Iridium-Catalyzed Regio- and Enantioselective Propargylic C–H Silylation

Jin Zhu,[a] Hai Chang,[a] and Yi-Ming Wang[a]*

[a]Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

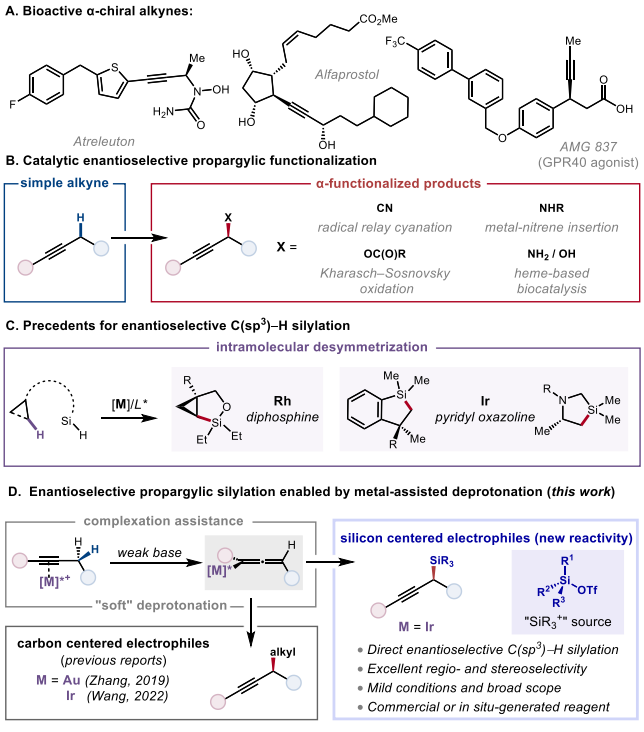
Supporting Information Placeholder

ABSTRACT: We report a highly enantioselective intermolecular silylation of the propargylic C(sp^3)–H bonds of alkynes for the formation of propargylic silanes. The optimized protocol afforded enantioenriched α-silylated alkynes in good to high yield with excellent levels of stereocontrol under mild conditions. A variety of silyl triflates, either commercial or *in situ*-generated, were used as the silylation reagents, and a broad range of simple and functionalized alkynes, including aryl alkyl acetylenes, dialkyl acetylenes, and 1,3-enynes, were successfully employed as substrates. In the case of dialkyl acetylene substrates, silylation took place in a highly regioselective manner. Preliminary mechanistic experiments suggest a catalytic cycle in which electrophilic addition of the silyl triflate reagent to the Ir center and subsequent deprotonation of a dicationic Ir–alkyne complex are key steps.

Alkynes bearing a stereocenter at the propargylic position are components of biologically active molecules and have served as useful building blocks for stereoselective synthesis (Scheme 1A).[1] Widely applied approaches for their synthesis include the substitution of propargylic alcohol derivatives[2] and the nucleophilic addition of acetylene anion to electrophiles.[3] As an alternative, the enantioselective transformation of propargylic C(sp^3)–H bonds constitutes a streamlined but underdeveloped approach for obtaining α-functionalized products (Scheme 1B).[4] The radical-based enantioselective Kharasch–Sosnovsky oxygenation represents an early example of such a transformation, though it remains limited in scope and underexplored for alkyne substrates.[4a,4b] More recently, Guosheng Liu and coworkers reported a successful radical relay-induced propargylic cyanation based on chiral Cu catalysts, which is also believed to involve radical and organocopper intermediates.[4c,4d] Metal nitrene insertion is another powerful tool for C(sp^3)–H functionalization, and these methods are particularly effective for intramolecular propargylic amination reactions.[4e-i] While intermolecular transformations remain rare, enzymatic methods have been successfully applied toward the synthesis of propargylic amines and alcohols.[4j,4k]

