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Design and synthesis of 3,3’-triazolyl biisoquinoline *N*,*N’*-dioxides via Hiyama cross-coupling of 4-trimethylsilyl-1,2,3-triazoles

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Abstract

A new strategy to effectively lock the conformation of substituents at the 3,3’-positions of axial-chiral biisoquinoline *N*,*N’*-dioxides was developed based on the strong dipole–dipole interaction between 1,2,3-triazole and pyridine *N*-oxide rings. The crystal structure and the DFT calculations of 3,3’-bis(1-benzyl-1*H*-1,2,3-triazole-4-yl)-1,1’-biisoquinoline *N*,*N’*-dioxide (**3a**) provided strong support for this strategy. Furthermore, we successfully demonstrated that readily available 4-trimethylsilyl-1,2,3-triazoles are viable nucleophiles for Hiyama cross-coupling.

Graphical Abstract

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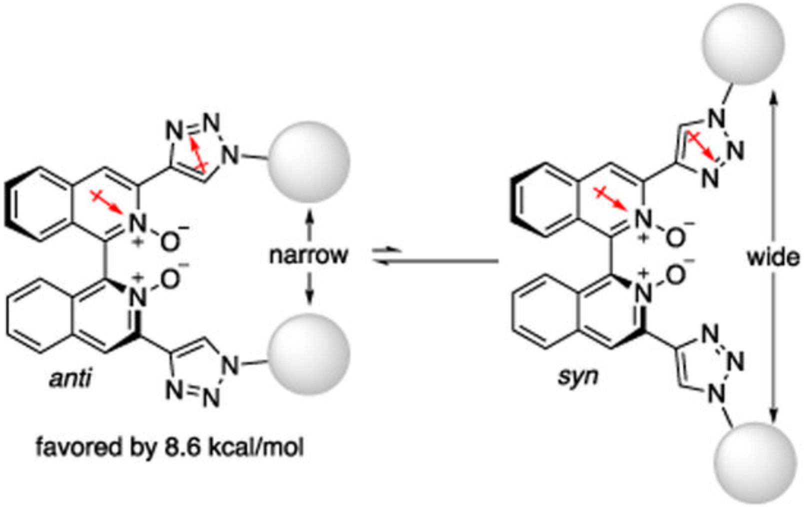
Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary Material
Experimental procedures and detailed characterization data of all new compounds including the X-ray structures of **3a** and **6d** are provided as a PDF. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 2082619 – 2082620 for compounds **3a** and **6d**. Copies of this information may be obtained free of charge from, The Director, CCDC 12 Union Road, Cambridge CB2 1EZ, UK [fax: (int.code) +44 (1223) 336–033 or deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk]. The DFT-optimized geometries are available in a separate file (TXT).



Keywords

axial-chiral Lewis bases; 1,2,3-triazoles; Hiyama cross-coupling; catalyst design; computational chemistry

Introduction

1,1’-Binaphth-2-ol (BINOL) is among the most successful chiral scaffolds ever developed.[1] Its strength comes from the substituents at its 3,3’-positions that have proven particularly effective to increase asymmetry around the reaction site (i.e., space proximal to its hydroxyls). In much the same way, axial-chiral 3,3’-functionalized biisoquinoline (or bipyridine) *N,N’*-dioxides (**1**) have emerged as an important class of chiral Lewis base catalysts for the activation of chlorosilanes (e.g., $SiCl_4$).[2] Their 3,3’-substituents can be readily extended by adding a phenyl linker,[3] but such a modification leads to a widemouthed cavity,[3a] projecting 3,3’-substituents away from the reaction space (**2**). Therefore, as part of our longstanding interests in the development of new chiral Lewis bases,[2b,4] we conceived of biisoquinolines bearing a deep chiral cavity (**3**). We envisioned that we could control the conformation of 3,3’-substituents by taking advantage of large dipole moments of a pyridine *N*-oxide ring and a 1,2,3-triazole ring (4.24 D and 4.38 D, respectively).[5,6] More specifically, the *anti*-conformation with respect to the directions of two dipole moments shown in Figure 1b is expected to be strongly favored over the *syn*-conformation.[6] Herein, we report the synthesis of 3,3’-triazolyl biisoquinoline *N,N’*-dioxides via Hiyama cross-coupling with readily available 1-substituted-4-trimethylsilyl-1*H*-1,2,3-triazoles, the crystal structure of a triazolyl biisoquinoline, and the computational conformational analysis of itself and its $SiCl_4$ complex.

