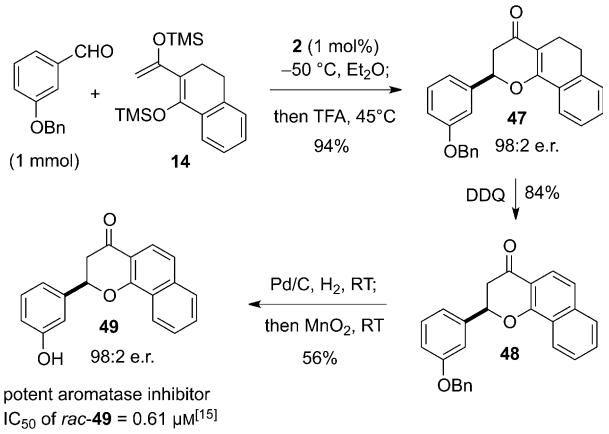


[a] Reaction conditions: 0.125 mmol of aldehydes, 0.25 mmol of diene, and 1 mol% of catalyst **2** were stirred in Et_2O [0.12 M] at −78 °C for 4 days. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] −60 °C. [e] −10 °C, 10 d.

tuted benzaldehydes with very good enantioselectivity and reasonable yields (**25**–**27**). The diene **7** was found to be more effective and versatile in our catalytic HDA reaction. Comparing the results of the reactions of **3** and **7** with 2-naphthaldehyde and *m*-tolualdehyde clearly demonstrated the superiority of **7** over **3** under our reaction conditions (compare: Table 1, entry 5 with Table 2, entry 3, and compound **27** with **36** in Table 3). With **7**, benzaldehyde and *para*-substituted benzaldehydes delivered the corresponding products **28** and **29**–**35** in good yields (83–96%) and enantioselectivity (e.r. = 91:9–98:2). Electron-deficient aldehydes such as *p*-fluoro- or *p*-chlorobenzaldehyde gave slightly lower enantioselectivity (**33** and **34**, respectively). Even stronger electron-withdrawing aldehydes such as *p*-nitrobenzaldehyde turned out to be unreactive under our reaction conditions. The *meta*-substituted benzaldehydes underwent product formation with uniformly good yields and enantioselectivity (**36**–**39**). 3,5-Dimethoxybenzaldehyde underwent the reaction with **7** and **8** in equal efficiency (**40** and **41**, respectively). A conjugated aromatic aldehyde and a heteroaromatic aldehyde could also be used as substrates (**42** and **43**, respectively). Unfortunately, aliphatic aldehydes were found to be extremely challenging substrates in our HDA reaction and low chemical yields and only moderate enantioselectivity of the desired products were obtained (**44**–**46**).

Absolute configurations of *R* were also determined for the compounds **27** and **34** by comparing the sign of the optical rotation with that of the literature data[14] and single-crystal X-ray structure analysis, respectively (see the Supporting Information).

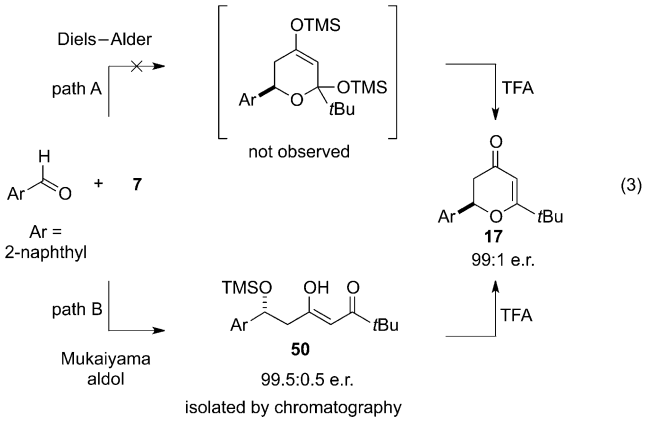
To demonstrate the utility of our methodology, we have developed the first asymmetric route to the 3′-hydroxy-substituted 7,8-benzoflavanone **49**, a potent aromatase inhibitor (Scheme 1). The compound **49** exhibits higher aromatase



