Regio- and Stereoselective Rhodium(II)-Catalyzed C–H Functionalization of Organosilanes by Donor/Acceptor Carbenes Derived from Aryldiazoacetates

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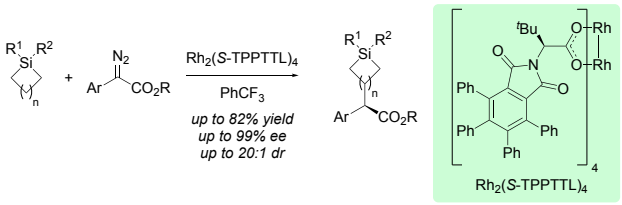
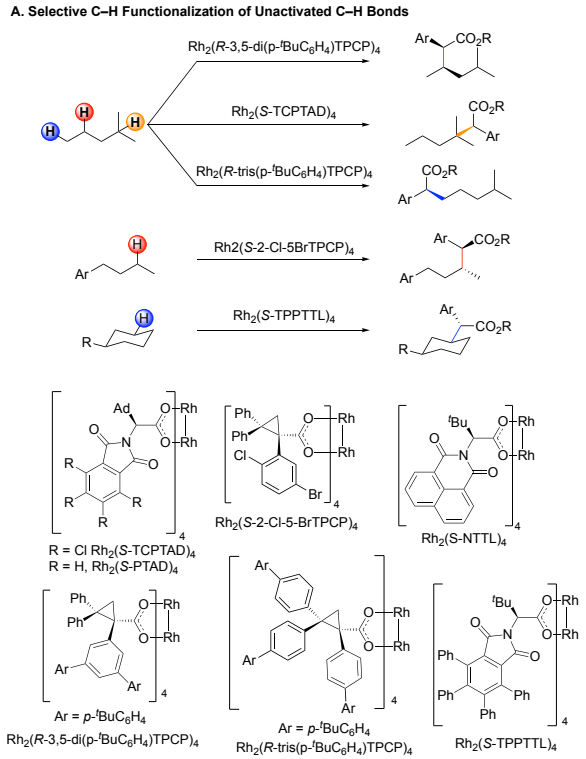
Supporting Information Placeholder



ABSTRACT: The regioselective and enantioselective intermolecular sp^3 C–H functionalization of silicon-substituted alkanes with aryldiazoacetates was accomplished using the recently developed dirhodium catalyst Rh$_2$(*S*-TPPTTL)$_4$. These reactions generate a diverse array of stereodefined substituted silacycloalkanes with high enantioselectivity and diastereoselectivity.

The selective functionalization of unactivated C–H bonds has rapidly matured into a useful and attractive synthetic strategy for constructing complex organic molecules.[1] One approach to C–H functionalization is the selective intermolecular insertion of donor/acceptor carbenes stabilized by dirhodium tetracarboxylate catalysts into C–H bonds.[2] Over the course of the development of this reaction, several functional groups have emerged which serve to stabilize the putative positive charge development in the transition state and ultimately enhance the lability of specific C–H bonds. These effects include conjugation, inductive, and steric effects. In addition to understanding and implementing these effects, our group is currently developing a suite of catalysts, which can functionalize C–H bonds at will depending on the catalyst and the functional groups present.[3] As shown in **Scheme 1**, several new catalysts can pinpoint specific C–H bonds through carbene-induced sp^3 C–H functionalization at a variety of different sites. For example, while transformations at activated benzylic sites are precedented,[3a,b] three different catalysts, Rh$_2$(*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$, Rh$_2$(*S*-TCPTAD)$_4$, and Rh$_2$(*R*-tris(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$ can selectively functionalize either secondary,[3c] tertiary,[3d] or primary[3e] unactivated C–H bonds, respectively. Furthermore, Rh$_2$(*S*-2-Cl-5BrTPCP)$_4$ achieved selective functionalization of remote C–H bonds in the presence of electronically activated benzylic C–H bonds.[3f] Most recently, Rh$_2$(*S*-TPPTTL)$_4$ was shown to be capable of desymmetrizing substituted cyclohexane derivatives, generating 3 stereocenters by the conversion of one C–H bond.[3g]