A sequence of Sonogashira coupling of 3,3’-diiodo-1,1’-biisoquinoline *N,N’*-dioxide (**4**, Scheme 1) followed by the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC)[7,8] appeared a most reliable approach since we previously developed a method to halogenate the 3,3’-positions of biisoquinoline *N,N’*-dioxide.[2b] However, Sonogashira coupling of (*S*)-3,3’-

diiodo-1,1’-biisoquinoline *N,N’*-dioxide and trimethylsilylacetylene turned out too elusive to move forward in our hands (see Supporting Information (SI) for details). As such, we considered a cross-coupling reaction of (*S*)-3,3’-dihalo-1,1’-biisoquinoline *N,N’*-dioxides and 4-metallo-1-substituted-1,2,3-triazoles. The Pd- or Cu-catalyzed direct arylations of 1-substituted-1,2,3-triazoles (i.e., 4, 5-unsubstituted) are exclusively C5-selective.[9] 4-Boronyl triazoles[10] remain an elusive substrate for Suzuki-Miyaura cross-coupling just like 2-pyridyl boronates (heterocyclic boronic acids and esters in which boron is attached to a carbon center adjacent to the ring heteroatom are often unstable due to their susceptibility to hydrolytic protodeboronation).[11] Although 4-stannyl triazoles[12] were shown to undergo Stille cross-coupling, only thermal azide-alkyne cycloaddition reactions are known for commercially available tributylstannylacetylene that was reported unreactive for some azides.[12f] Negishi cross-coupling is reported only for 1,5-disubstituted-4-zincio-1,2,3-triazoles and 1-substituted-5-zincio-1,2,3-triazoles.[13] Kumada cross-coupling of 4-magnesio-1,2,3-triazoles,[14] and Hiyama cross-coupling of 4-silyl-1,2,3-triazoles[15] are not known to the best of our knowledge. Underdevelopment of the methods to prepare 1,4-disubstituted-1,2,3-triazoles via C4 arylation is presumably because this motif can be readily prepared by CuAAC from the corresponding azides and acetylenes. In this context, we opted to investigate the feasibility of the corresponding Hiyama cross-coupling with readily available 1-substutited-4-trimethylsilyl-1*H*-1,2,3-triazoles (**6**) because of the clear benefits of organo(trialkyl)silanes that include low toxicity, high stability, good solubility and easy handling.[16] It should be mentioned that in contrast to heteroatom substituted silanes, aryl(trialkyl)silanes have drawn little attention as cross-coupling nucleophiles and have remained a long-standing important challenge.[16]

We began our investigation based on the Hiyama cross-coupling reactions of 2-trimethylsilylpyridines reported independently by the groups of Gros, Whittaker, and Marples.[17] We chose 1-benzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**6a**) and (*S*)-**4** or **5** as our model substrates and tested them with $Pd(PPh_3)_4$ in the presence of $TBAF{\cdot}3H_2O$ and Ag_2O in THF. In contrast to those previous reports, neither desired **3a** nor the corresponding mono-coupled by-product formed in isolable quantities (Table 1, entries 1 & 2). Therefore, we screened several commercially available Pd catalysts and found that $PdCl_2$(dppe), $PdCl_2$(dppp), and $PdCl_2$(BINAP) provided the desired product (**3a**) in 12%, 15% and 7% yields, respectively along with trace amount of the mono-coupled by-product (entries, 4, 5 & 8). We then evaluated different solvents, fluoride sources using $PdCl_2$(dppp) and Ag_2O, and in turn, metal additives with $PdCl_2$(dppp) and $TBAF{\cdot}3H_2O$, and found that THF, $TBAF{\cdot}3H_2O$ and Ag_2O were best out of all tested (see SI for details). We next probed the reaction temperatures and catalyst loading, and found that 40 °C and 40 mol % catalyst loading were optimum (entry 12) which gave **3a** in 41% yield. Since our main objective of this study was to develop a preparative method for catalyst **3**, we proceeded to test the model substrates on a 1 mmol scale and obtained the desired product in 46% yield with only trace amount of the corresponding mono-coupled product. As we used 40 mol % of a Pd catalyst, 46% yield corresponds to the catalyst turnover of 2.3 times (two coupling sites in **5**). We evaluated three more triazoles on a 1 mmol scale. 1-Mesityl-4-trimethylsilyl-triazole (**6b**) worked in a similar efficiency (54% yield). 1-Benzhydryl-4-trimethylsilyl-triazole (**6c**) provided the desired product in 31% yield with trace amount of the mono-coupled product and 1-(1-adamantyl)-4-trimethylsilyl-triazole (**6d**) afforded the desired product in 23% and the mono-coupled product in 19%. These results represent the first example of the Hiyama cross-coupling of 4-trimethylsilyl-1,2,3-triazoles, and demonstrated that the transformation was feasible. It should be mentioned that 5-unsubstituted 1,2,3-triazoles have proven useful as hydrogen bond donors and have been incorporated into organocatalysts, anion-binding receptors, etc.[7,18,19] These molecules were made by a sequence of Sonogashira and CuAAC reactions. Since Sonogashira reactions are often limited to aryl iodides[20] that are not always readily available, the present method could possibly complement the currently adapted synthetic sequence as demonstrated herein (vide supra).

