Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Axial-Chiral Biisoquinoline *N,N′*-Dioxides Bearing Polar Aromatic C-H Bonds as Catalysts in Sakurai-Hosomi-Denmark Allylation

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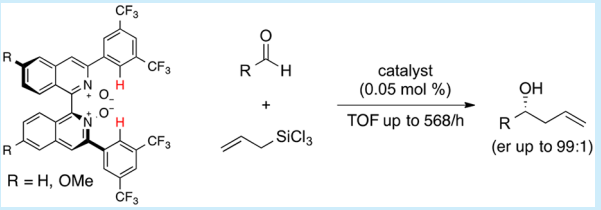
Supporting Information

ABSTRACT: The design, synthesis, and evaluation of axial-chiral biisoquinolines bearing polar aromatic C-H bonds as Lewis base catalysts are reported. Lewis bases containing the 3,5-bis-(trifluoromethyl)phenyl group were found to be significantly more enantioselective for a wider range of substrates than those bearing aromatic residues that are not strongly electron-deficient in the allylation of aldehydes with allyltrichlorosilane. Also, optically pure 3,3′-dibromo-1,1′-biisoquinoline *N,N′*-dioxide that has not been previously reported was synthesized as a common catalyst precursor to facilitate the study.



Hypervalent silicon complexes generated from chiral Lewis base catalysts and chlorosilanes ($LSiCl_3$, L = H, Cl, alkyl, enolates, etc.) are very reactive intermediates and continue to be an important source for the development of new enantioselective synthetic methods.[1] Reported examples include reduction of imines and ketones (L = H),[2] chlorination of epoxides (L = Cl),[3] alkylation of carbonyls (L = allyl, etc.),[4,5] and aldol reactions (L = enolates).[5] Also, it was established that chiral Lewis bases bind $SiCl_4$ to generate in situ powerful Lewis acids for the activation of electrophiles.[6] This field of catalysis research is largely triggered and driven by the seminal and leading studies of Denmark et al.[1] Significant contributions also include those from Kočovský, Malkov, and Nakajima.[1] Regarding the stereochemical aspects of these transformations, the ligand configuration of such a hypervalent silicon complex is considered to play a central role for the enantioselectivity of a reaction because the relative orientation of a chiral catalyst and reacting substrates in the enantioselectivity-determining transition state largely depends on it.[2−7] For example, a C_2 symmetric bidentate Lewis base, $LSiCl_3$, and an electrophile can produce five diastereomeric complexes that have different enantioselectivities (Figure 1a). Currently, the *trans*-Cl complex is thought to form preferentially based on the stereoelectronic theories.[7f,g,i] On the other hand, the recent computational studies regarding alkylation of aldehydes disclosed by Wheeler et al. support arrangements with *cis* chlorines.[7a,b,d,e] This *cis* model is based on stabilizing electrostatic interactions among ligands that were characterized by DFT calculations (e.g., stabilizing interaction between a formyl H and a Cl on Si). Even with these notable advances made, however, the control of such ligand configurations remains largely elusive and significantly challenging. In this context, we envisioned a strategy to selectively generate the *trans*-Cl complex by the internal H-bonding from the catalyst (Figure 1b).[8] In this scenario, not only the *trans*-Cl complex could be selectively generated over the other diastereomeric complexes but also the expected complex

