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Chiral Sulfide Catalysis for Desymmetrizing Enantioselective Chlorination

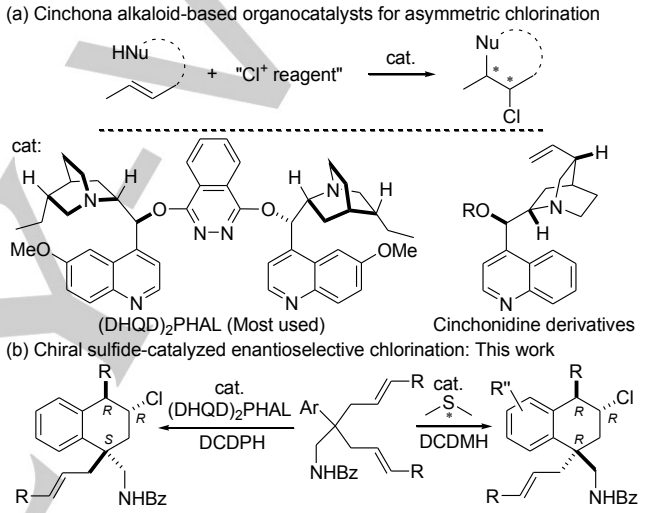
Qingxiang Cao, Jie Luo, and Xiaodan Zhao*

Abstract: *Unprecendented chiral sulfide-catalyzed desymmetrizing enantioselective chlorination is disclosed. Various aryl-tethered diolefins and diaryl-tethered olefins afforded teralins or tricyclic hexahydrophenalene derivatives bearing multiple stereogenic centers in high yields with excellent enantio- and diastereoselectivities. In contrast, tertiary amine catalyst (DHQD)$_2$PHAL led to a diastereomer product. The products could be transformed to diverse compounds such as spiro N-heterocycles.*

Catalytic halogenation has received considerable attention in recent years.[1-3] As a very important subdivision in this field, electrophilic halofunctionalization provides a convenient pathway to quickly construct chiral halogenated molecules.[2,3] However, enantioselective electrophilic chlorination, especially with alkenes, has been far less explored than the corresponding bromination and iodination[1-8] although chlorine atom is a good convertible group and widely exists in a huge number of bioactive compounds and natural products.[9] To date, most methods for electrophilic chlorination rely on the use of cinchona alkaloid-based organocatalysts such as (DHQD)$_2$PHAL and cinchonidine derivatives to deliver enantioselectivity (Scheme 1a).[4-8] But the relatively strong basicity of these organocatalysts limits the reactivity and scope of substrates. Furthermore, their specific chiral scaffold cannot satisfy the requirement of chiral environment in some cases. These features largely hamper the development of enantioselective chlorination.

Lewis basic organochalcogen catalysis has emerged as a powerful tool in enantioselective alkene transformations due to the particular catalytic properties and readily availability of chiral organochalcogen catalysts.[10-12] These catalysts have less basicity and are more compatible with neutral or acidic conditions in contrast to *N*-based chiral Lewis base catalysts. They can properly catch ArS^+, Br^+ or CF_3S^+ to form a complex, and then react with alkenes to generate chiral iranium ions, followed by nucleophilic attack to give products. It is reasoned that this unique catalytic fashion might be suitable for enantioselective chlorination. Nevertheless, no successful enantioselective example has been demonstrated until now although Denmark and Yeung groups have made great efforts in this regard.[11a,f,13] The great potential of this catalysis triggers us to explore its application in chlorination. Herein, we report our discovery that a bifunctional chiral sulfide can efficiently catalyze desymmetrizing chlorination of aryl-tethered diolefins to give chiral chlorinated tetralins with an all-carbon quaternary stereocenter (Scheme 1b). Interestingly, tertiary amine catalyst (DHQD)$_2$PHAL led to a diastereomer product bearing an opposite absolute configuration at the quaternary center.