Chiral compounds containing silicon are of significant interest to drug and agrochemical discovery efforts.[5,6] Enantioenriched organosilicon compounds are also versatile synthetic intermediates that can be transformed stereospecifically into a range of other functionalized products.[7] Although the selective and efficient synthesis of enantioenriched silanes has been achieved through approaches that include olefin addition,[8a-j] allylic substitution,[8k,8l] cross coupling,[8m-o] and carbene insertion reactions,[8p-t] the direct construction of stereodefined C(sp^3)–Si bonds through metal-catalyzed enantioselective C(sp^3)–H silylation remains underexplored and seldom reported.[9] Known protocols for enantioselective C(sp^3)–H silylation are, to the best of our knowledge, limited to the intramolecular desymmetrization of substrates bearing pendant cyclopropyl or *gem*-dimethyl moieties (Scheme 1C).[10] Given the broad availability and accessibility of alkynes and the synthetic versatility of propargylic silanes,[7,11,12] we felt that a generally applicable, enantioselective silylation of the α-C–H bonds of alkynes would serve as an attractive, yet thus far unrealized, route to enantioenriched organosilicon compounds.[13]

Scheme 1. Asymmetric propargylic functionalization



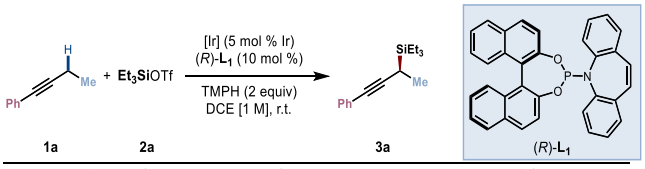
We posited that a *complexation-assisted deprotonation* strategy for the catalytic generation of a allenylmetal reagent from an alkyne (Scheme 1D, top left) could enable the desired enantioselective propargylic C–H silylation reaction.[14-16] Liming Zhang and coworkers previously demonstrated the utility of this approach using bifunctional Au/Brønsted base catalyst for intramolecular coupling of alkyne and aldehydes,[16a] while, more recently, our group reported an intermolecular propargylic allylation in the presence of an Ir catalyst (Scheme 1D, bottom left).[16b] Given these results, the substantial precedent for Ir-catalyzed silylation chemistry,[17] and the high affinity of Ir toward Si,[18] we hypothesized that an Ir/chiral phosphoramidite system[19] would allow for the stereocontrolled installation of silyl groups at the propargylic position through the interception of an allenyliridium intermediate[16b,20] with a silicon-centered electrophile.[21]

In this Communication, we disclose the successful implementation of this strategy using silyl trifluoromethanesulfonate (triflate) reagents as electrophiles, leading to the development of a highly enantioselective and regioselective protocol for the Ir-catalyzed propargylic α-C–H silylation of alkyl aryl, alkyl alkenyl, and dialkyl acetylenes (Scheme 1D, right).

In our initial studies, 1-phenyl-1-butyne (**1a**) was selected as the model alkyne substrate for propargylic silylation. Based on the hypothesis that a cationic Ir species is the active catalyst, [16b] a cationic precursor, $[Ir(cod)_2]^+BF_4^-$ (cod = 1,5-cyclooctadiene) was first evaluated.[22] Together with triethylsilyl triflate (TESOTf, **2a**) as the silylation reagent, the desired product was obtained with excellent enantioselectivity though in modest yield (Table 1, entry 1). However, contrary to initial expectations, $[Ir(cod)Cl]_2$ exhibited superior reactivity among commercially available Ir(I) sources (entries 1 to 3). Subsequent experiments demonstrated that, under reaction conditions, the silyl triflate reagent rapidly abstracts Cl^- from the phosphoramidite-ligated Ir center to generate the active cationic catalyst (*vide infra*). A 2:1 ratio of chiral ligand to metal was found to give considerably better catalytic activity compared to a 1:1 ratio (entry 4 vs. entries 3 and 5).

In contrast to previously reported Ir-catalyzed C(sp^3)–H silylation reactions, the hydrosilane Et_3SiH was found to be ineffective (entry 6).[17g-i] The use of triethylsilyl chloride as the reagent likewise did not afford the product (entry 7). However, when a prestirred mixture of Et_3SiH and TfOH was used as the reagent,[23] the silylation product was formed in high yield and excellent enantioselectivity (entry 8), indicating that silyl triflate formed *in situ* was an effective reagent. Among a range of organic and inorganic bases examined, 2,2,6,6-tetramethylpiperidine (TMPH) was found to be uniquely effective (entry 9 and Supporting Information). Finally, control experiments omitting iridium source, ligand, and base one at a time demonstrated the necessity of each of these components in this transformation (entry 10).

