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Evaluation of 3,3′-Triazolyl Biisoquinoline *N*,*N*′-Dioxide Catalysts for Asymmetric Hydrosilylation of Hydrazones with Trichlorosilane

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Abstract: A new class of axial-chiral biisoquinoline *N*,*N*′-dioxides was evaluated as catalysts for the enantioselective hydrosilylation of acyl hydrazones with trichlorosilane. While these catalysts provided poor to moderate reactivity and enantioselectivity, this study represents the first example of the organocatalytic asymmetric reduction of acyl hydrazones. In addition, the structures and energies of two possible diastereomeric catalyst–trichlorosilane complexes (**2a**–$HSiCl_3$) were analyzed using density functional theory calculations.

Keywords: Lewis base catalysis; trichlorosilane; hydrosilylation; hydrazone; computational chemistry

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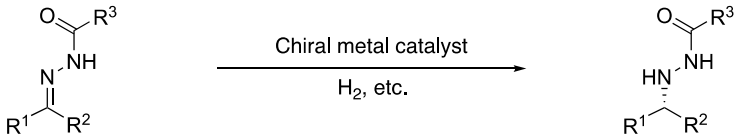
1. Introduction

The chiral hydrazine is an important structural motif found in pharmaceuticals, agrochemicals, natural products, synthetic chiral catalysts, etc. and the catalytic asymmetric reduction of readily available, bench-stable acyl hydrazones provides direct access to such chiral hydrazine derivatives in an enantio-enriched form [1–24]. In 1992, Burk and Feaster reported the first example of the catalytic enantioselective hydrogenation of acyl hydrazones by employing a rhodium/DuPhos catalyst [13]. Since this initial breakthrough, many excellent transition metal-catalyzed methods for the asymmetric reduction of hydrazones have been developed. The majority of these examples utilized rhodium-based catalysts [3–13] but palladium- [14–17], iridium- [18], ruthenium- [19], nickel- [20–23] and cobalt- [24] based catalysts are also reported (Scheme 1, Equation (1)). While their reaction scopes are impressive, no metal-free 'green' counterpart (i.e., organocatalysis method) has been reported to the best of our knowledge, except for two scattered examples. There is a patent literature that described one example of the asymmetric hydrosilylation of a tosylhydrazone with trichlorosilane catalyzed by a chiral *N*-formylpyrrolidine (4-methylbenzensulfonic acid 2-(1-phenylethylidene)hydrazide was reduced to the corresponding hydrazine in 94% yield with 36% ee) [25]. The other example is reported by Wang and Sun [26]. Here, it was the trichlorosilane-mediated reductive amination of acetophenone with phenylhydrazine catalyzed by a chiral bis-sulfinamide, which afforded the corresponding 1,1-disubstituted hydrazine in 93% yield with 74% ee.

Among the reported reducing agents that are amenable for organocatalysis (selected reviews; [27–29]), trichlorosilane is particularly attractive because it is a readily available, inexpensive and easy-to-handle liquid (selected reviews; [30–32]). Furthermore, it only produces innoxious NaCl and SiO_2 as by-products upon quenching with aqueous NaOH or $NaHCO_3$ solutions, which are easily separable from the reaction products (i.e., organic compounds). Trichlorosilane reversibly forms a hypervalent silicon complex with Lewis-bases