According to the literature,[11a,f,13] organochalcogen-catalyzed enantioselective electrophilic chlorination of alkenes is quite difficult. Notably, there are two issues to be more challenging compared with similar reactions of alkenes involving bromiranium, arylthiiranium or trifluoromethylthiiranium ion: i) chlorenium ion is more reactive to be quenched by nucleophiles before the formation of chloriranium ion; ii) unstable chloriranium ion is more prone to form a free carbocation to erode the enantioselectivity of reaction or decompose. On the basis of our previous studies on bifunctional chalcogenide-catalyzed trifluoromethylthiolation,[12] we envisioned that bifunctional binding strategy might be able to solve the above issues in electrophilic chlorination of alkenes. This bifunctional binding might stabilize the chloriranium ion to prevent its decomposition and the formation of free carbocation to avoid the racemization. On the other hand, the binding might accelerate the nucleophilic attack toward the chloriranium ion, especially in an intramolecular way. The improvement of the rate of reaction could diminish the possibility that the chlorenium ion is quenched by nucleophiles.



Scheme 1. Catalytic enantioselective chlorination.

Based on the hypothesis, we would like to pursue an unprecedented desymmetrizing enantioselective chlorination. Aryl-tethered diolefin **1a** was selected as a model substrate (Table 1). This class of substrates possess an NHBz group as H-bonding donor and an aryl group as nucleophile. The chlorocyclization is particularly attractive since the resulting tetralins are a class of valuable compounds,[14] and contain a convertible alkene group and three stereogenic centers including an all-carbon quaternary center. Due to the excellent catalytic activity of selenide catalysts **C1** and **C2** in trifluoromethylthiolation,[12] they were first tested using 1.5 equivalents of NCS as chlorine source. It was found that the reactions almost did not work with or without TFA (entries 1-3). It was rationalized that the problem mainly stemmed from the deactivation of catalysts. This drove us to use chiral sulfide catalysts, a Lewis base that is harder and more resistant to oxidation than the corresponding selenide. Gratifyingly, when sulfide **C3** was utilized, the desired product **2a** was formed in 39% yield with 53% ee and 8:1 *dr* (entry 4). Slightly better result was obtained with catalyst **C4** bearing two methoxy groups (entry 5).

To further improve the reaction, different chlorine sources were screened. Highly reactive $(PhSO_2)_2$N-Cl and saccharin-Cl gave products in higher yields with lower selectivity, possibly because of the strong background reaction of non-catalyzed chlorination (entries 6 and 7). In contrast, relatively inert DCDMH improved the enantioseletivity to 73% ee (entry 8). But

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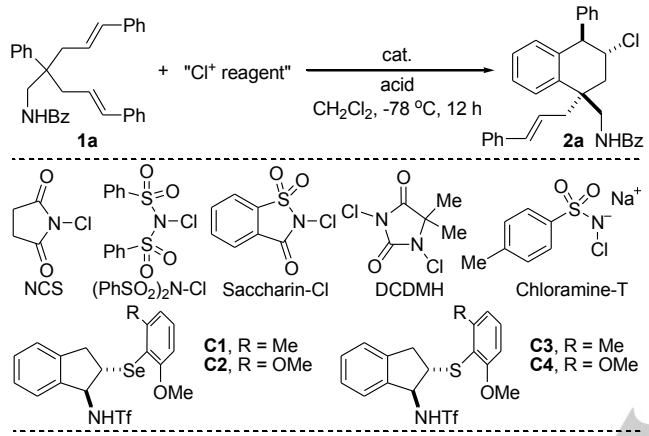
Chloramine-T gave little product because of the solubility problem (entry 9). Due to the important role of acid in electrophilic functionalization,[12] different acids were examined instead of TFA. To our surprise, enantiomer of **2a** was formed using Lewis acid TMSOTf or $BF_3{\cdot}OEt_2$ (entries 10 and 11). This result might be ascribed to which the anion derived from acid has a big impact on the configuration of intermediate during the reaction.[12d] This interesting result indicates that the control of enantioselectivity of reaction can be adjusted by acid. Instead, when Tf_2NH was used, the selectivity improved (entry 12), but the yield was low. When the amount of chlorinating reagent and acid was adjusted, product **2a** could be yielded in excellent yield, ee and *dr* (entry 14). Apparently, no catalyst resulted in no reaction (entry 15).