Scheme 1. Recent Developments in Selective C–H Functionalization Reactions with Donor/Acceptor Carbenes

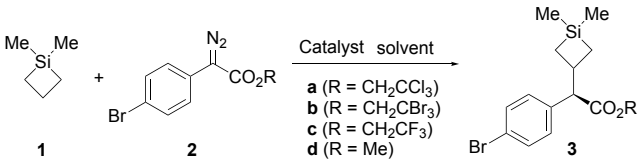


Despite extensive work in the functionalization of C–H bonds, hyperconjugation has been understudied as a prominent interaction for enhancing site-selective and stereoselective C–H bond functionalization. While early work demonstrated the feasibility of utilizing the β-silicon effect to control regioselectivity in carbene reactions, none of these studies showcased a stereoselective reaction.[4] Additional interest in organosilanes is evident in the literature related to the agrochemical,[5] materials,[6] and pharmaceutical industries.[7] In particular, silicon can be incorporated into bioactive compounds for manipulating pharmacokinetic properties.[7]

Due to the paucity of stereoselective investigations for elucidating the role of hyperconjugation towards enhancing specific C–H bond lability, the selective C–H functionalization of organosilanes using Rh_2(S-NTTL)$_4$ and 1,2,3-*N*-sulfonyl triazoles as carbene precursors was recently reported.[8] These reactions were effective for generating functionalized organosilanes bearing amino groups, but several limitations prompted our inquiries into improving this reaction. First, the most effective catalyst for the transformation of 1,2,3-*N*-sulfonyl triazoles was Rh_2(*S*-NTTL)$_4$, but this catalyst was only able to achieve modest diastereoselectivity (~5:1 dr) in reactions with unsymmetrical silanes. Additionally, challenges arose in expanding the substrate scope of the donor group on the donor/acceptor carbene. For example, the incorporation of heteroaromatic groups as the donor on 1,2,3-*N*-sulfonyltriazole has yet to be reported for carbene C–H insertion reactions. We reasoned that changing to aryldiazoacetate compounds could provide an opportunity to improve the stereoselectivity of the chiral substituted silacycloalkanes by testing the catalyst collection we have developed. Moreover, utilization of aryldiazoacetates would allow the exploration of heteroaromatic donors on the carbene precursor.[9]

To this end, we set out to optimize the reaction using commercially available silacyclobutane **1** and aryldiazoacetate **2** (Table 1). It was quickly determined that the current set of available catalysts were unsuitable for attaining enantioselectivities higher than 90% ee (entries 1-6). Even the use of Rh_2(*S*-NTTL)$_4$, which was effective for 1,2,3-*N*-sulfonyl triazoles,[8] failed to provide satisfactory results (entry 4). Fortunately, the implementation of a recently developed catalyst, Rh_2(S-TPPTTL)$_4$, was able to achieve product formation in 74% yield and 96% ee (entry 7). This catalyst is readily made in two steps from commercially available reagents, and it has recently demonstrated a remarkable ability to desymmetrize cyclohexane derivatives,[3g] but its utility with other types of substrates had not been reported. Further optimization studies indicated that the trichloroethyl ester provided the best results compared to other ester derivatives (entries 8-10). Also, a small increase in enantioselectivity was obtained from a solvent screen in which α,α,α-trifluorotoluene was deemed optimal (entries 11-14). Finally, the reaction could be conducted on 1 mmol scale (entry 16) without negatively influencing the outcome of the reaction.