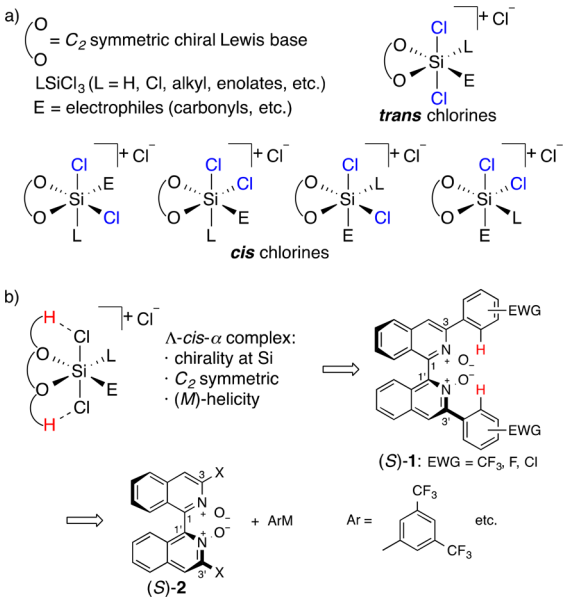


Figure 1. Catalyst design. (a) Five possible diastereomeric hexacoordinate complexes of a bidentate catalyst, $LSiCl_3$ and an electrophile. (b) Internal H-bonding concept and design of corresponding catalysts.

adopts a Λ-*cis*-α structure[9] by virtue of H-bonding in which chirality is at the Si atom (the reaction center) and its two coordination sites for L and E are identical (two C_2 symmetric sites). Thus, high enantioselectivity could be expected from such a structure. Herein we introduce a new concept to enhance the stereoselectivity in Lewis base catalysis of chlorosilane-mediated reactions.

Received: August 1, 2018

DOI: 10.1021/acs.orglett.8b02457
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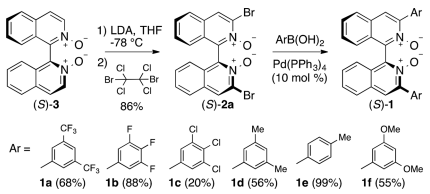
With the aforementioned idea in hand, some of the attributes that we deemed to be important for our initial catalyst design are the following; (1) a scaffold should be C_2 symmetric and rigid to minimize the number of possible complexes, (2) H-bond donors such as alcohols and amides should be avoided because these have Lewis basic lone pairs that might form extra dative bonds to chlorosilanes (i.e., undesired aggregations), and (3) H-bond donor units should be easily tuned to facilitate the study. On the basis of these criteria, an axial-chiral biisoquinoline motif bearing polar aromatic C-H bond donors at its 3, 3′-positions appeared to be a suitable starting point. It should be mentioned that this kind of axial-chiral Lewis base catalyst bearing aromatic residues that are not strongly electron-deficient at the corresponding positions is reported in the literature.[10]

While the H-bond donor ability of the *ortho*-CH bonds of the 3,5-bis(trifluoromethyl)phenyl group[11,12] was clearly demonstrated by Schreiner et al. and transition-metal-bound chlorines are reported to accept H-bonds,[13] the extent to which peripheral Cl atoms of a hypervalent chlorosilane could accept H-bonds cannot be easily discerned without computational analysis.[14] As such, we began our study by performing a preliminary energy minimization of a neutral complex of **1a** (Scheme 1) and $SiCl_4$ in

Scheme 1. Synthesis of Lewis Base Catalysts[a]



[a]The conventional Suzuki coupling protocols were used without further optimization. See Supporting Information (SI) for details.

the gas phase with the B97-D exchange-correlation functional[15] and the 6-31G* basis set.[16] The result shows that the distances between the distal Cl atoms and the relevant H atoms on the 3,5-bis(trifluoromethyl)phenyl groups are 2.4 Å (Figure 2),

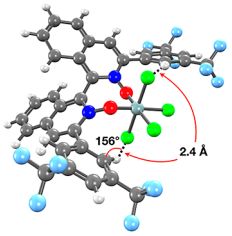


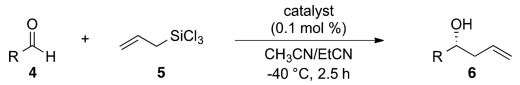
Figure 2. A preliminary structure of the neutral (*S*)-**1a**·$SiCl_4$ complex in the gas phase.

confirming the possible formation of two distal H-bonding interactions. While the magnitude and nature of electrostatic interactions between the catalyst and Cl atoms will substantially change upon ionization (i.e., formation of cationic hypervalent silicon complexes by the dissociation of a chloride anion), we interpreted this result as support for our internal H-bonding concept at this point and proceeded to synthesize the corresponding catalysts.