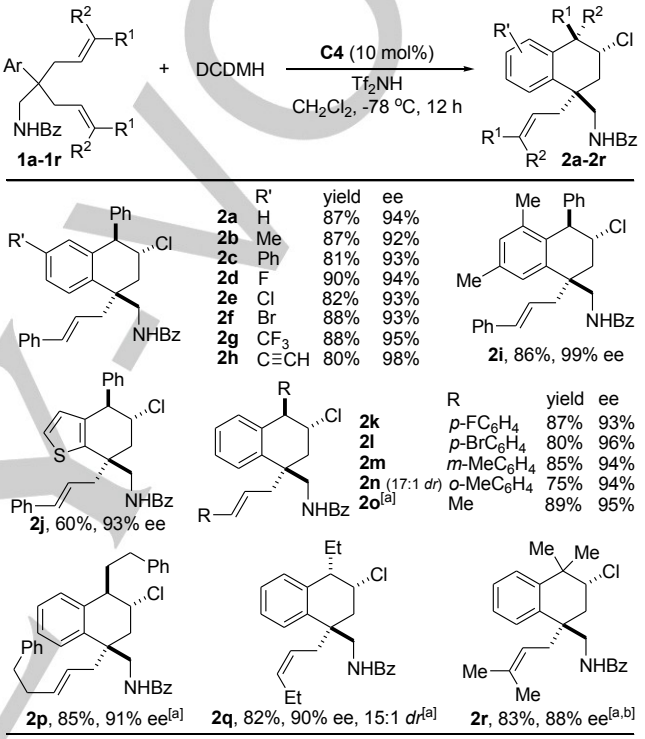
Table 1: Condition optimization.[a]



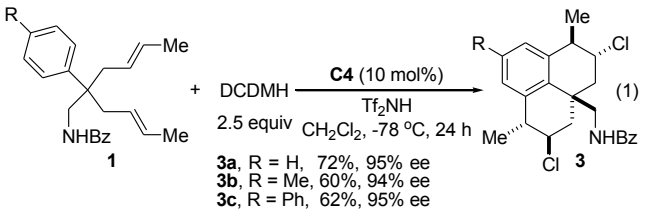
Entry	Cat.	Cl^+ reagent	Acid	Yield [%][b]	Ee [%][c]	*Dr*[d]
1	**C1**	NCS	-	<5	-	-
2	**C1**	NCS	TFA	<5	-	-
3	**C2**	NCS	TFA	<5	-	-
4	**C3**	NCS	TFA	39	53	8:1
5	**C4**	NCS	TFA	45	57	7:1
6	**C4**	$(PhSO_2)_2N$-Cl	TFA	63	21	2:1
7	**C4**	Saccharin-Cl	TFA	35	21	2:1
8	**C4**	DCDMH	TFA	40	73	10:1
9	**C4**	Chloramine-T	TFA	<5	-	-
10	**C4**	DCDMH	TMSOTf	35	-60	2:1
11	**C4**	DCDMH	$BF_3{\cdot}OEt_2$	32	-25	3:1
12	**C4**	DCDMH	Tf_2NH	31	66	8:1
13[e]	**C4**	DCDMH	Tf_2NH	68	74	7:1
14[e,f]	**C4**	DCDMH	Tf_2NH	91	93	31:1
15[e,f]	-	DCDMH	Tf_2NH	0	-	-

[a] Reaction conditions: **1a** (0.05 mmol), Cl^+ reagent (1.5 equiv), acid (2.0 equiv), catalyst (10 mol%), CH_2Cl_2 (2.0 mL), -78 °C, 12 h. [b] NMR yield using benzyl benzoate as the internal standard. [c] Determined by chiral HPLC analysis. [d] Determined by NMR. [e] DCDMH (1.0 equiv). [f] Tf_2NH (0.5 equiv).