Table 1. Optimization of the Ir-catalyzed propargylic silylation[a]



1a 2a 3a (*R*)-L_1

Entry	Selected reaction conditions	% yield	% ee
1	$[Ir(cod)_2]^+BF_4^-$ as [Ir]	61	99
2	$[Ir(cod)(OMe)]_2$ as [Ir]	58	99
3[b]	$[Ir(cod)Cl]_2$ as [Ir]	99 (91)	98 (97)
4	$[Ir(cod)Cl]_2$ (5 mol % Ir), L_1 (5 mol %)	44	99
5	$[Ir(cod)Cl]_2$ (1 mol % Ir), L_1 (2 mol %)	56	99
6[c]	Et_3SiH instead of Et_3SiOTf	NP	ND
7	Et_3SiCl instead of Et_3SiOTf	NP	ND
8[d]	Prestirred Et_3SiH + TfOH as reagent	95	98
9	Et_3N, DBU or Na_2CO_3 instead of TMPH	NP	ND
10	no [Ir], L_1, or TMPH	NP	ND

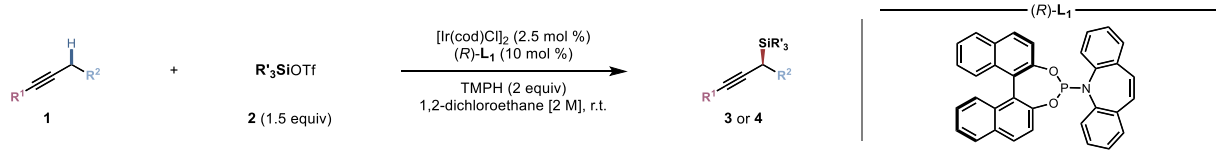
[a]On 0.1 mmol scale. Yields were determined by ^1H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as the internal standard, DCE: 1,2-dichloroethane. [b]Yield and enantioselectivity of isolated product (0.2 mmol scale, 2 M) in parentheses. [c]NP: no desired product observed, ND: not determined. [d]Et_3SiH and TfOH were mixed and stirred for 5 min before adding to the reaction mixture.

With optimized reaction conditions established, the scope of the transformation was investigated. Using commercially available trimethylsilyl (TMS) and triethylsilyl triflates as the silyl source, a diverse collection of aryl alkyl acetylenes were first examined (Table 2). Substrates bearing electron withdrawing and donating aryl groups (**1b–1f**) provided the desired products (**3b–3f**) in moderate to good yield and excellent enantioselectivity, as did an *ortho*-substituted substrate (**1c**). In addition, substrates bearing a number of functional groups could all be successfully employed to deliver the desired products, including those with esters (**3d**, **3u**), a tertiary amide (**3m**), a tertiary arylamine (**3l**), an imide (**3n**), a diaryl ketone (**3t**), and a sulfonamide (**3i**). Moreover, a variety of heterocycles were well tolerated in this transformation, including benzofurans (**3g**, **3h**), thiophenes (**3j**, **3k**), a pyrazole (**3o**), a carbazole (**3p**), an indole (**3q**), a phenothiazine (**3r**), and a quinoline (**3s**). In all cases examined, the protocol delivered propargylic silanes with excellent levels of stereocontrol (≥95% ee).

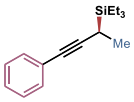
Structurally distinct conjugated enynes (**1v**, **1w**) and dialkyl acetylenes (**1x**, **1y**) were also successful substrates, delivering products (**3v, 3w, 3x** and **3y**) in moderate to high yield and good to excellent enantioselectivity (≥85% ee). Remarkably, unsymmetrical acetylene (**1y**) bearing two primary alkyl substituents (ethyl and phenethyl) still provided silylation product with synthetically useful regioselectivity (8.3:1 rr) for the less substituted position(**3y**). The regioselectivity of this transformation was examined further by subjecting methyl alkyl acetylenes to the standard reaction conditions. In the cases, silylation took place cleanly (>20:1 rr) at the terminal methyl position to give achiral propargylic silanes **4**. Regioselectivity was unaffected by the presence of nitrogen or oxygen substituents on the alkyl chain. The incorporation of fragments based on bioactive molecules and pharmaceuticals, including nortriptyline (**3za**), sertraline (**3zb**), cholesterol (**3zc**), fenofibric acid (**4f**), probenecid (**4g**), and adapalene (**4h**), highlights the broad scope and functional group compatibility of this silylation protocol.