Inspired by Nakajima's landmark report[17] that introduced 1,1′-biisoquinoline *N*,*N*′-dioxide (**3**) as a Lewis base catalyst, Hayashi, Kočovský, Malkov, and Kotora independently developed the axial-chiral biisoquinoline (or bipyridine) *N*,*N*′-dioxides containing aromatic residues at their 3,3′-positions.[10] However, these catalysts either take 11 steps to make[10c] or require that the 3,3′-aromatic groups must be introduced in the first step of their syntheses, and optical resolution of each aromatic variant must be addressed individually.[10a,b] On the other hand, 1,1′-biisoquinoline *N*,*N*′-dioxide is readily accessed in optically pure form on gram scale in just three steps from commercially available isoquinoline,[18] although the functionalization of its 3,3′-position is reported to be nontrivial.[19] Therefore, we decided to pursue a possibility that the protocol we previously developed for the corresponding functionalization of helicene-derived pyridine *N*-oxides[20] would work on **3**.[18] To our delight, it provided desired (*S*)-3,3′-dibromo-1,1′-biisoquinoline *N*,*N*′-dioxide (**2a**) in 86% yield, which underwent the Suzuki coupling without loss of enantiopurity. Notably, this step (tuning of steric and electronic properties of catalysts) is the last step in our synthesis.[21] It is worth mentioning that given the privileged use of the pyridine *N*-oxide group in asymmetric catalysis,[1,22] **2a** is expected to be of general interest to chemists in the fields of catalysis, synthesis, drug discovery, etc., just like 3,3′-dibromo-BINOL.[21]

Allylation of aldehydes with allyltrichlorosilane[23] catalyzed by chiral Lewis bases[17,24] (a.k.a. Sakurai-Hosomi-Denmark allylation[24c]) has been a testing ground for new chiral Lewis bases (Table 1).[4] We chose 4-methoxybenzaldehyde for an initial

Table 1. Evaluation of Catalysts[a]



entry	catalyst	4, R =	yield (%)	er
1	**1a**	4-MeO-Ph	87	98:2
2	**1b**	4-MeO-Ph	83	98:2
3	**1c**	4-MeO-Ph	81	95.5:4.5
4	**1d**	4-MeO-Ph	86	97.5:2.5
5	**1e**	4-MeO-Ph	96	6:94[b]
6	**1f**	4-MeO-Ph	83	91:9
7	**2a**	4-MeO-Ph	0	
8	**1a**	(*E*)-PhCH=CH	71	95:5
9	**1b**	(*E*)-PhCH=CH	68	88.5:11.5
10	**1d**	(*E*)-PhCH=CH	62	84.5:15.5

[a]Reactions were performed with aldehyde (1.0 mmol), (*S*)-catalyst (0.1 mol %), allyltrichlorosilane (1.2 equiv), and *N*,*N*-diisopropylethylamine (3.0 equiv) in 1.0 mL of solvents (1.0 M in MeCN:EtCN[26] = 3:1). Yields are those of chromatographically purified compounds. The er values were determined by HPLC analysis; see the SI for details. [b](*R*)-**1e** was used.

model substrate because a huge range of enantioselectivities for its allylation was reported with structurally related catalysts.[25] To our delight, **1a** provided the product in 87% yield with 98:2 er. The catalyst with 3,4,5-trifluorophenyl group (**1b**) was equally effective. The catalysts with less electron-deficient Ar units (**1c**,**e**,**f**) were found to be clearly less selective except for 3,5-dimethylphenyl substituted catalyst **1d**. Strangely, 3,3′-dibromo-1,1′-biisoquinoline *N*,*N*′-dioxide (**2a**) did not catalyze the reaction. Next, we evaluated the three best catalysts identified (**1a**,**b**,**d**) for structurally distinct cinnamaldehyde (Table 1, entries 8−10) because a similar catalyst[10c] was reported to give the corresponding product in 69% ee. The catalyst bearing 3,5-bis(trifluoromethyl)phenyl unit (**1a**) was found to be significantly more selective than the other two