With the optimal conditions in hand, the scope of diolefins was evaluated (Scheme 2). When diolefins tethered by different aryl groups were utilized, the corresponding products were obtained in high yields with excellent enantio- and diastereoselectivities (**2a**-**2h**, 92-98% ee, >20:1 *dr*). To our surprise, electron-deficient aryl groups such as CF_3-substituted aryl group could act as an efficient nucleophile. In comparison, they are difficult nucleophiles in electrophilic trifluoromethylthiolation of alkenes.[12d] This result shows the highly reactive property of chloriranium ion. Alkyne group well tolerated the conditions, which offers an opportunity for further transformation (**2h**, 98% ee). Bulky 3,5-dimethyl substituted substrate **1i** gave the product with extremely high enantioselectivity. Moreover, it is interesting to find that electron-rich diolefinic thiophene also efficiently underwent chlorination to give the desired product with excellent enantioselectivity (93% ee). Using substrates with different aryl groups directly connecting to the double bond, the reactions afforded the desired products in good yields with excellent diastereoselectivities (**2k**-**2n**, 90-96% ee), even if the substituent lies at the *ortho*-position of the phenyl group. The conditions allowed for efficient chlorination of aliphatic diolefins as well (**2o**-**2r**, 88-95% ee). In these transformations, the catalyst loading could reduce to 5 mol% when prolonging the reaction time to 24 h. It is noted that the reactions of (*Z*)-olefin **1q** and trisubstituted olefin **1r** worked well to form the corresponding products. The absolute configuration of products was assigned to 1*R*, 3*R*, 4*R* based on the X-ray crystallographic study of **2o**. The developed method is effective for aliphatic olefins to undergo twice cyclizations to construct tricyclic products **3a-3c** in good yields with excellent enantio- and diastereoselectivities using 2.5 equivalents of DCDMH (eq 1). This method provides a convenient route for the synthesis of valuable chiral hexahydrophenalene derivatives.[15]



Scheme 2. Desymmetrizing enantioselective chlorination of aryl-tethered diolefins. Reaction conditions: **1** (0.1 mmol), DCDMH (1.0 equiv), Tf_2NH (0.5 equiv), **C4** (10 mol%), CH_2Cl_2 (4.0 mL), -78 °C, 12 h. The yields refer to isolated yields. The ee value was determined by HPLC analysis. Without note, all the diasteresoselectivities are >20:1. [a] **C4** (5 mol%), 24 h. [b] TFA (1.0 equiv) instead of Tf_2NH.



Chlorination of *gem*-diaryl-tethered olefins was also examined under similar conditions (Scheme 3). The reactions of most substrates proceeded very efficiently to produce the desired products in excellent yields and selectivities (up to 99% ee and >20:1 *dr*). It is worthy to mention that the enantiomer of **5a** could be obtained using TMSOTf instead of Tf_2NH. When **C3** was utilized as catalyst, the enantioselectivity improved to 90%. Additionally, (*Z*)-alkene **4h** worked very well to generate product **5h**. By this method, two all-carbon quaternary stereocenters could be formed simultaneously (**5i**, 90% ee). This is rare in

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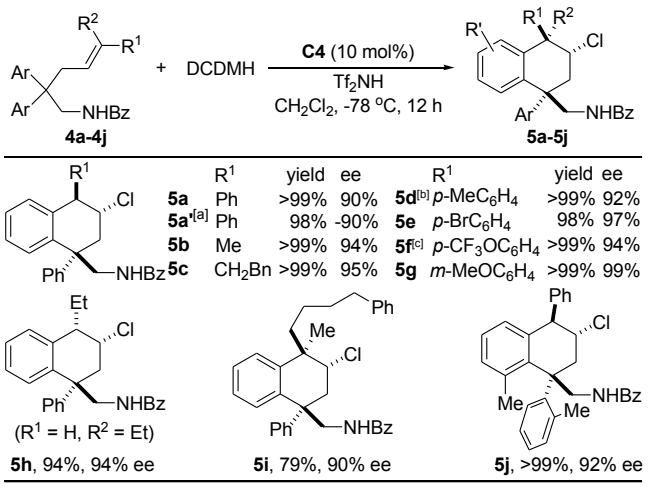
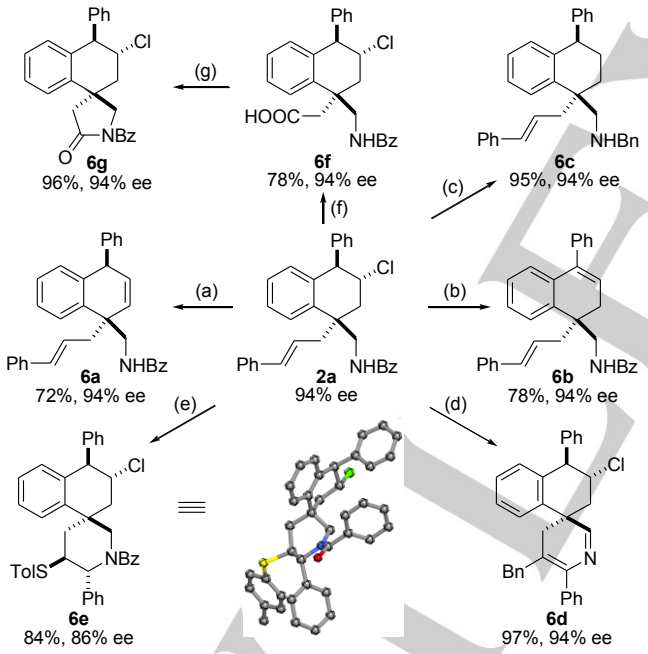
enantioselective catalysis and difficult to achieve by other electrophilic reactions.[1-8] These results reveal the specific advantages of sulfide-catalyzed electrophilic chlorination.



