The Design, Synthesis and Validation of Recoverable and Readily Reusable Siloxane Transfer Agents for Pd-Catalyzed Cross-Coupling Reactions
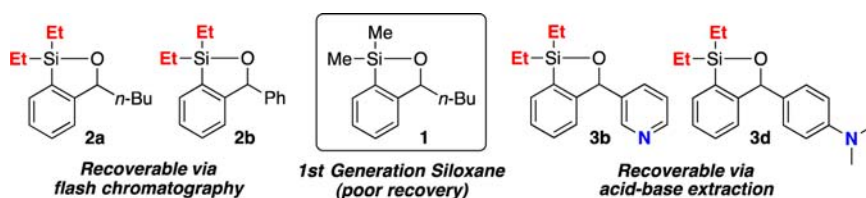
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ABSTRACT

The development of competent, recoverable and reusable 1-oxa-2-silacyclopentene (siloxane) transfer agents for Pd-catalyzed cross-coupling reactions (CCRs) of organolithium reagents with aryl and alkenyl iodides has been achieved. Drawbacks of the first-generation siloxane-transfer agent (1), relating to facile recovery for potential recycling, have been addressed.

Transition-metal catalyzed cross-coupling reactions (CCRs) comprise one of the most studied[1] and celebrated classes of transformations in chemistry, as noted by the 2010 Nobel Prize in chemistry to Heck, Negishi, and Suzuki.[2] Silicon being more abundant, stable, and environmentally benign holds the promise as a potential alternative to tin, boron, and zinc for "green" cross-coupling reactions. Indeed, Hiyama[3] and Denmark[4] have independently reported significant advancements in silicon-based CCRs.[5] However, a major drawback is the need to construct the individual silane cross-coupling partners, frequently accessed via the corresponding organolithium species. Additional issues include the use of stoichiometric amounts of base or fluoride and/or elevated temperatures, which may be incompatible with common functional groups and/or lead to substrate decomposition. On the other hand, palladium-catalyzed CCRs of organolithium reagents have been limited to the early examples pioneered by Murahashi[6] where slow addition of the aryllithium is required to avoid homocoupled products resulting from competitive lithium–halogen exchange. In this Letter, we report the rational design, synthesis, and validation of a

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Scheme 1. Cross-Coupling Reaction Inspired by Anion Relay Chemistry (ARC) Featuring Silicon Transfer Agent **1**
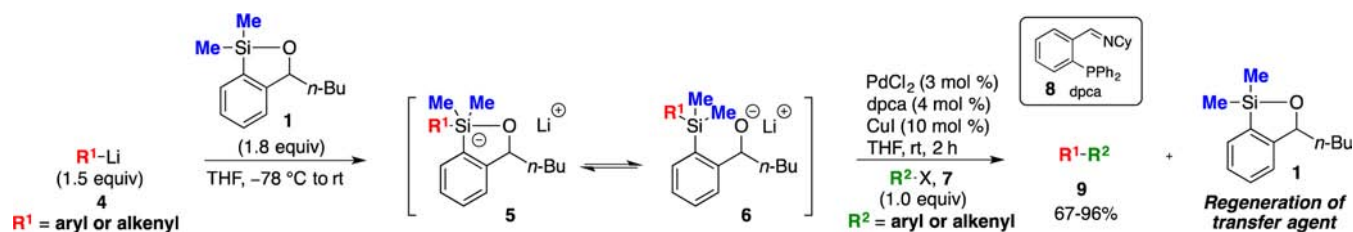
series of recoverable and readily reusable siloxane transfer agents for efficient room temperature, base- and fluoride-free CCRs of readily accessible organolithium reagents with aryl and alkenyl iodides.

In conjunction with the evolution of **A**nion **R**elay **C**hemistry (ARC), we recently explored the reactivity of 1-oxa-2-silacyclopentenes (siloxanes) such as **1** (Scheme 1) with organolithium reagents and their behavior in alkylation and cross-coupling reactions.[7] During these studies, we encountered a side product that appeared to result via intermolecular cross-coupling between the organolithium nucleophile and the aryl halide electrophile catalyzed by palladium (i.e., Murahashi cross-coupling).[6] This process was significantly enhanced through the use of both a nonpolar solvent (THF) and an ambient reaction temperature. While not only demonstrating the unification of the Takeda[8] and Hiyama[3] cross-coupling reaction manifolds with the ARC protocol, the siloxane study suggested an effective method to achieve cross-coupling of aryl- and alkenyllithium reagents (cf. **4**) with aryl and alkenyl iodides and electron-deficient bromides (cf. **7**), employing catalytic Pd and Cu to furnish biaryl, styrenyl, and dienyl cross-coupled products (cf. **9**), *importantly* with regeneration of the siloxane transfer agent **1** (Scheme 1), and *without* observation of homocoupled products (i.e., R[1]–R[1] and/or R[2]–R[2]).[9]