Table 1. Catalyst Optimization Studies



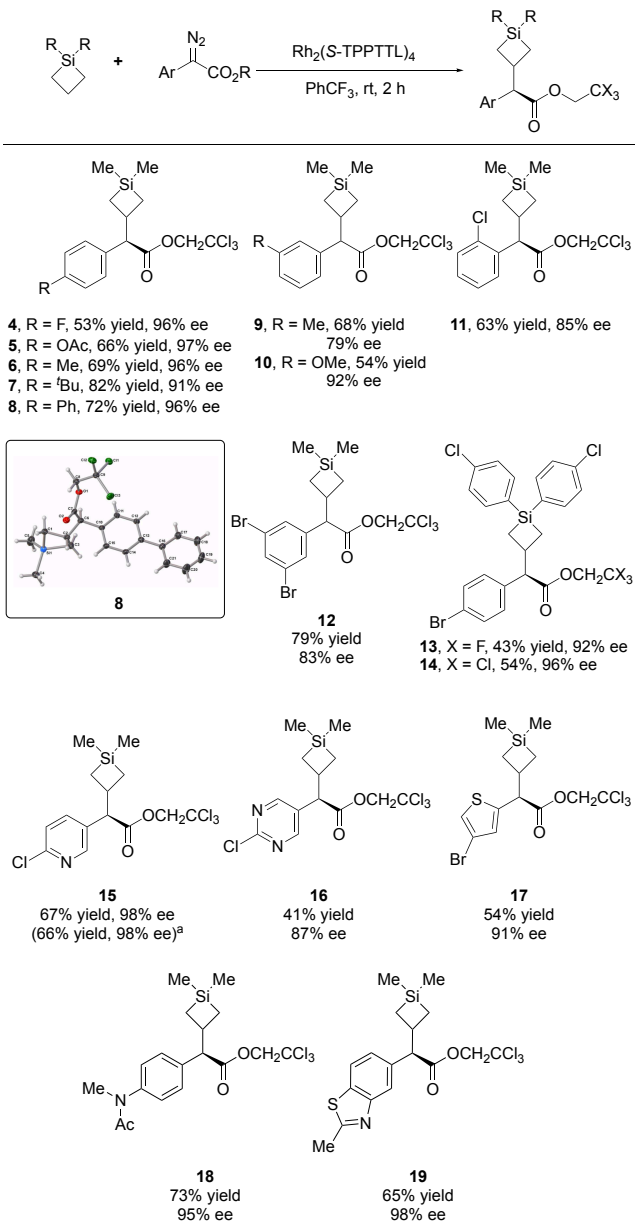
1 2 3

entry	catalyst	product	solvent	yield, %[a]	ee, %[b]
1	Rh_2(*S*-DOSP)$_4$	**3a**	CH_2Cl_2	55	58
2	Rh_2(*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP)$_4$	**3a**	CH_2Cl_2	67	-62
3	Rh_2(*S*-pPhTPCP)$_4$	**3a**	CH_2Cl_2	45	72
4	Rh_2(*S*-NTTL)$_4$	**3a**	CH_2Cl_2	70	38
5	Rh_2(*S*-PTAD)$_4$	**3a**	CH_2Cl_2	59	-40
6	Rh_2(*S*-TCPTAD)$_4$	**3a**	CH_2Cl_2	57	88
7	Rh_2(*S*-TPPTTL)$_4$	**3a**	CH_2Cl_2	74	96
8	Rh_2(*S*-TPPTTL)$_4$	**3b**	CH_2Cl_2	67	88
9	Rh_2(*S*-TPPTTL)$_4$	**3c**	CH_2Cl_2	54	92
10	Rh_2(*S*-TPPTTL)$_4$	**3d**	CH_2Cl_2	68	93
11[c]	Rh_2(*S*-TPPTTL)$_4$	**3a**	CH_2Cl_2	72	94
12	Rh_2(*S*-TPPTTL)$_4$	**3a**	$CHCl_3$	61	94
13	Rh_2(*S*-TPPTTL)$_4$	**3a**	$ClCH_2CH_2Cl$	64	95
14	Rh_2(*S*-TPPTTL)$_4$	**3a**	TFT	61	98
15[d]	Rh_2(*S*-TPPTTL)$_4$	**3a**	TFT	69	98
16[e]	Rh_2(*S*-TPPTTL)$_4$	**3a**	TFT	74	98