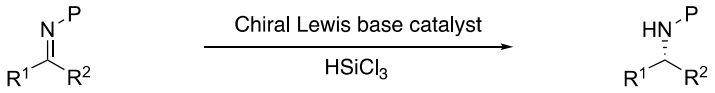
that is believed to be the active reducing species. Since Matsumura's seminal work, that employed *N*-formylproline-derived catalysts [33,34], and the milestone achieved by Malkov and Kočovský with their *N*-methyl-L-valine-based catalysts [35–37], numerous chiral Lewis-base catalysts have been reported for the asymmetric hydrosilylation of ketimines with trichlorosilane (selected reviews; [30–32], selected references; [38–45]). While the majority of these catalysts are amide-based Lewis-bases, other kinds of Lewis-bases are also reported, which includes pyridine *N*-oxides (selected references; [46–51]), phosphine oxides (selected references; [52–54]), and sulfinamides (selected references; [55,56]). Despite a plethora of reports in this area, the Lewis-base-catalyzed trichlorosilane-mediated reduction of ketimines currently remains limited to *N*-aryl and alkyl protected ones (Scheme 1, Equation (2)). The lack of acyl hydrazones as substrates for this method is presumably because their N–C=O unit could possibly bind trichlorosilane competitively with amide-based catalysts to produce racemic products. As a matter of fact, the only examples of the hydrazones that were enantioselectively reduced with chiral Lewis-bases and trichlorosilane are *N*-tosyl- and *N*-phenylhydrazones as mentioned above [25,26]. In this context, we became interested in evaluating axial-chiral 3,3′-triazolyl biisoquinoline *N*,*N*′-dioxide catalysts [57] for the hydrosilylation of acyl hydrazones with trichlorosilane (Scheme 1, Equation (3)). Herein describes our preliminary investigations in this area.

eq (1): Transition metal-catalyzed enantioselective hydrogenation of hydrazones.



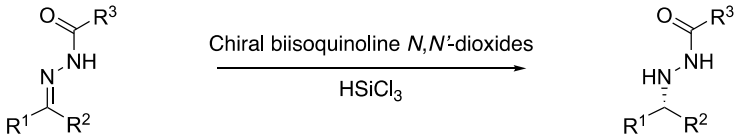
$R^1 = R^2$ = aryl, alkyl, alkenyl, alkynyl, R^3 = Ph, CH_3, OBn, O^{t}Bu, etc.
Metal = Rh, Pd, Ir, Ru, Ni, Co

eq (2): Lewis base-catalyzed hydrosilylation of *N*-aryl or alkyl ketimines with trichlorosilane.



$R^1 = R^2$ = aryl, alkyl, P = Ph, PMP, Bn, allyl, etc.

eq (3): This work: Lewis base-catalyzed hydrosilylation of hydrazones with trichlorosilane.



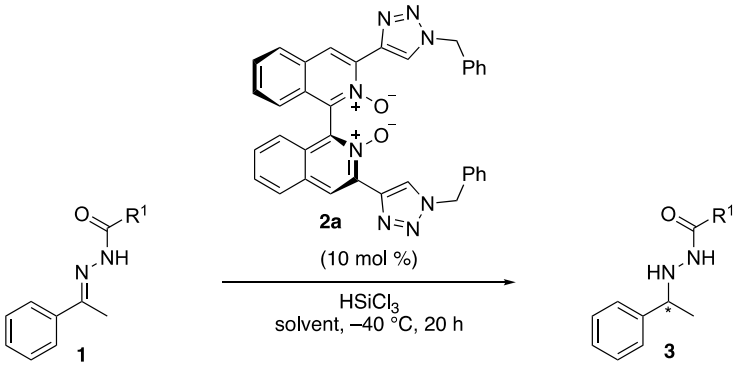
$R^1 = R^2$ = aryl, alkyl, R^3 = Ar, OBn, O^{t}Bu.

Scheme 1. Catalytic asymmetric reduction of C=N bonds.

2. Results and Discussion

We recently developed the modular method to synthesize axial-chiral 3,3′-triazolyl biisoquinoline *N*,*N*′-dioxides from readily available triazoles and optically pure 3,3′-dibromobiisoquinoline *N*,*N*′-dioxide [57] as part of our longstanding interests in developing new chiral Lewis-bases [58–62]. Since this new class of catalysts was found capable of activating trichlorosilane at relatively low temperatures, we envisioned that they might be able to catalyze the reduction of acyl hydrazones under conditions where no background reaction would take place. We set out on our investigation by employing benzoyl hydrazone **1a** as a