While the initial siloxane (**1**) proved effective in both Takeda and Hiyama CCRs as reported in 2012,[9] there were a number of concerns associated with **1** as a cross-coupling transfer agent. Most important was the chromatographic behavior on silica gel (i.e., streaking), which significantly complicates purification and recovery. In such cases, the regenerated siloxane (Scheme 1) was removed by employing a Fleming–Tamao oxidation[10] to furnish the corresponding phenol; oxidation of **1** of course eliminates the

possible reuse of the siloxane. The synthesis of **1** was also not optimal, requiring four steps, including protection and deprotection.[7,11] We therefore set two goals for the development of an effective class of siloxane transfer agents: (A) the optimal agent must be recoverable either by routine column chromatography or preferably via an acid/base extraction; and (B) the synthesis of the transfer agent must be short, scalable, and inexpensive. A third option, currently being explored, is attachment of the siloxane to a recoverable polymer or solid support.

Inspired by the work of Akiba[12] and Britton,[13] the synthesis of **1** was improved by eliminating the previously required protection and deprotection steps (Scheme 2A; see Supporting Information). We also discovered that the initially derived mixture of siloxane **1** and the benzylic alcohol **12** (4:1 by ^{1}H NMR) required treatment with catalytic KOt-Bu to achieve ring closure to generate **1** with concomitant evolution of H_2.[14] However, final treatment with KOt-Bu is not required for siloxanes **2a−d** and **3a−d** (Scheme 2B and Scheme 4). For example, addition of

Scheme 2. Improved Siloxane Synthesis

A. Two-Pot Synthesis of Siloxane 1 from Benzaldehyde 10.
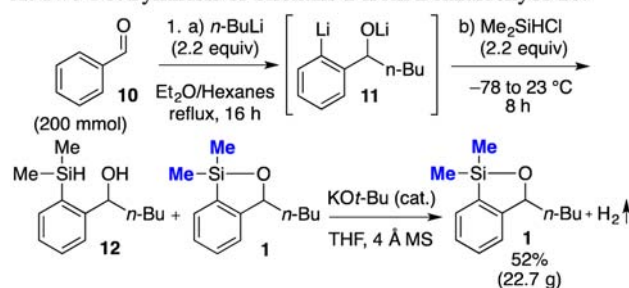
B. One-Pot Synthesis of Siloxane 2a from Benzaldehyde 10.
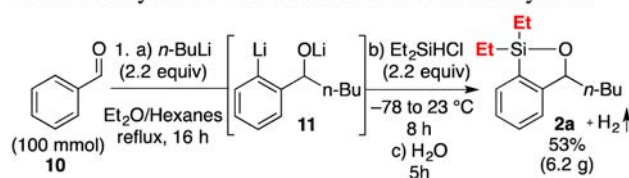
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2.2 equiv of n-BuLi, in Et$_2$O/hexane, to benzaldehyde (10) followed by heating at reflux leads to the desired directed metalation to generate dianion 11. Cooling the reaction mixture to −78 °C, adding Et$_2$SiHCl (2.2 equiv), and warming the mixture to room temperature followed by a water workup completes a "one-pot" construction of 2a in 53% yield. Pleasingly, this general reaction sequence proved scalable.

Having developed an effective synthetic strategy to 1 and 2a, substitution at the benzylic position was explored to gain insight into the cross-coupling reactivity of the siloxane congeners, with particular emphasis on defining improved chromatographic properties. To this end, we constructed siloxanes 1a−f (Figure 1) in similar fashion
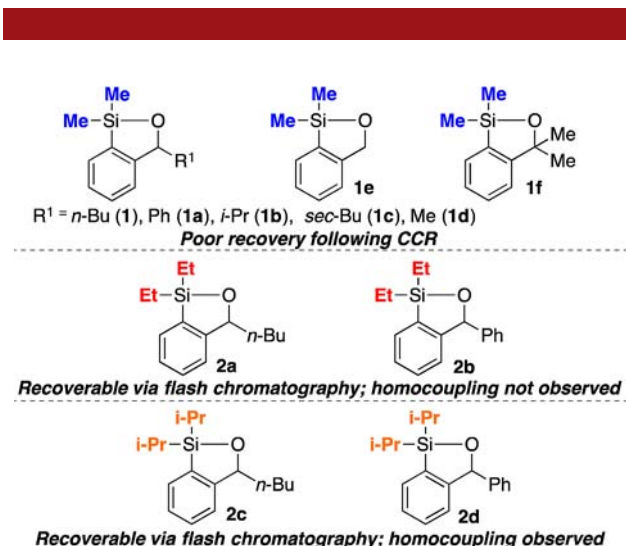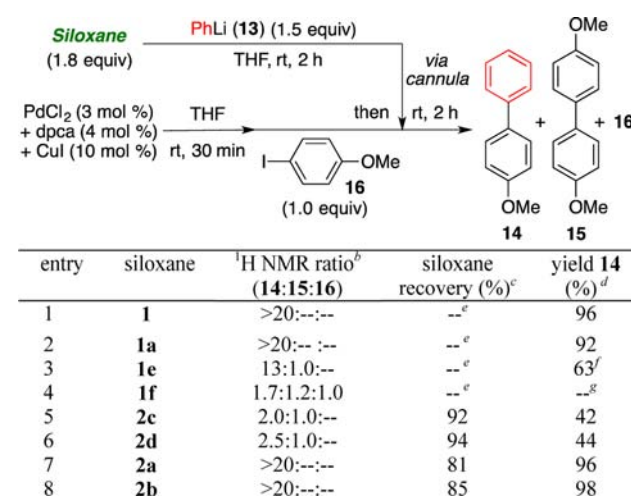