We then briefly investigated the scope of silyl triflate reagents suitable for this transformation (Table 3). In the case of reagents that were not available commercially (**2aa–2af**), we found that they could be conveniently generated by the protonolysis of the corresponding allyl- or arylsilanes with TfOH and used *in situ* without purification.[23] In all cases examined, propargylic silylation products (**5a–5f**) were obtained in moderate to excellent yield and uniformly excellent enantiocontrol (≥94% ee). Notably, a chiral racemic silyl triflate could be used to give **5f** with high levels of enantiocontrol at the propargylic position, though as a mixture of diastereomers at silicon.

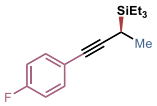
Table 2. Substrate scope of alkynes[a]



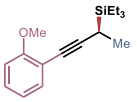
applicability of alkyne with silyl triflate



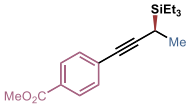
3a
91% *yield*, 97% *ee*



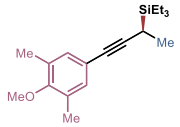
3b
80% *yield*, 97% *ee*



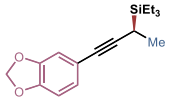
3c
94% *yield*, >99% *ee*



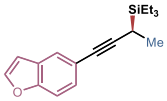
3d
67% *yield*, 97% *ee*



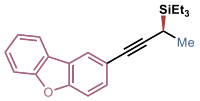
3e
67% *yield*, 96% *ee*



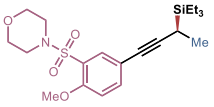
3f
89% *yield*, 98% *ee*



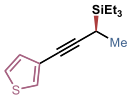
3g
91% *yield*, 96% *ee*



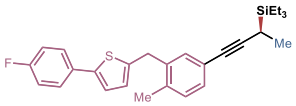
3h
92% *yield*, 97% *ee*



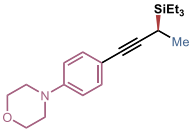
3i
89% *yield*, 95% *ee*



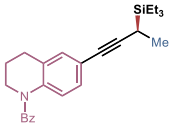
3j
93% *yield*, 97% *ee*



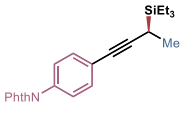
3k *Canagliflozin precusor*
97% *yield*, 97% *ee*



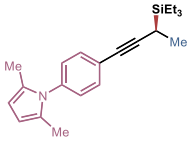
3l
95% *yield*, 97% *ee*
5 mmol : 92% *yield*, 98% *ee*[b]



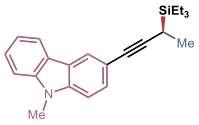
3m
49% *yield*, 97% *ee*



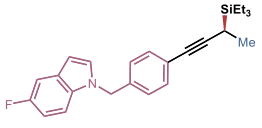
3n
86% *yield*, 97% *ee*



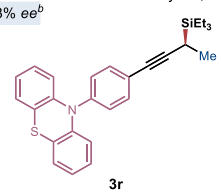
3o
78% *yield*, 98% *ee*



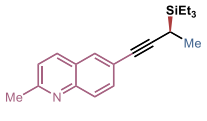
3p
93% *yield*, 97% *ee*



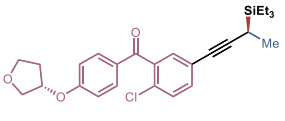
3q
99% *yield*, 95% *ee*



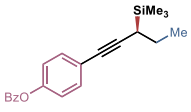
3r
40% *yield*, 96% *ee*



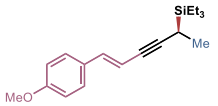
3s
55% *yield*, 94% *ee*



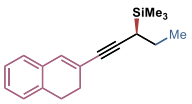
3t *Empagliflozin precusor*
51% *yield*, 98% *de*



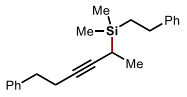
3u
93% *yield*, 98% *ee*



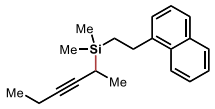
3v
68% *yield*, 94% *ee*



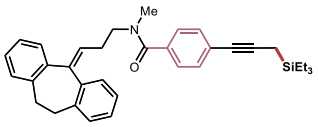
3w
54% *yield*, 96% *ee*



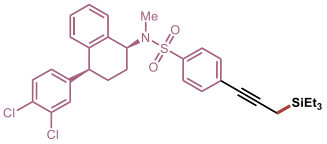
3x[c]
57% *yield*, 8.3:1 *rr*, 85% *ee*



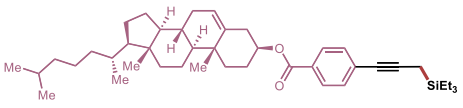
3y[d]
66% *yield*, 90% *ee*



3za *Nortriptyline*
74% *yield*

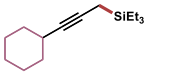


3zb *Sertraline*
82% *yield*

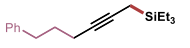


3zc[e] *Cholesterol*
95% *yield*

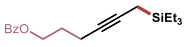
regoiselective silylation of dialkyl acetylene