model substrate (Scheme 2). To our delight, the background reaction was found negligible at −40 °C, and catalyst **2a** provided hydrazine (*R*)-**3a** in 48% yield with 53% ee (entries 1 and 2). Next, we looked at several solvents that are commonly used for trichlorosilane-mediated reactions. Chloroform provided the product with a lower yield but with a slightly higher enantioselectivity (34% yield, 66% ee). Acetonitrile gave **3a** in a comparable yield but with a lower ee of 32%. The reaction in tetrahydrofuran afforded the opposite enantiomer (*S*)-**3a** with a much lower yield and selectivity (entry 5). Overall, dichloromethane was found optimum. We tested with twice as much solvent since benzoyl hydrazone **1a** was not fully dissolved under the reaction conditions (entry 6). However, it did not improve the result. Previously, we found that 4 Å molecular sieve was an effective acid scavenger for adventitious HCl in trichlorosilane [63], but its use did not positively impact the outcome in the present case (entry 7). The use of 3.0 equivalent of trichlorosilane did not improve the yield, either (entry 8). As the protecting groups on hydrazones are known to influence their reactivities and enantioselectivities in many cases (e.g., see; [19]), we evaluated the Boc and Cbz protected hydrazones (**1b** and **1c** in entries 9 and 10, respectively). While enantiomeric excesses of the corresponding products were slightly higher than that of the benzoyl counterpart, both Boc and Cbz protecting groups adversely affected the yields. Since the C=O unit of Boc or Cbz group is more Lewis basic than that of the benzoyl counterpart, we tested a less Lewis basic hydrazone (**1d**). However, the yield decreased to 14% albeit with a slightly higher enantioselectivity (entry 11). Overall, the present method was found to be quite sensitive to reaction solvents and the hydrazone protecting groups.

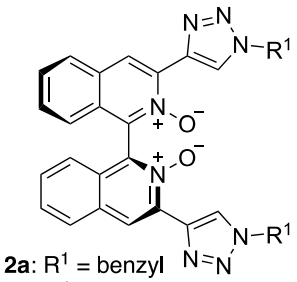


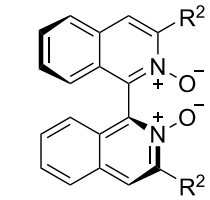
Entry	R^1	Solvent	Product	Yield (%)[a]	Ee (%)
1[b]	Ph (**1a**)	CH_2Cl_2	**3a**	trace	—
2	Ph (**1a**)	CH_2Cl_2	(*R*)-**3a**	48	53
3	Ph (**1a**)	$CHCl_3$	(*R*)-**3a**	34	66
4	Ph (**1a**)	CH_3CN	(*R*)-**3a**	50	32
5	Ph (**1a**)	THF	(*S*)-**3a**	26	14
6[c]	Ph (**1a**)	CH_2Cl_2	(*R*)-**3a**	44	58
7[d]	Ph (**1a**)	CH_2Cl_2	(*R*)-**3a**	40	58
8[e]	Ph (**1a**)	CH_2Cl_2	(*R*)-**3a**	42	58
9	O^{t}Bu (**1b**)	CH_2Cl_2	(*R*)-**3b**	36	71[f]
10	OBn (**1c**)	CH_2Cl_2	(*R*)-**3c**	21	64
11	4-NO_2-Ph (**1d**)	CH_2Cl_2	(*R*)-**3d**	14	69

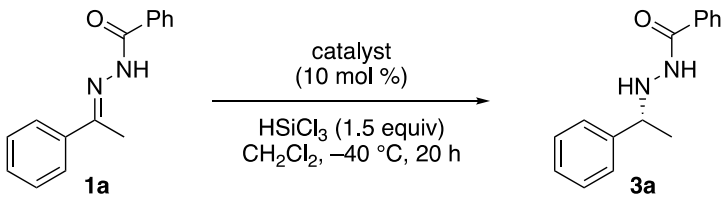
Unless otherwise noted, all reactions were carried out with **1** (0.25 mmol), $HSiCl_3$ (1.5 equiv), **2a** (10 mol %), and solvent (1.0 mL). [a]NMR yield was determined using 1,1,2,2-tetrachloroethane as an internal standard. [b]Without catalyst. [c]2.0 mL of solvent was used. [d]250 mg of 4 Å molecular sieve was used. [e]3.0 equiv of $HSiCl_3$ was used. [f]An estimated value as enantiomers were not completely separated at the baseline by chiral HPLC; see the SI for details.