DOI: 10.1021/acs.orglett.8b02457
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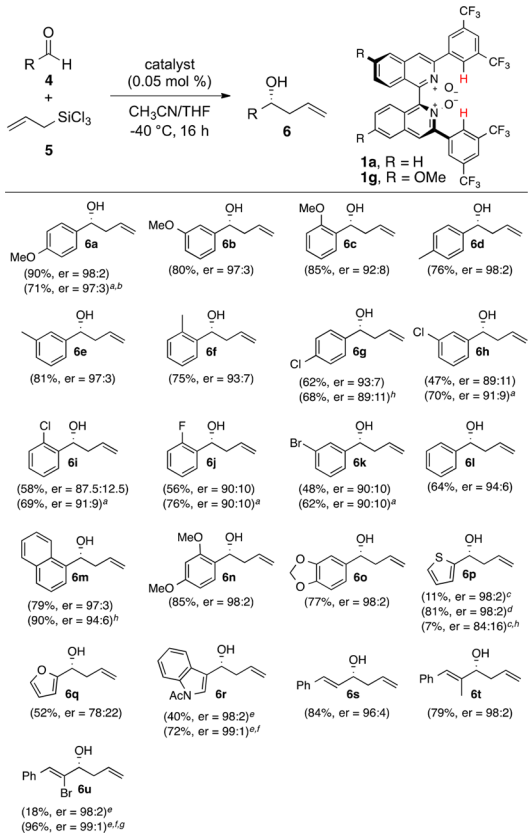
catalysts, identifying it as an optimum catalyst among those evaluated.

Because enantio-enriched homoallylic alcohols are indispensable for the synthesis of therapeutic agents and natural products, a plethora of allylation methodologies has been developed over the last several decades.[27] However, it still remains an important problem for the allylation of aldehydes that a relatively large amount of the catalyst is required for a reasonable reaction rate in most cases (even with metal catalysts). Highly enantioselective catalysts that work at the 0.1 mol % loading or less are extremely rare.[10b−e,28] Hayashi's catalyst[10c−e] was the first example of such catalysts (state-of-the-art in terms of the catalyst loading), but it is only highly enantioselective for 4-alkoxybenzaldehydes and 3,4-dimethoxybenzaldehyde (94% and 98% ee, respectively). Therefore, the substrate scope investigation of **1a** was warranted. Overall, good to excellent levels of enantioselectivities were observed for a range of synthetically useful substrates (Scheme 2). Electron-rich aldehydes were generally excellent substrates for **1a**, but halogen-substituted benzaldehydes were found to be not only less selective but also less reactive. Because electron-rich Lewis base catalysts are often more reactive in chlorosilane-mediated reactions, we prepared **1g** for those substrates. To our delight, **1g** provided products in substantially higher yields with no effect on enantioselectivity (**6h−k**). As such, we evaluated its activity on our model aldehyde and found that **1g** provided the product **6a** in 71% yield in only 2.5 h with essentially the same selectivity, which corresponds to the turnover frequency of 568/h. Strangely enough, the product of thiophene-2-carbaldehyde (**6p**) appeared to inhibit the catalyst turnover (0.5 mol % loading was needed to complete the reaction), but that of 2-furaldehyde did not (**6q**). On the other hand, er of **6p** was found to be significantly higher than that of **6q**. Notably, **1a** effectively catalyzed the allylation of highly functionalized 1-acetyl-3-indolecarboxaldehyde and α-bromocinnamaldehyde despite the fact that these aldehydes were not soluble under the reaction condition even with twice as much solvent (0.5 M). Hydrocinnamaldehyde (i.e., aliphatic aldehyde) did not provide the product, as is often the case for Sakurai-Hosomi-Denmark allylation, presumably due to the formation of an α-chloro silyl ether as reported by Denmark.[29]