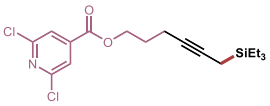
4a
74% *yield*, >20:1 *rr*



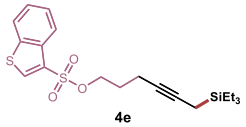
4b
68% *yield*, >10:1 *rr*



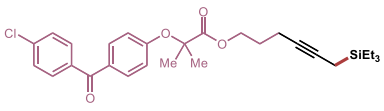
4c[f]
94% *yield*,>20:1 *rr*



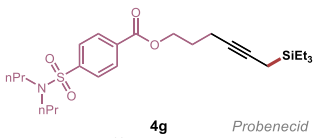
4d
69% *yield*, >20:1 *rr*



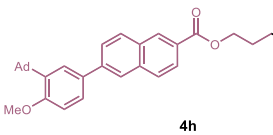
4e
59% *yield*, >20:1 *rr*



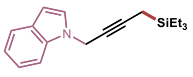
4f *Fenofibric acid*
74% *yield*, >20:1 *rr*



4g *Probenecid*
87% *yield*, >20:1 *rr*



4h *Adapalene*
60% *yield*, >20:1 *rr*

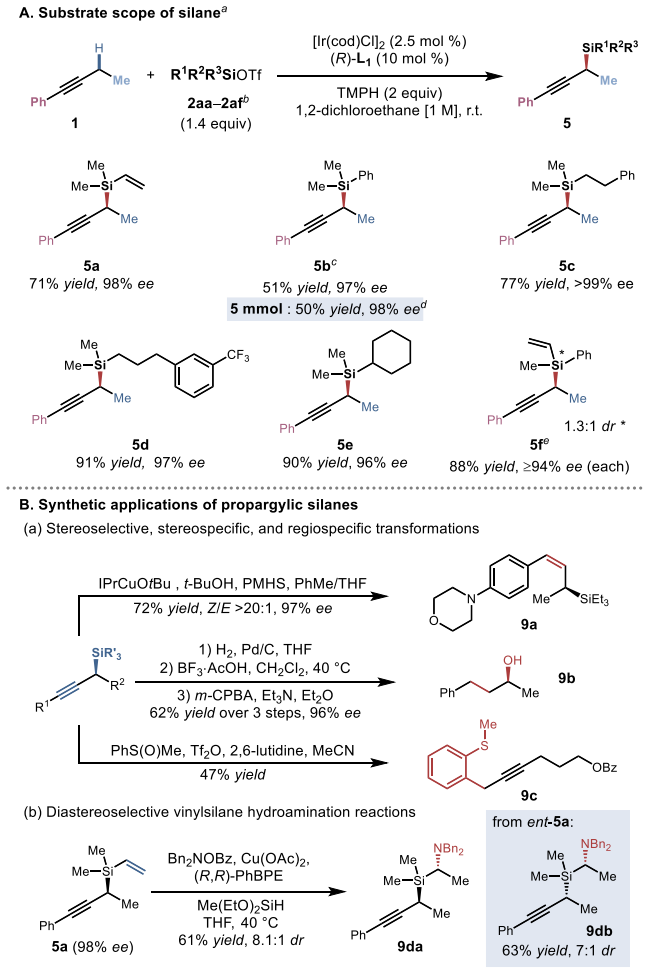


4i
96% *yield*, >20:1 *rr*

[a]Isolated yields. Enantiomeric excesses were determined by chiral HPLC. Regisomeric ratios were determined by ^{1}H NMR spectroscopy of the crude material. [b][Ir(cod)Cl]$_2$ (2 mol %) and (*R*)-**L**$_1$ (8 mol %) were used. [c]Dimethyl(phenethyl)silyl triflate was generated *in situ* from dimethyl(phenethyl)(phenyl)silane and TfOH. [d]Dimethyl(2-(naphthalen-1-yl)ethyl)silyl triflate was generated *in situ* from dimethyl(2-(naphthalen-1-yl)ethyl)(phenyl)silane and TfOH. [e]On 0.1 mmol scale. [f]0.2 mL 1,2-dichloroethane (1M) was used as the solvent.