Scheme 2. Evaluation of the reaction parameters.

Next, we evaluated different triazolyl groups on the biisoquinoline that are expected to play important roles on the catalyst's reactivity and selectivity (Scheme 3, entries 1–4). Catalyst **2a** was clearly superior to the other three catalysts (**2b**–**d**) in terms of their reactivity. Catalyst **2c** was more enantioselective than others, albeit with a low yield. These results indicate that the reactivity and selectivity of this new class of catalysts can be tuned by changing the triazolyl groups. We also compared these triazolyl catalysts to conventional 3,3′-substituted biisoquinoline *N*,*N*′-dioxides (entries 5 and 6). To our surprise, neither **2e** nor **2f** promoted the reaction although **2f** was as reactive as **2b**–**d** for the hydrosilylation of an *N*-phenyl ketimine with trichlorosilane [57]. Nonetheless, these results clearly demonstrated that this new class of axial-chiral biisoquinolines is indeed complementary to the existing Lewis-base catalysts and bode well for the development of their applications.







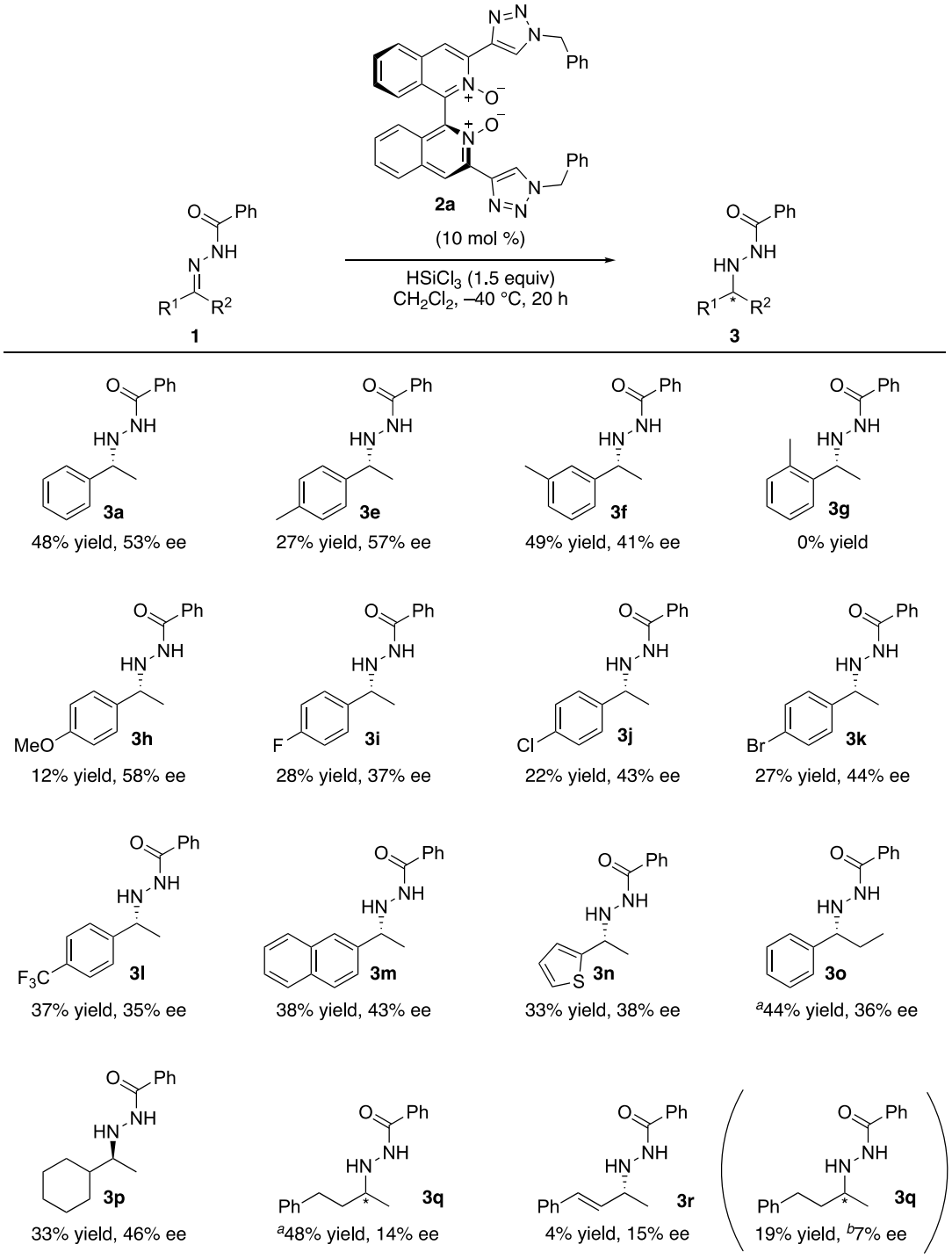
Entry	Catalyst	Yield (%)[a]	Ee (%)
1	**2a**	48	53
2	**2b**	8	18
3	**2c**	19	74
4	**2d**	14	54
5	**2e**	trace	N/D[b]
6	**2f**	trace	N/D[b]