[a]Reaction conditions: 2 (0.25 mmol) in 3.0 mL solvent was added over 3 h to a solution of the silane substrate (0.75 mmol, 3.0 equiv.) and catalyst (1.0 mol%) in 1.5 mL solvent at room temperature. The reaction was allowed to stir an additional 2 h. All yields are isolated yields. [b]The enantioselectivity was determined by chiral HPLC analysis of the isolated product. [c]The reaction was conducted at reflux. [d]0.5 mmol scale. [e]1 mmol scale.

Next, the substrate scope was examined, and a number of different aryldiazoacetates were found to be effective. This included a variety of different substituted aryl rings that were competent in this transformation (**Scheme 2**). The reaction tended to suffer from lower yields for silanes bearing bulky aryl groups even though the enantioselectivity remained high.[10] Importantly, the substrate scope of the aryl donor could be expanded to heteroaromatic donors such as pyridine, pyrimidine, and thiophene (entries 15-17). The absolute configuration was determined by X-ray crystallographic analysis of **8**.[11]

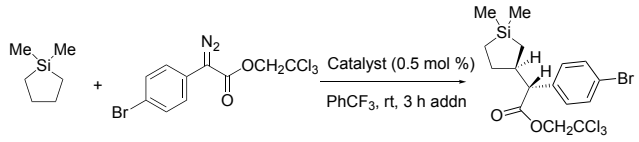
Scheme 2. Scope of Silacyclobutane C–H Functionalization



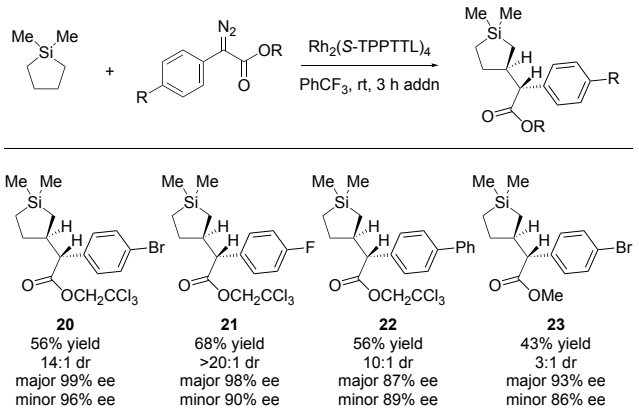
Reaction conditions: Diazo compound (0.5 mmol) in 6.0 mL $PhCF_3$ was added over 3 h to a solution of the silane substrate (1.5 mmol, 3.0 equiv.) and catalyst Rh_2(S-TPPTTL)$_4$ (0.5-1.0 mol%) in 3.0 mL $PhCF_3$ at room temperature, and then the reaction was allowed to stir for an additional 2 h. All yields are isolated yields. The enantioselectivity was determined by chiral HPLC analysis of the isolated product. [a]Reaction conducted on 3 mmol scale.