The protocol was found to be scalable. On 5 mmol scale, **3l** could be prepared without significant loss in synthetic efficiency or stereoselectivity (1.52 g isolated, 92% yield, 98% ee). In addition, a series of derivatization reactions could be carried out on **3l**, **5b** and **4c** to deliver products **9a**,[24a] **9b**,[7a,8q] and **9c**[24b] with high levels of stereoselectivity, enantiospecificity, and regiospecificity, respectively. Notably, comparison of chiral HPLC retention times and optical rotation of **9b** with those reported in the literature allowed the absolute configuration of silane **5b** to be deduced and those of other enantioenriched silane products **3** and **5** to be assigned by analogy. Furthermore, vinyl silane **5a** bearing a stereocenter at the propargylic position could undergo CuH-catalyzed hydroamination with catalyst control of diastereoselectivity.[8h]

Scheme 2. Substrate scope of silane and synthetic application of propargylic silanes

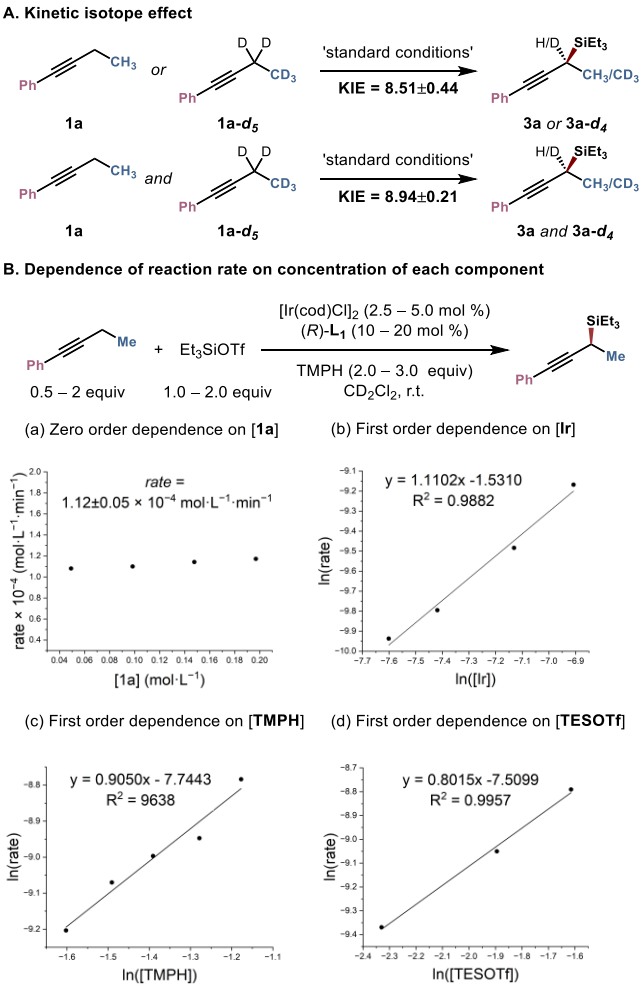


[a]Isolated yields. Enantiomeric excesses were determined by chiral HPLC. [b]Generated *in situ* from corresponding $R^1R^2R^3SiPh$ and TfOH. [c]Dimethyl(phenyl)silyl triflate was generated *in situ* from allyldimethyl(phenyl)silane and TfOH. [d]$[Ir(cod)Cl]_2$ (2 mol %) and (*R*)-**L**$_1$ (8 mol %) were used. [e]Methyl(phenyl)(vinyl)silyl trifluoromethanesulfonate was generated *in situ* from (4-methoxyphenyl)(methyl)(phenyl)(vinyl)silane and TfOH.