All reactions were carried out with **1a** (0.25 mmol) and CH_2Cl_2 (1.0 mL). [a]NMR yield was determined using 1,1,2,2-tetrachloroethane as an internal standard. [b]Not Determined.

Scheme 3. Evaluation of 3,3′-substituents of axial-chiral biisoquinoline catalysts.

As we determined the basic reaction parameters, we proceeded to evaluate the extent to which the present catalytic system could enantioselectively promote the hydrosilylation of various benzoyl hydrazones with trichlorosilane (Scheme 4). To our surprise, a para-methyl substitution (**3e**)—which is a minimal change from the model substrate (**3a**)—had a detrimental effect on the chemical yield while the corresponding meta-substitution (**3f**) did not. An ortho-methyl substitution (that is known to push the aromatic ring out of conjugation with a C=N bond) completely shut down the reaction (**3g**). Eventually, it was gleaned that the para-substitutions have adverse effects on the reactivity but not much on the enantioselectivity regardless of their electronic nature (**3e**, **3h**–**m**) (these enantioselectivities are approximately the same). A heteroaromatic hydrazone was moderately less reactive and selective than the model substrate (**3n**). Although an ethyl group at the C=N bond is in general expected to lead to an increased steric demand in the TS, it did not affect the reactivity in the present case (**3o**). It is noteworthy that a cyclohexyl counterpart provided the opposite sense of enantioselection to the model substrate (**3p**). Differentiation of the two similar alkyl groups franking the C=N bond was difficult by the present catalytic system (**3q**). Unreacted hydrazones and corresponding ketones were the major components of the crude reaction mixtures besides the desired products, and no significant amounts

of by-products were observed for **1a**–**1q**. An α,β-unsaturated hydrazone was not a viable substrate for this method as the conjugate reduction took place (**3r**) [64].

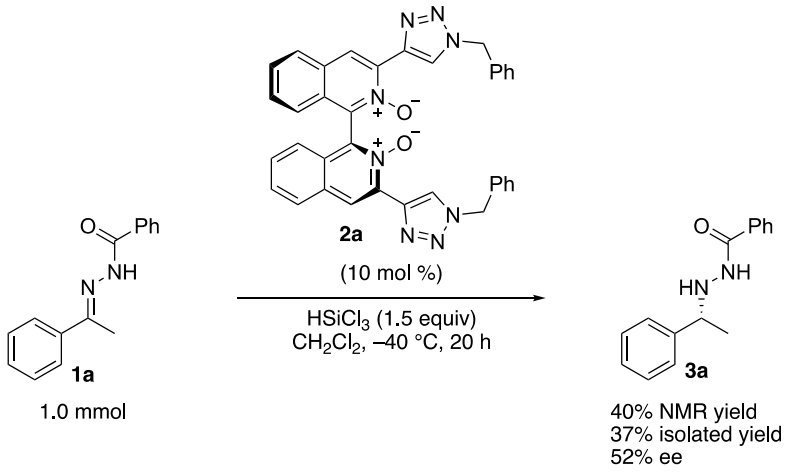


All reactions were carried out with **1** (0.25 mmol) and CH_2Cl_2 (1.0 mL). Yields refer to NMR yields determined using 1,1,2,2-tetrachloroethane as an internal standard. [a]Isolated yields for **3o** and **3q** are 40% and 43%, respectively. [b]An estimated value; see the SI for details.