We were able to obtain crystals of **3a** suitable for the X-ray structural analysis (Figure 2). In the solid state, **3a** was found to adapt the *anti*-conformation in accordance with our hypothesis based on the dipole–dipole interaction (Figure 1). The dihedral angle between its triazole and pyridine *N*-oxide rings is 7.66 °. At least in the solid state, the 3,3'-substituents effectively embrace the reaction space, forming a deep chiral cavity. We also performed a computational conformational analysis of **3a** using density functional theory. Calculations have been performed with the PBEh-3c method and the C-PCM solvation model with the dielectric constant of dichloromethane (DCM). The calculated most stable conformation of **3a** turned out almost identical to its crystal structure (see Figure S1 in SI). The *anti*-conformation was found to be favored by 8.6 kcal/mol over the *syn*-conformation and the calculated average dihedral angle between its triazole and pyridine *N*-oxide rings is 7.75 °, providing further support for our hypothesis that the dipole-dipole interaction effectively locks the conformation of 3,3'-substituents. This energy difference roughly corresponds to the equilibrium ratio of 1,000,000:1 (= *anti*:*syn*).

The binding geometry of **3a** to $SiCl_4$ was computationally investigated (Figure 3). To our delight, **3a** was found to bind to $SiCl_4$ through its two oxygen atoms with the binding energy of 30.8 kcal/mol in contrast to some 1,2,3-triazole bearing ligands that are known to coordinate to a metal via its triazole nitrogen atoms.[18f,21] Furthermore, the dipole–dipole interaction between the triazole and pyridine *N*-oxide rings appeared to dominate their relative conformation even after **3a** complexed with $SiCl_4$ although those two rings slightly twisted out of the co-planarity (the dihedral angle in the complex is = 20.57 °). Furthermore, the anion–π-type interaction[22] between chlorine atoms of a hypervalent chlorosilane and phenyl rings of the benzyl units was found in **3a**–$SiCl_4$ complex, which brought the benzyl groups to embrace the reaction space, leading to a structurally well-defined, deep chiral pocket. It should be mentioned that a pileup of electron density occurs at the peripheral chlorine atoms of a hypervalent silicon complex of this kind.[2b,23, 24]

Next, we conducted preliminary tests to probe the catalytic performance of **3a–d** in comparison to a conventional Lewis base catalyst (**2a**)[2b,25] (Scheme 2). The asymmetric transfer hydrogenation of *N*-aryl ketimines with trichlorosilane is a proven testing ground for new chiral Lewis bases (eq. 1).[26] To our delight, **3a–d** were found more enantioselective than **2a** (44–56% ee vs. 24% ee). Furthermore, **3a** was substantially more reactive than the others (71% yield). As **3a–d** provided promising reactivity and enantioselectivity for the testing ground reaction, we preliminarily evaluated them for the direct catalytic asymmetric synthesis of α-chiral primary amine that is among the long-standing important challenges in organic synthesis (eq. 2).[27] Catalysts **3a**, **c** and **d** enantioselectively catalyzed the reduction of amine salt **9** albeit with low yields while **2a** and **3b** were ineffective. Catalyst **3a** was found distinctively more enantioselective than **3c** or **d**. It should be mentioned that the Lewis base-catalyzed asymmetric transfer hydrogenation of ketimines with trichlorosilane currently remains limited to *N*-aryl and alkyl protected ones.[26] These preliminary observations clearly demonstrated that 3,3'-triazolyl biisoquinoline *N,N'*-dioxides are complementary to existing Lewis base catalysts, and bode well for the development of their applications.