We also evaluated 5-membered ring silacyclopentane to determine if high levels of diastereoselectivity could be achieved using Rh_2(*S*-TPPTTL)$_4$. When 1-sulfonyl-1,2,3-triazoles were used previously for the C–H insertion of five-membered rings, lower levels of diastereoselectivity were achieved (up to 5:1 dr). To investigate the unique aptitude of this new catalyst for controlling diastereoselectivity, a catalyst screen was conducted using a variety of catalysts that have demonstrated recent success with similar transformations (**Scheme 3**).[12] While all the catalysts delivered the desired compound, the levels of diastereoselectivity were low, but when Rh_2(*S*-TPPTTL)$_4$ was utilized as the catalyst the dr of **20** was improved up to ~13:1.[13] The relative configuration was assigned based on shielding effects arising from preferred conformers of the products.[14] The general success of Rh_2(*S*-TPPTTL)$_4$ for achieving highly stereoselective reactions was further evidenced by the formation of **21** with 20:1 dr and 98% ee for the major diastereomer and the formation of **22** with 10:1 dr and 87% ee for the major diastereomer. The importance of the trichloroethyl ester group was also assessed by using methyl 2-(4-bromophenyl)-2-diazoacetate in the reaction for the generation of **23**. The diastereoselectivity for this reaction dropped to 3:1 dr even though both diastereomers were produced with high enantioselectivity (major = 93% ee; minor 86% ee).

Scheme 3. Diastereoselective Silacylopentane C–H Functionalization



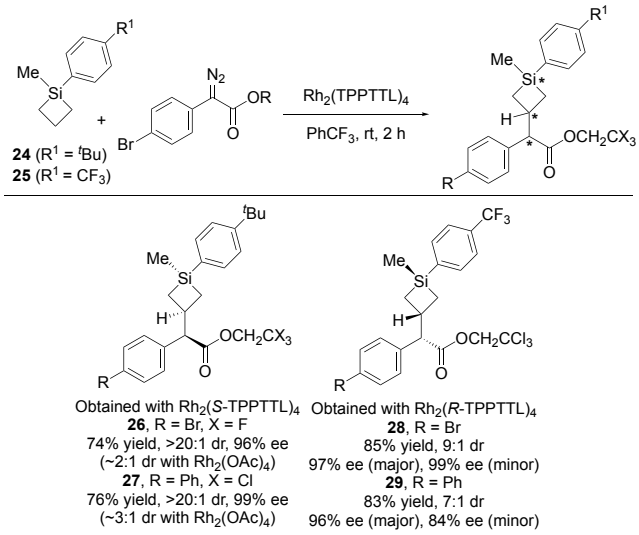
Catalyst	Combined Yield	dr
Rh_2(*S*-DOSP)$_4$	50%	1.9:1
Rh_2(*S*-*p*-Ph-TPCP)$_4$	56%	1.5:1
Rh_2(*R*-PTAD)$_4$	72%	2:1
Rh_2(R-TCPTAD)$_4$	73%	2.2:1
Rh_2(S-NTTL)$_4$	33%	4:1
Rh_2(S-TPPTTL)$_4$	56%	14:1



The success of Rh_2(*S*-TPPTTL)$_4$ in generating highly diastereoselective reactions made us curious about the possibility of selectively functionalizing either an equatorial or axial C–H bond when the substituents on silicon were different (**Scheme 4**). For this to be accomplished, substrates like **24** and **25** needed to undergo preferential C–H insertion at either an equatorial or axial C–H bond relative to the aryl substitution. Normally, C–H functionalization occurs preferentially at equatorial C–H bonds where sterics are minimized, so if any conformational bias is present in the molecule, some diastereoselectivity may be achieved. Indeed, the slight conformational bias of **24** was evidenced by the modest diastereoselectivity of 2:1-3:1 when $Rh_2(OAc)_4$ was utilized as the catalyst for formation of **26** and **27**. This suggested that a catalyst framework was necessary to further enhance selectivity. This was confirmed by evaluating Rh_2(*S*-TPPTTL)$_4$ as the catalyst, where the generation of **26** and **27** was achieved

with high levels of diastereoselectivity (>20:1) in addition to high levels of enantioselectivity (96% ee and 99% ee). Additionally, the formation of **28** and **29** was accomplished with good diastereoselectivity (9:1 dr and 7:1 dr) and great enantioselectivity (97% ee and 96% ee for each major compound).[15] The relative configuration was established by ^{1}H nOe analysis of the products and the absolute stereochemistry was tentatively assigned by analogy to **8** (see Supporting Information).