We performed a series of experiments to probe the mechanism of this iridium-catalyzed process. We began by examining the kinetic isotope effect using 1-phentyl-1-butyne (**1a**) and its deuterated isotopologue (**1a-*d*$_5$**). Initial rate experiments conducted in parallel yielded a k_H/k_D of 8.51±0.44, and an intermolecular competition experiment resulted in a KIE value of 8.94±0.21. The close agreement of the primary kinetic isotope effect measured in these two sets of experiments suggests an irreversible and turnover limiting proton abstraction step (Scheme 3A).

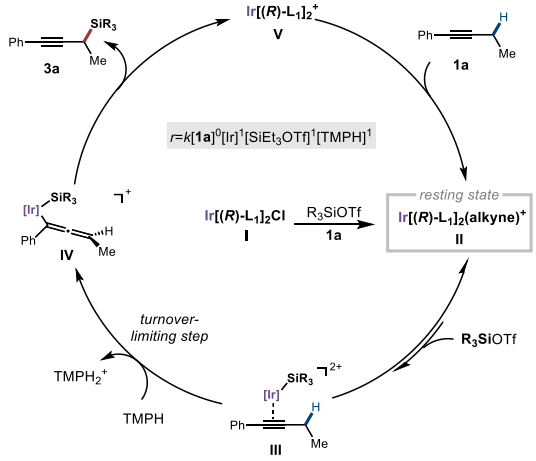
We then sought to determine the kinetic order of each of the reagents and the catalyst by varying the concentration of each component (alkyne **1a**, [Ir]/**L**$_1$ (**L**$_1$:Ir = 2:1), TMPH, and TESOTf) and measuring initial rates of reaction to provide silylation product **3a** (Scheme 3B). These experiments revealed first order dependence on catalyst, base, and silyl triflate but zero order dependence on the alkyne. Stoichiometric NMR experiments demonstrate that, in the presence of alkyne, silyl triflate reagents abstracts Cl^- completely from the phosphoramidite-ligated Ir center within 10 min to generate the cationic alkyne complex **II** (Scheme 4, see the Supporting Information).[25c] Moreover, ^{31}P NMR analysis of the reaction mixture indicates that **II** is the major phosphorus-containing species during the course of the reaction (up to 50% conversion). These observations suggest that complex **II** is the catalyst resting state and are consistent with the zero order kinetic dependence on [**1a**]. To account for the first order dependence on [TESOTf], we propose that **II** engages the silylation reagent before deprotonation takes place.

Scheme 3. Mechanistic studies of Ir-catalyzed alkyne-allyl coupling reaction



Based on these experimental observations and inferences, we propose a plausible mechanism in Scheme 4. Initially, upon addition of silyl triflate and alkyne into a catalyst mixture containing Ir[(*R*)-**L**$_1$]$_2$Cl (**I**), complex **II** is generated by halide abstraction and alkyne coordination. Complex **II** then undergoes electrophilic addition of "R$_3$Si$^+$", likely through an S$_N$2-type attack of the silyl triflate by the Ir center, to give dicationic Ir(III) species **III**.[25] Dicationic iridium complexes with similar ligand environments have previously been structurally characterized or invoked as catalytically active intermediates.[26] The enhanced electron deficiency of the dicationic Ir center could then facilitate the turnover-limiting deprotonation of the propargylic proton and afford allenyliridium complex **IV**,[20] which then undergoes C–Si bond-forming reductive elimination on the Ir center to give the product and regenerate the Ir(I) catalyst as coordinatively unsaturated species **V**.

Scheme 4. Working model of the catalytic cycle



In summary, we developed a direct enantioselective C(sp^3)–H silylation at the propargylic position. This method features high enantio- and regioselectivity, and a catalytic cycle is proposed involving attack of silyl triflate reagent by an Ir(I) center based on kinetic and other mechanistic data. Further studies of the detailed mechanism and explorations of additional applications of this strategy toward installation of propargylic stereocenters are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data for the substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

ym.wang@pitt.edu

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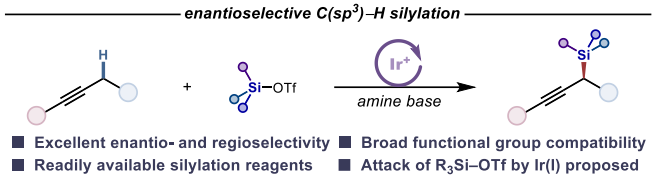
TOC graphic:



- Excellent enantio- and regioselectivity
- Readily available silylation reagents
- Broad functional group compatibility
- Attack of R_3Si–OTf by Ir(I) proposed