In summary, we developed a new strategy to effectively control the conformation of substituents at the 3,3'-positons of axial-chiral biisoquinoline (or bipyridine) *N,N'*-dioxides on the basis of the strong dipole–dipole interaction between 1,2,3-triazole and pyridine *N*-oxide rings. The X-ray structure and the DFT calculations of **3a** provided strong support for this strategy. Furthermore, we successfully demonstrated that readily available 4-trimethylsilyl-1,2,3-triazoles are viable nucleophiles for Hiyama cross-coupling reaction where aryl(trialkyl)silanes have drawn little attention as cross-coupling nucleophiles and have remained a long-standing important challenge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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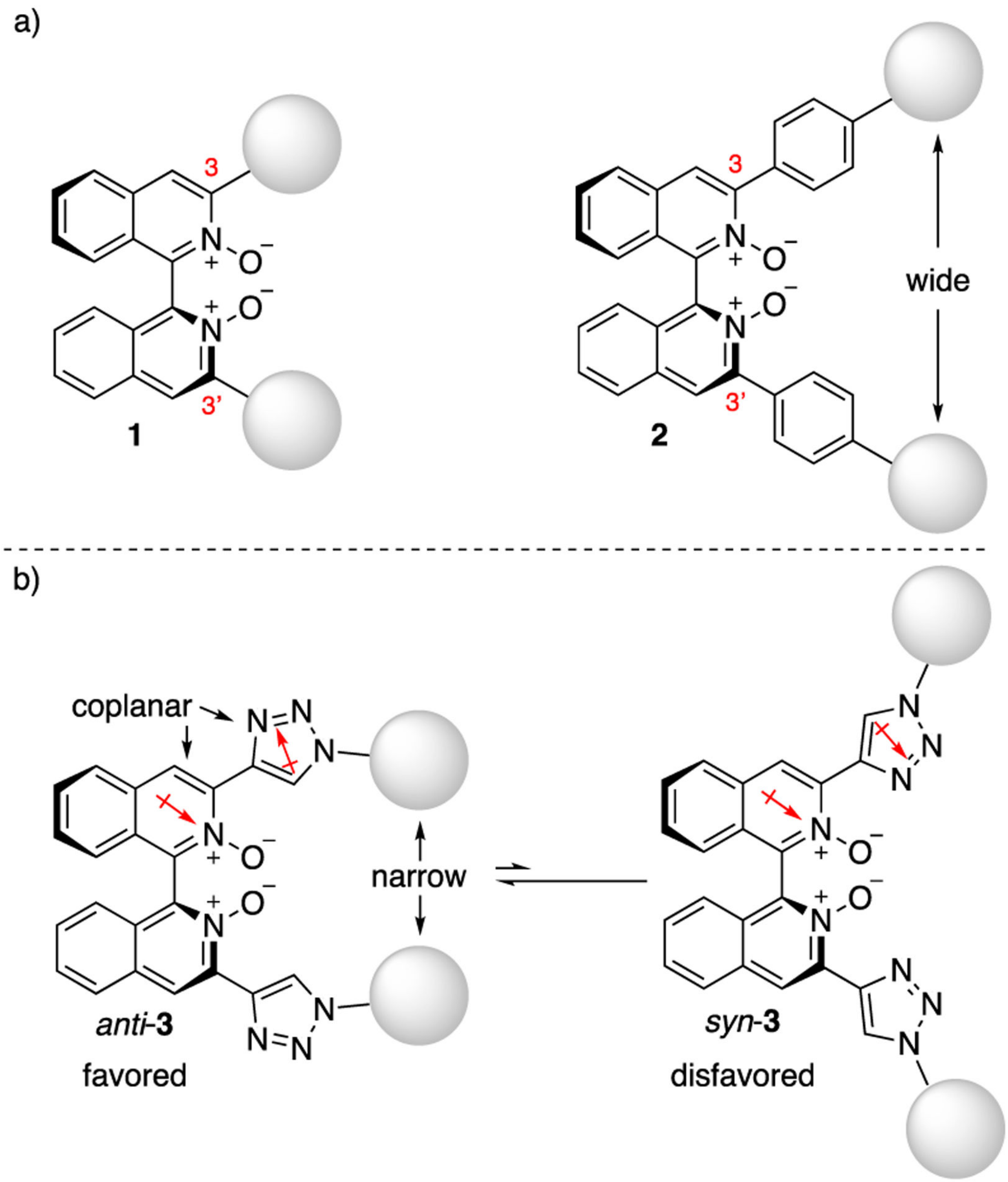


Figure 1.