Scheme 4. Diastereoselective C–H Functionalization of Silacyclobutanes with Different Slyl Substituents



Obtained with Rh_2(*S*-TPPTTL)$_4$
26, R = Br, X = F
74% yield, >20:1 dr, 96% ee
(~2:1 dr with $Rh_2(OAc)_4$)
27, R = Ph, X = Cl
76% yield, >20:1 dr, 99% ee
(~3:1 dr with $Rh_2(OAc)_4$)

Obtained with Rh_2(*R*-TPPTTL)$_4$
28, R = Br
85% yield, 9:1 dr
97% ee (major), 99% ee (minor)
29, R = Ph
83% yield, 7:1 dr
96% ee (major), 84% ee (minor)

The structure of Rh_2(*S*-TPPTTL)$_4$ has been studied by means of X-ray-crystallographic analysis and computational studies.[3g] The catalyst has a deep cavity, as illustrated in Figure 1, and the sixteen phenyl rings on the four phthalimido groups adopt an orientation resulting in propeller chirality. When Rh_2(*S*-TPPTTL)$_4$ was used for the desymmetrization of alkylcyclohexanes, the enantioselectivity at the carbene center was very high, favoring the *R* configuration, and the shape of the cavity within the catalyst caused the reactions to be highly site-selective and diastereoselective. In the case of the current studies, the asymmetric induction at the carbene site again favors the formation of the *R* configuration. The distinctive shape of the pocket is likely to be a major factor explaining why reactions with this catalyst proceed with higher levels of diastereocontrol compared to all other chiral dirhodium catalysts examined.

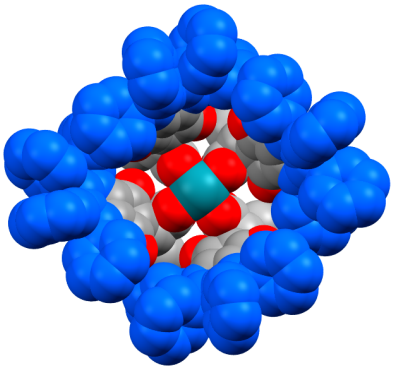


Figure 1. Space-filling representation of the structure of Rh_2(*S*-TPPTTL)$_4$ (Top-down view; 16 phenyl rings in blue)

In conclusion, the regio- and stereoselective C–H functionalization reaction of silicon-substituted alkanes was realized using aryldiazoacetates and the sterically encumbered catalyst Rh_2(*S*-TPPTTL)$_4$. These reactions show high stereoselectivity, including diastereoselectivity at the β position of silacycloalkanes, and are amenable to the incorporation of heteroaromatic donors. (Word Style "TA_Main_Text"). For full instructions, please see the journal's Instructions for Authors. A checklist is available for Organic Letters formatting conventions at the journal's home page. Do not modify the font in this or any other section, as doing so will not give an accurate estimate of the formatting for publication.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information, consisting of complete experimnetal data and images of the NMR spectra and HPLC traces, is available free of charge on the ACS Publications website at DOI: XX.XXXX/XXX

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Notes

HMLD is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued 3/10/2015). The other authors have no competing financial interests.

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(10) Even the use of the smaller trifluoroethyl ester resulted in poorer yield and enantioselectivity.

(11) The X-ray crystallographic data for 8 was submitted to the Cambridge Structural Database (CCDC 1902706).

(12) See SI for comparative details.

(13) The second best catalyst Rh_2(*S*-NTTL)$_4$ generated the desired compound with 4:1 dr, which was similar to the levels of diastereoselectivity obtained using 1-sulfonyl-1,2,3-triazoles as carbene precursors. See reference 8.

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(15) The opposite enantiomer of the catalyst was utilized to obtain sufficient separation by chiral HPLC chromatography for determining enantiomeric ratios.