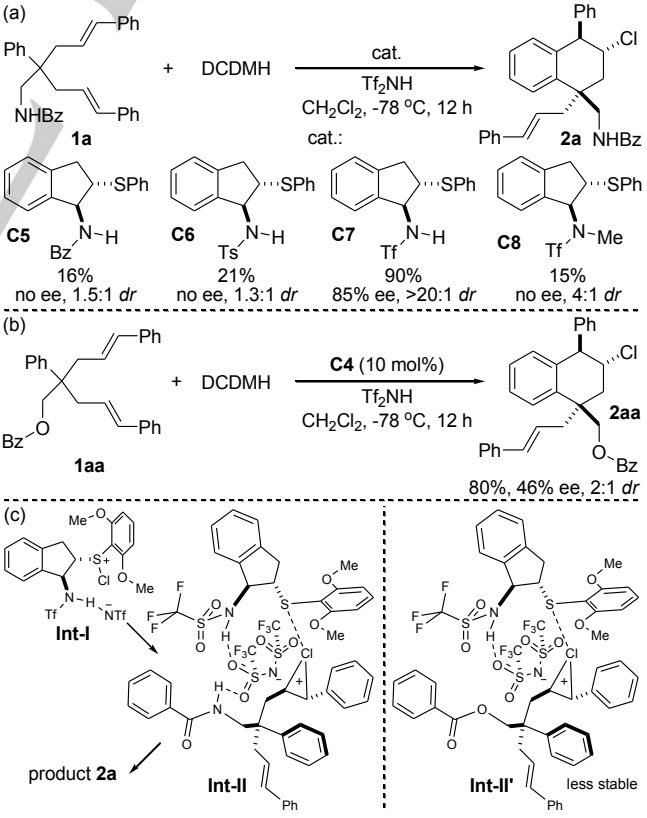
Scheme 3. Desymmetrizing enantioselective chlorination of *gem*-diaryl-tethered olefins. Reaction conditions: **4** (0.1 mmol), DCDMH (1.2 equiv), Tf_2NH (0.5 equiv), **C4** (10 mol%), CH_2Cl_2 (4.0 mL), -78 °C, 12 h. The yields refer to isolated yields. The ee value was determined by HPLC analysis. Without note, all the diasteresoselectivities are >20:1. [a] **C3** (10 mol%) instead of **C4**, TMSOTf (1.0 equiv) instead of Tf_2NH. [b] With 17:1 *dr*. [c] With 18:1 *dr*.



Scheme 4. Further transformations of products. Reaction conditions: (a) AgOTf, THF, 75 °C, 36 h. (b) KO^{t}Bu, *i*-Pr_2O, 80 °C, 12 h. (c) $LiAlH_4$, Et_2O, 0 °C, 4 h. (d) $POCl_3$, PhMe, 120 °C, 24 h. (e) *N*-TolS-succinimide, PhSePh, CH_2Cl_2, -78 °C, 12 h. (f) $RuCl_3$, $NaIO_4$, MeCN/CCl_4/H_2O, rt, 2 h. (g) CH_3COCl, Et_2O, rt, 12 h. All the diasteresoselectivities are >20:1.

To demonstrate the synthetic applications of products, diverse transformations of **2a** were conducted based on the manipulation of the functional groups. The use of AgOTf and KO^{t}Bu led to the selective elimination of HCl to give different alkenes **6a** and **6b** in good yields. The chlorine atom could be removed by reduction (**6c**, 95%). When **2a** was treated with $POCl_3$, valuable spiro dihydropyridine derivative **6d** was efficiently formed. Moreover, electrophilic reactions such as sulfenylation could promote the aminocyclization of **2a** to give spiro bicyclic molecule **6e**. The tethered double bond could be oxidized to afford carboxylic acid **6f** in good yield. It was easily converted to spiro naphthyl pyrrolidone **6g**, a derivative of important bioactive compounds.[16] In these reactions, the enantio- and diastereoselectivities remained same except for the formation of **6e**. More transformations of products are placed in the Supporting Information.