The design of new Lewis bases based on dipole–dipole interaction.

Figure 2.

The crystal structure of **3a**.

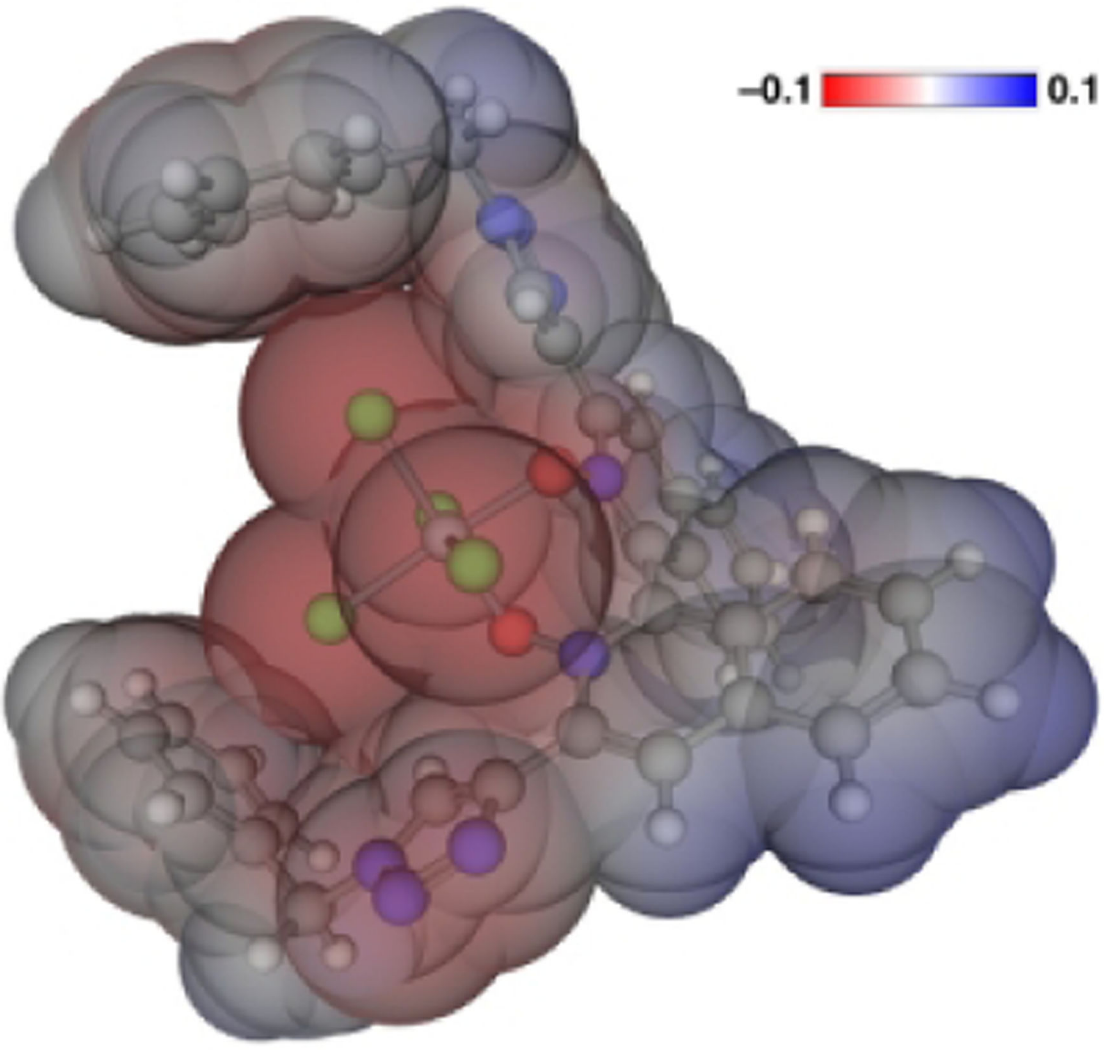
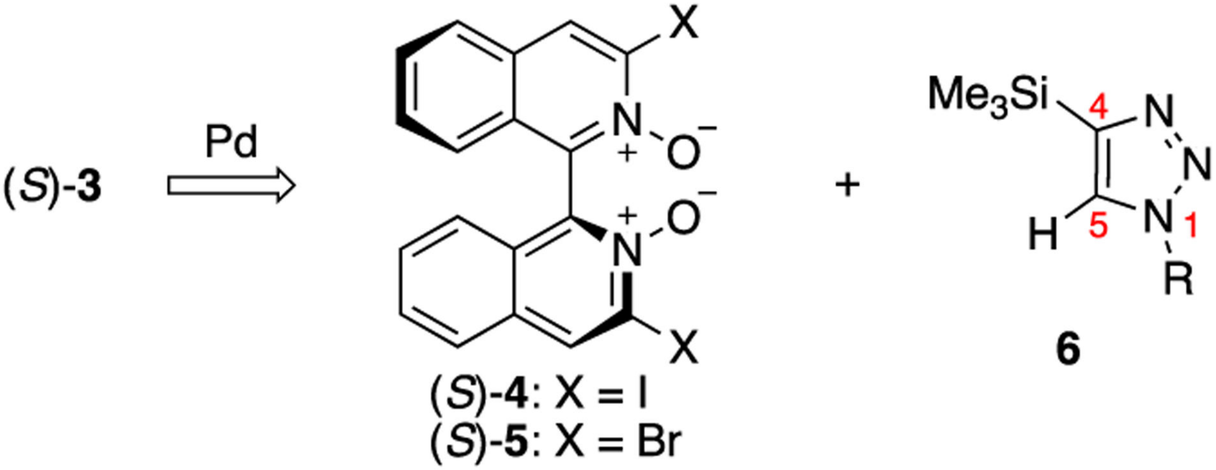
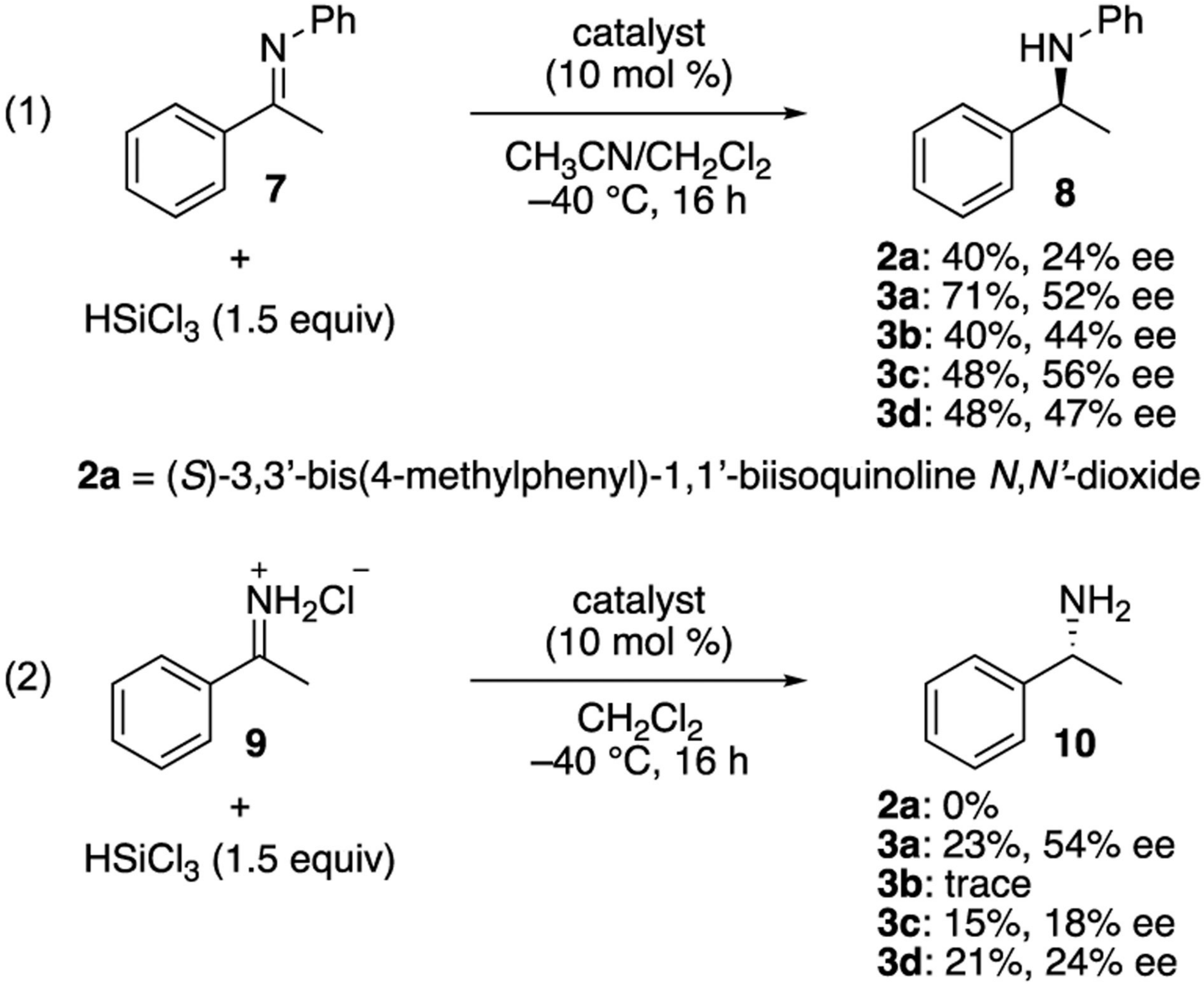