Figure 1. Siloxanes possessing substitution at the benzylic position and on silicon.

as 1 by use of the corresponding organolithium reagents (Scheme 2; see Supporting Information); 1a proved to be crystalline (mp 45.5−46.5 °C). With respect to cross-coupling efficiency, benzylic substitution with n-Bu and Ph (1 and 1a) proved optimal furnishing 14 in 96 and 92% yield, respectively (Scheme 3, entries 1−2). Surprisingly, the unsubstituted derivative 1e did not participate in the cross-coupling reaction at room temperature, but required heating to 50 °C (Scheme 3, entry 3); minor amounts of homocoupled product 15 were also observed. Siloxane congeners with geminal substitution at the benzylic position (cf. 1f) also did not perform well in cross-coupling reactions due to steric hindrance (Scheme 3, entry 4), forming instead a mixture of products (14−16). To explain these observations, we postulate that the single benzylic substituent increases the reactivity of siloxanes (cf. 1a−d) by facilitating silicon activation via the proximal alkoxide[5] (Scheme 1, 6), whereas the geminal substitution pattern creates a prohibitively large steric environment around silicon that leads to inefficient reactivity and the observed distribution of products (14−16).

Unfortunately, the chromatographic behavior of siloxanes 1a−f remained problematic, which we reasoned might

Scheme 3. Evaluation of Siloxanes Possessing Substitution at the Silicon and Benzylic Positions[a]

entry	siloxane	¹H NMR ratio[b] (14:15:16)	siloxane recovery (%)[c]	yield 14 (%)[d]
1	1	>20:--:--	--[e]	96
2	1a	>20:-- :--	--[e]	92
3	1e	13:1.0:--	--[e]	63[f]
4	1f	1.7:1.2:1.0	--[e]	--[g]
5	2c	2.0:1.0:--	92	42
6	2d	2.5:1.0:--	94	44
7	2a	>20:--:--	81	96
8	2b	>20:--:--	85	98

[a] All reactions were performed on a 0.45 mmol scale with 4-iodoanisole 16 as the limiting reagent. [b] ¹H NMR analysis of the crude reaction mixture. [c] Recovered via column chromatography. [d] Isolated yields. [e] Siloxanes were unrecoverable. [f] Reaction was carried out at 50 °C. [g] Compounds 14 and 16 coelute.

be attributed to the nucleophilic susceptibility of the silyl group to the Lewis basic nature of the SiO$_2$ oxygens. Based on a recent report by Hartwig,[15] and observations of Denmark[16] in which similar diethyl and diisopropyl siloxane derivatives respectively were purified by silica gel chromatography, we turned to increasing the steric environment around the silicon atom to improve the chromatographic properties, thereby permitting facile recovery following the cross-coupling reaction. Accordingly, derivatives 2a−d (Figure 1; see Supporting Information) were constructed in similar fashion to their dimethylsilyl congeners; yields again were good.
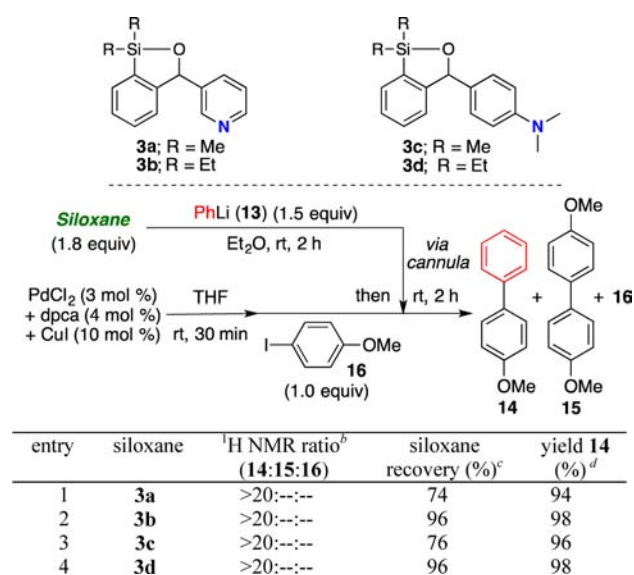
Pleasingly, the increased size of the substituents eliminated the chromatographic challenges. However, cross-coupling conversions employing the diisopropyl siloxanes (2c−d; Scheme 3) were modest when aryllithiums were employed as the initiating nucleophiles, with observation of significant homocoupling (i.e., 15, Scheme 3, entries 5−6). Best results were obtained with diethyl siloxanes 2a−b, furnishing cross-coupled products in excellent yield, without leading to the homocoupled products (Scheme 3, entries 7−8). *Importantly, excellent recovery of the siloxane transfer agent was routinely achieved by silica gel chromatography.*