To compare the difference between the developed chlorination system and tertiary amine catalysis, we also used commercially available cinchona alkaloid-based organocatalysts to optimize enantioselective chlorination of **1a**. Many conditions were tried by changing chlorinating reagents, additives, and solvents, but the cyclized product was formed generally in low enantioselectivity and poor diastereoselectivity. Interestingly, in most cases, a diastereomer of **2a** as product bearing an opposite absolute configuration at the quaternary center was formed. When $(DHQD)_2PHAL$ catalyst commonly used for enantioselective chlorination was utilized, **2a'** was obtained in mixed solvents with 80% ee (eq 2). The conditions were effective for the reactions of alkyl diolefins. The similar products were formed, but in moderate enantioselectivities. These results indicate the unique character of sulfide catalysis has great potential to synthesize molecules that cannot be made by other methods.



Scheme 6. Mechanistic insight.

To gain insight into reaction mechanism, control experiments

were carried out (Scheme 5). The H-bonding ability of catalyst was first investigated. When chiral sulfide was protected by different groups such as Bz, Ts, and Tf, only **C7** with strong H-bond donor Tf group led to product in high ee and excellent *dr* (Scheme 5a). In contrast, **C5**, **C6** and **C8** with an improper or no H-bond donor gave racemic products in low yields with poor *dr*. These results indicate that the TfNH group of catalyst is pivotal for the reactivity and construction of chiral environment of the transformation. However, when substrate did not contain H-bond donor, e.g., **1aa** with an OBz group, the reaction gave the product with low ee and poor *dr* (Scheme 5b). In light of these results, H-bonding interaction is essential for the success of reaction. Besides, when the sulfoxide from the corresponding sulfide catalyst was used as catalyst for chlorination of **1a**, almost no reaction took place under similar conditions, which reveals that sulfoxide cannot be the catalyst (see the Supporting Information). Based on these observations and our previous studies,[12] the mechanism is proposed to go through **Int-I** formed by the reaction of catalyst and DCDMH (Scheme 5c). It interacts with diolefin to generate **Int-II** with an acid-derived anion bridge built by H-bond binding. The anion bridge might guarantee the reactivity of substrate by accelerating the attack of the phenyl group towards the chloriranium ion and the stereoselectivity of reaction. As shown on **Int-II′**, when H-bond donor does not exist, the bridge cannot be formed, which possibly leads to the collapse of the chloriranium ion, and then poor stereoselectivity.

In summary, we have developed an efficient approach toward enantioselective chlorination and desymmetrization of aryl-tethered diolefins and diaryl-tethered olefins by bifunctional sulfide catalysis. Valuable teralins bearing one or two quaternary stereocenters and tricyclic hexahydrophenalene derivatives were obtained with excellent enantio- and diastereoselectivities. This work successfully merges chalcogenide catalysis into asymmetric chlorination for the first time, which provides a new opportunity for asymmetric chlorination. Further studies on mechanisms and other asymmetric chlorination reactions by chalcogenide catalysis are underway.

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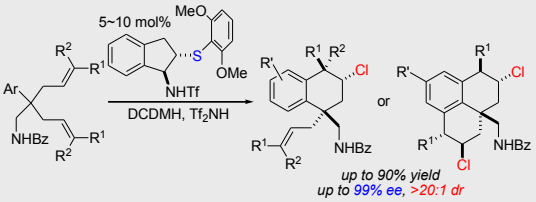

Unprecendented chiral sulfide-catalyzed desymmetrizing enantioselective chlorination is disclosed. Various aryl-tethered diolefins and diaryl-tethered olefins afforded teralins or tricyclic hexahydrophenalene derivatives bearing multiple stereogenic centers in high yields with excellent enantio- and diastereoselectivities. In contrast, tertiary amine catalyst $(DHQD)_2PHAL$ led to a diastereomer product. The products could be transformed to diverse compounds such as spiro *N*-heterocycles.

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