Figure 3.

The most stable conformation and potential of **3a**-$SiCl_4$ complex calculated with PBEh-3c/C-PCM(DCM).



Scheme 1.
A cross-coupling approach.

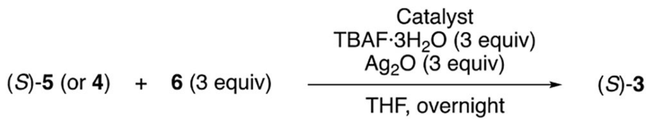


Scheme 2.

Preliminary evaluation of catalysts (reaction conditions were not fully optimized). Yields refer to ^{1}H NMR yield determined with 1,1,2,2-tetrachloroethane as an internal standard (see SI for details).

Table 1.

Hiyama cross-coupling of 4-TMS-triazoles.



Entry	ArX	6	Catalyst	mol %	Temp (°C)	Yield (%)[a]
1	**4**	**6a**	$Pd(PPh_3)_4$	20	rt	**3a**, trace
2	**5**	**6a**	$Pd(PPh_3)_4$	20	rt	**3a**, trace
3	**5**	**6a**	$Pd_2(dba)_3/P(o\text{-tol})_3$	20	rt	**3a**, 0
4	**5**	**6a**	$PdCl_2$(dppe)	20	rt	**3a**, 12
5	**5**	**6a**	$PdCl_2$(dppp)	20	rt	**3a**, 15
6	**5**	**6a**	$PdCl_2$(dppb)	20	rt	**3a**, trace
7	**5**	**6a**	$PdCl_2$(dppf)	20	rt	**3a**, 0
8	**5**	**6a**	$PdCl_2$(BINAP)	20	rt	**3a**, 7
9	**5**	**6a**	$Pd_2(dba)_3$/Xantphos	20	rt	**3a**, trace
10	**5**	**6a**	$PdCl_2$(dppp)	20	60	**3a**, 24
11[b]	**5**	**6a**	$PdCl_2$(dppp)	40	60	**3a**, 42
12[b]	**5**	**6a**	$PdCl_2$(dppp)	40	40	**3a**, 41
13[b,c]	**5**	**6a**	$PdCl_2$(dppp)	40	40	**38**,46[d]
14 [b,c]	**5**	**6b**	$PdCl_2$(dppp)	40	40	**3b**, 54[d]
15[b,c]	**5**	**6c**	$PdCl_2$(dppp)	40	40	**3c**, 31[d]
16[b,c]	**5**	**6d**	$PdCl_2$(dppp)	40	40	**3d**, 23[d]

0.1 mmol of **4** or **5** was used for entries 1 – 12. **6a**(R = Bn), **6b** (R = Mes), **6c** (R = Bzh) & **6d** (R = 1-ad).

[a] ^{1}H NMR yield estimated with 1,1,2,2-tetrachloroethane as an internal standard unless otherwise noted.

[b] 4.8 equiv of **6**, TBAF·3H_2O, and Ag_2O.

[c] 1 mmol scale reaction.

[d] Isolated yield after flash chromatography on silica gel.