Scheme 1. Synthesis of aromatase inhibitor **49**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

inhibitory activity than aminogluthetimide, which is the first nonsteroidal aromatase inhibitor used clinically in the treatment of breast cancer.[15] Treating 3-benzyloxybenzaldehyde with **14** under optimized reaction conditions gave ketone **47** in excellent yield and enantioselectivity on a 1 mmol scale. The resulting dihydropyrone **47** was easily aromatized to the corresponding 7,8-benzoflavanone **48** upon DDQ oxidation. After the sequential treatment of compound **48** with H_2/Pd-C and MnO_2 (to reoxidize the obtained benzylic alcohol), the desired benzoflavanone **49** was obtained in good overall yield and without erosion of enantiopurity.

Toward elucidation of the mechanism of our disulfonimide-catalyzed HDA reaction, we could isolate an intermediate in the reaction of **7** with 2-naphthaldehyde. This compound was shown to be the trimethylsilyloxy 1,3-diketone **50**, which easily cyclized to the corresponding HDA product **17** upon treatment with TFA, and only with a slight deterioration of enantiomeric ratio [Eq. (3)]. This observation suggests that our HDA reaction proceeds through a Mukaiyama aldol pathway [path B, Eq. (3)], which is in agreement with the widely accepted mechanism of other (though not all)[3o] Lewis acid catalyzed HDA reactions of Danishefsky's diene with aldehydes.[3t,16]



In summary, we have presented an efficient catalytic enantioselective HDA reaction of Danishefsky's diene, as well as the challenging linear- and inner-outer-ring 1,3-bis(silyloxy)-1,3-dienes, with aldehydes catalyzed by a novel chiral disulfonimide. Several previously inaccessible highly enantioenriched 2,6-disubstituted and 2,5,6-trisubstituted dihydropyrones have been synthesized. Polycyclic dihydropyrones can be easily modified (e.g. by aromatization), thus giving access to enantioenriched biologically active benzoflavanone derivatives. Moreover, a wide range of aldehydes can be used as substrates. A Mukaiyama aldol reaction mechanism has been established by isolating the corresponding intermediate. Our new highly fluorinated disulfonimide catalyst represents a significant improvement over the originally reported catalyst and further strengthens the potential of disulfonimide catalysis. Additional studies aim at identifying a suitable catalyst for using aliphatic aldehydes and ketones, and the application of our methodology in the synthesis of enantioenriched natural products and bio-active materials.

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Communications

Asymmetric Catalysis

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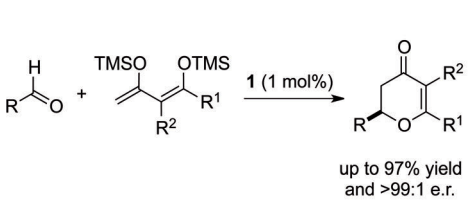
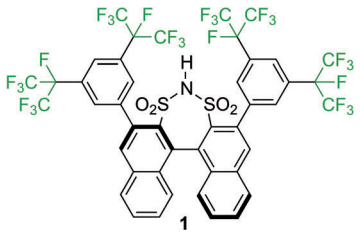
Highly Enantioselective Hetero-Diels–Alder Reaction of 1,3-Bis(silyloxy)-1,3-dienes with Aldehydes Catalyzed by Chiral Disulfonimide





Bulking up with F: The title reaction proceeds using 1 mol% of the new perfluoroisopropyl chiral disulfonimide catalyst **1** to deliver several 2,6-disubstituted and 2,5,6-trisubstituted dihydropyrones in good yields and with excellent enantiomeric ratios. The utility of this methodology is illustrated with the first enantioselective synthesis of a potent aromatase inhibitor.