We next turned to introduction of a Brønsted base in the siloxane structure, with the intention to recover the regenerated transfer agent formed in the CCR via an acid−base extraction protocol (Scheme 4). Success here would represent a significant advance in the utility of siloxane transfer agents. To this end, we constructed siloxanes

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Scheme 4. Performance of **3a–d** in Cross-Coupling Reaction with 4-Iodoanisole **16**[a]

entry	siloxane	¹H NMR ratio[b] (14:15:16)	siloxane recovery (%)[c]	yield 14 (%)[d]
1	3a	>20:--:--	74	94
2	3b	>20:--:--	96	98
3	3c	>20:--:--	76	96
4	3d	>20:--:--	96	98

[a] All reactions were performed on a 0.45 mmol scale with 4-iodoanisole **16** as the limiting reagent. [b] ¹H NMR analysis of the crude reaction mixture. [c] Recovered via acid–base extraction. [d] Isolated yields.

Table 1. Validation of the Optimal Siloxanes across a Series of Cross-Coupling Reactions[a]

R¹-Li	R²-I	siloxane (% recovery)	CCR yield,[b] (%)
13	16a	2a (87)[c]	92
		2b (89)[c]	91
		3b (98)[d]	96
		3d (96)[d]	94
13a	16b	2a (85)[c]	92
		2b (88)[c]	91
		3b (98)[d]	96
		3d (95)[d]	99
13b	16	2a (84)[c]	97
		2b (90)[c]	96
		3b (97)[d]	95
		3d (94)[d]	94
13c	16	2a (86)[c]	87
		2b (87)[c]	89
		3b (97)[d]	96
		3d (96)[d]	94

[a] All reactions were performed on a 0.45 mmol scale with R₂–I as the limiting reagent. [b] Isolated yields. [c] Recovered via column chromatography. [d] Recovered via acid–base extraction.

3a–d (Scheme 4; see Supporting Information), varying the silicon substituent (Me or Et) and location of a Brønsted nitrogen. Exposure of the siloxanes illustrated in Scheme 4 to a biphasic mixture of 1 N or 3 N HCl in H_2O and Et_2O (1:1), respectively for **3b** and **3d** followed by separation of the acidic aqueous phase and treatment with 1 N NaOH permitted *near-quantitative recovery* of the silicon transfer agents.

Having validated a possible acid–base recovery protocol, we explored siloxanes **3a–d** in the context of palladium-mediated CCRs (Scheme 4). Best results, with regard to both the integrity of the siloxane and recoverability, were obtained with siloxanes **3b** and **3d**, possessing diethyl substitution on silicon (Scheme 4, entries 2 and 4). To illustrate the utility of these siloxane transfer agents, a series of CCRs were carried out with electron-deficient and -rich coupling partners as illustrated in Table 1.

For direct comparison, we also include in Table 1 the corresponding yields derived from siloxane transfer agents **2a** and **2b**, both recoverable by column chromatography. Importantly, vis-à-vis reusability, single batches of siloxanes **2a–b**, **3b**, and **3d** could be recovered and reused without sacrificing the reactivity of the transfer agent or nucleophile carryover/scrambling of the CCR products when the cross-coupling reaction partners were changed in subsequent reactions.

In summary, the rational design, synthesis, and validation of a new class of effective siloxane transfer agents for Pd-catalyzed CCRs of aryl and alkenyl organolithium reagents with aryl and alkenyl iodides have been achieved. The transfer agents are readily available on a multigram scale via short, efficient and cost-effective routes and importantly are easy to recover and recycle either via flash chromatography or by an acid/base extraction protocol. Taken together, these now validated "green" transfer agents eliminate the need for multiple synthetic manipulations and isolations of reactive intermediates in order to generate suitable nucleophilic coupling partners for CCRs.

Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.