Scheme 2. Substrate Scope[a]



[a]Reactions were performed with aldehyde (1.0 mmol), catalyst (0.05 mol %), allyltrichlorosilane (1.5 equiv), and *N,N*-diisopropylethylamine (4.5 equiv) in 1.0 mL of solvents (1.0 M in MeCN:THF[26] = 3:1). Yields are those of chromatographically purified compounds. The er values were determined by HPLC analysis; see SI for details. (a) Catalyst **1g**. (b) 2.5 h. (c) NMR yield. (d) 0.5 mol % of **1a**. (e) 0.5 M concentration. (f) 71 h. (g) 0.1 mol % of **1a**. (h) Catalyst **1d** (see Scheme 1).

Given that **1a** and **1d** provided the similar results for 4-methoxybenzaldehyde while **1a** was much more enantioselective than **1d** for cinnamaldehyde (Table 1), the extent to which the 3,5-bis(trifluoromethyl)phenyl group influenced the outcome of these reactions was not so clear. Therefore, we evaluated **1d** for 4-chlorobenzaldehyde, 1-naphthylaldehyde, and thiophene-2-carbaldehyde which are different from 4-methoxybenzaldehyde in terms of electronic, steric, and structure, respectively (Scheme 2, footnote h). Catalyst **1d** provided the corresponding products (**6g**, **6m**, and **6p**) in similar yields but in substantially lower enantioselectivities (89:11, 94:6, and 84:16 er, respectively). It is interesting to note that **1d** has the essentially same chiral pocket as Hayashi's best bipyridine catalyst which contains a 4-methoxy-3,5-dimethyl phenyl group at the corresponding positions,[10c] and substrate scopes of these two catalysts were found very similar (i.e., only highly enantioselective for 4-alkoxybenzaldehydes). We also performed a preliminary energy minimization of a neutral complex of **1d** and $SiCl_4$ in the same manner and found that its *ortho*-CH bonds do not H-bond to chlorines as strongly as **1a** (the corresponding distance is 2.8 Å, see Figure S2, SI). These results are consistent with the hypothesis that H-bonding interactions provided by **1a** substantially contributed to the overall energies of accessible diastereomeric transition states (Figure 1) favoring the *trans*-Cl arrangement. On the other hand, the fact that the behavior of **1d** is largely substrate-dependent may be attributable to possible electrostatic interaction between a formyl H and a Cl on Si that could be an important factor to determine the accessible transition states in the absence of sufficient electrostatic interactions from the catalyst.[7a,b,d,e]

In summary, we have introduced Lewis base catalysts with C-H bond donors as a new and highly generalizable concept in the Lewis base catalysis. This strategy led to the discovery of highly enantioselective Lewis bases that work at 0.05 mol % catalyst loading for a synthetically useful substrate scope for the first time. The detailed mechanistic investigation is underway, with which we hope to shed light on the stereochemical mode of this transformation. Also, we developed the practical synthesis of optically pure 3,3′-dibromo-1,1′-biisoquinoline *N,N*′-dioxide **2a** that is expected to be of general interest to chemists. Further applications of this concept and the catalysts are currently being developed in our laboratory and will be reported in due course.

DOI: 10.1021/acs.orglett.8b02457
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02457.

Experimental procedures and detailed characterization data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (CHE1461196) and the Florida Institute of Technology for financial support of this work.

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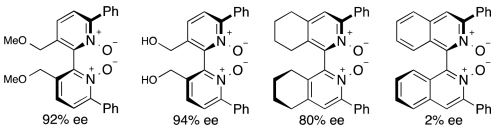

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DOI: 10.1021/acs.orglett.8b02457
Org. Lett. XXXX, XXX, XXX−XXX

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