Scheme 4. Evaluation of the extent to which **2a** catalyzed the reduction.

We also tested a 1.0 mmol scale reaction with the model substrate. To our delight, it provided essentially the same result (Scheme 5), demonstrating a potential robustness of the method. Furthermore, catalyst **2a** was quantitatively recovered after a flash column

chromatography on silica gel (see Supplementary Materials for details). The recovered catalyst promoted the model reaction (**1a** on 0.25 mmol scale) with no loss in reactivity and enantioselectivity.



Scheme 5. The 1.0 mmol scale reaction.

The structure of the active reducing species generated from a chiral catalyst and $HSiCl_3$ is considered to play a central role for the enantioselectivity of a reaction. Even with notable advances made in this area (selected references; [35–45]), it remains largely elusive and significantly challenging to control the relative populations and reactivities of diastereomeric reducing species that are reversibly produced from a chiral Lewis-base and trichlorosilane. C_2-symmetric **2a** and $HSiCl_3$ can give rise to two diastereomeric complexes that are expected to have different enantioselectivities (as long as **2a** acts as a bidentate Lewis-base). Therefore, the binding geometry of **2a** to $HSiCl_3$ was investigated computationally with the aim of shedding some light on the structure of the active reducing species. To our delight, **2a** was found to bind to $HSiCl_3$ through its two oxygen atoms (i.e., a C_2-symmetric bidentate ligand), generating two diastereomeric complexes (Figure 1). Complex 1 was found to be 1.91 kcal/mol lower in energy than the complex 2. The analysis of their electrostatic potentials revealed an anion–π-type interaction between the hydrogen atom in complex 1 or one of the chlorine atoms in complex 2 and the phenyl ring. It should be mentioned that a pileup of electron density occurs at the peripheral atoms of a hypervalent silicon complex of this kind [59,65,66]. This anion–π-type interaction appears to effectively lock the conformation of the benzyl group at least at the ground state, leading to a well-defined chiral pocket around the hypervalent silicon atom. This computationally identified non-covalent attractive interaction could offer a possible basis to rationalize why **2a** (benzyl) was as enantioselective as **2d** (1-adamantyl), and why **2c** (benzhydryl) was substantially more enantioselective than **2d** (53% ee, 54% ee and 74% ee, respectively; Scheme 3).

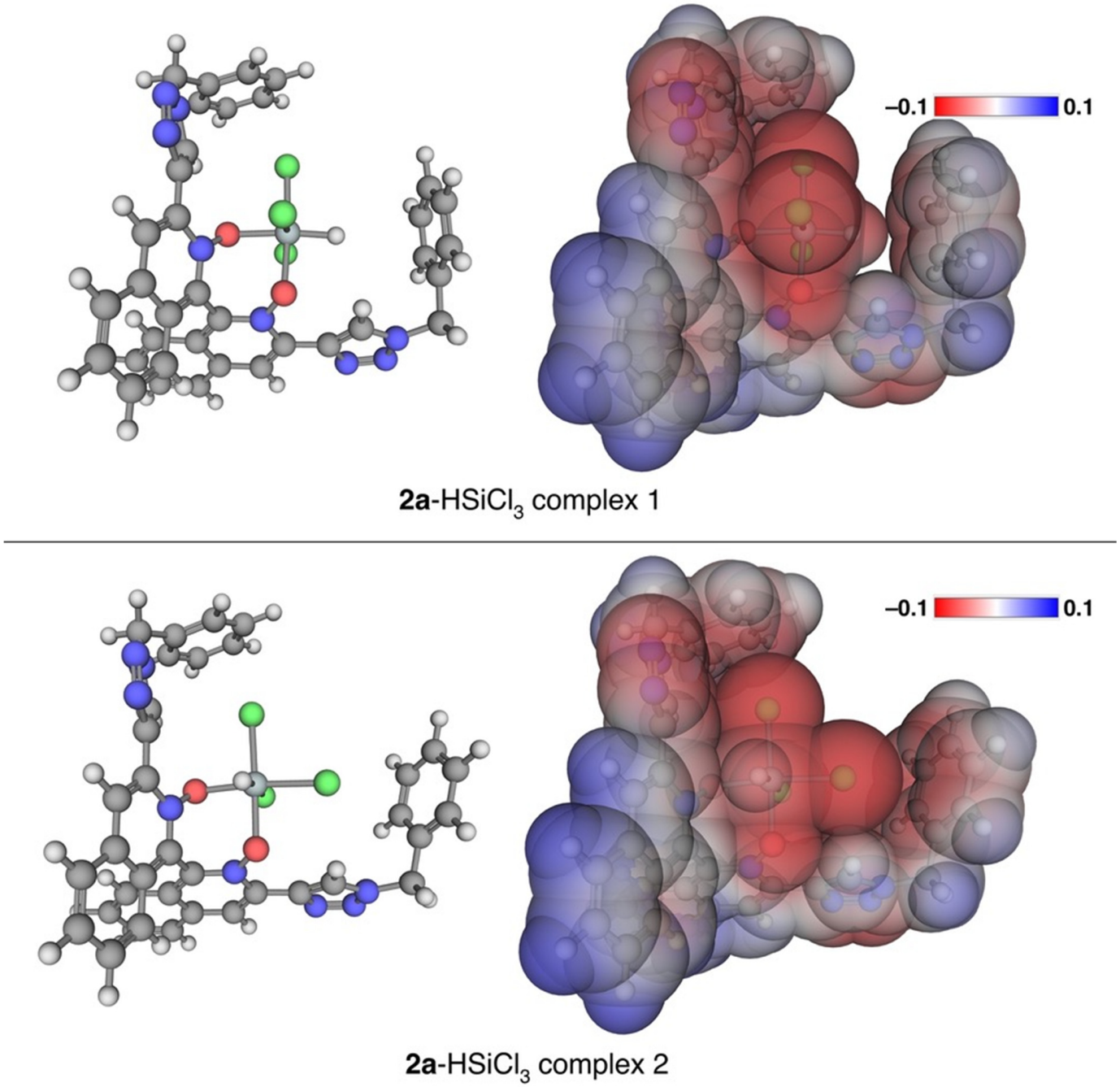


Figure 1. Computed structures of the two lowest energy minima for the **2a**-$HSiCl_3$ complex (i.e., two diastereomeric complexes) calculated with PBEh-3c//C-PCM (DCM). Both are shown with balls-and-sticks (**left**) and space filling (**right**) models. Molecular electrostatic potentials are also shown in the space filling models. Complex 1 (**top**) is 1.91 kcal/mol lower in energy than complex 2 (**bottom**).

3. Conclusions

Axial-chiral 3,3′-triazolyl biisoquinoline *N*,*N*′-dioxides offer potential for functioning as effective catalysts for the asymmetric hydrosilylation of acyl hydrazones with trichlorosilane. Since catalyst's triazolyl units indeed tuned the reactivity and enantioselectivity of the reaction and our modular synthesis allows ready access to a variety of 3,3′-triazolyl biisoquinoline *N*,*N*′-dioxides, potential for the identification of more effective catalysts than those presented herein clearly exits.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11091103/s1, Experimental procedures and detailed characterization data of all new compounds (PDF).

Author Contributions: N.T. conceptualized the project and also conceived and designed the experiments. S.S., C.X., J.J., P.N., B.N. and A.S. performed the experiments and analyzed the empirical data (J.J., P.N., B.N. and A.S. equally contributed to these tasks). R.P. performed all computational tasks. All authors discussed the results and contributed to writing the paper. All authors have read and agreed to the published version of the manuscript.

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