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Polymer-Supported Siloxane Transfer Agents for Pd-Catalyzed Cross-Coupling Reactions

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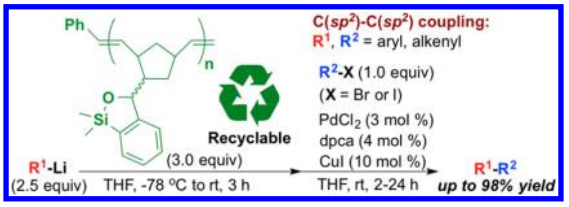
ABSTRACT



The design, synthesis, and validation of a ring-opening metathesis polymerization (ROMP) polymer supporting siloxane transfer agents have been achieved that permit efficient palladium-catalyzed cross-coupling reactions. The solubility properties of the polymer facilitate not only product purification but also polymer recycling without significant loss of cross-coupling activity.

Palladium-catalyzed cross-coupling reactions (CCRs) of organometallic reagents with electrophiles is one of the most important reactions utilized for the construction of both simple and complex structures involving C–C and C–heteroatom bond formation.[1] Recently we reported a highly atom-efficient process for intermolecular cross-coupling of aryl and alkenyl organolithiums with aryl and alkenyl iodides exploiting a siloxane transfer agent (Scheme 1).[2] In this tactic readily available organolithium reagents serve as the nucleophilic coupling partners, eliminating the need for stoichiometric toxic metals (e.g., zinc and tin as used in Negishi[3] and Stille[4] CCRs, respectively), as well as the manipulation and purification steps required by the Hiyama,[5] Denmark,[6] and Suzuki[7] CCRs to access the nucleophilic coupling partners. Importantly, the use of siloxane transfer agents holds promise for a solution to the intrinsic limitation of Murahashi[8] and the recent Feringa[9] cross-coupling protocols where slow addition of the organolithium is required to avoid homocoupled products resulting from competitive lithium–halogen exchange. Although siloxane **1** proved highly effective in CCRs, recovery of **1** via flash chromatography in some cases proved less than optimal (i.e., streaking). This shortcoming

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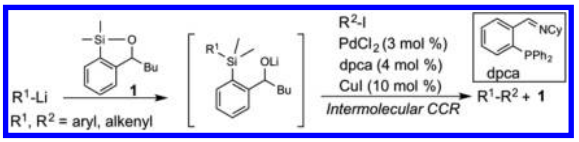
Scheme 1. CCRs Using Siloxane Transfer Agent

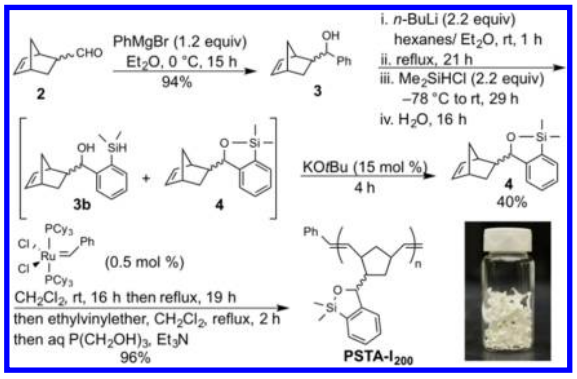


was recently addressed by careful redesign with incoporation of Brønsted bases.[10] Nonetheless, the development of a solid-supported siloxane transfer agent would further simplify both product purification and siloxane recycle, facilitating use of the siloxane tactic by the chemical community.[11]

Ring-opening metathesis polymerization (ROMP), a powerful method among living polymerization techniques, permits access to a wide range of polymers with unique architectures, reactivities, and physical properties (i.e., solubility).[12] One of the most common monomers employed in the ROMP protocol comprise norbornene and derivatives thereof, due to both their high ROMP activity and ease of incorporation of diverse functional groups.[13] Herein, we report the design, synthesis, and validation of a readily recyclable ROMP polymer-supported siloxane transfer agent (PSTA) for efficient Pd-catalyzed CCRs.

From the outset, we envisioned the ideal polymer to be soluble in THF, the optimal CCR solvent, and insoluble upon addition of a more polar solvent (ca. CH_3CN or H_2O) to permit facile recovery of both the CCR product and polymer. With these considerations in mind, treatment of commercially available 5-norbornene-2-carboxaldehyde (a mixture of *endo*- and *exo*-isomers) with PhMgBr furnished benzylic alcohol **3** (94%), which upon *ortho*-lithiation with *n*-BuLi, followed by anion capture with Me_2SiHCl and treatment with H_2O, led to a mixture of benzyl alcohol **3b** and siloxane **4** (^{1}H NMR), which in turn was treated with catalytic KO*t*Bu[14] to complete conversion to the desired siloxane monomer **4** (Scheme 2). Polymerization of **4** (ROMP) was then achieved in 96% yield with the first generation Grubbs catalyst.[15] Pleasingly, the conversion of **2** to PSTA-I_{200} can be achieved on multigram scale. The residual Ru was removed by treatment with an aqueous solution of $P(CH_2OH)_3$.[16] Precipitation via dropwise addition of the concentrated reaction mixture into CH_3CN afforded the desired polymer-supported siloxane transfer

Scheme 2. Synthesis of PSTA



agent PSTA-I_{200} as a white solid. Given that the polymer was obtained in near quantitative yield, without use of cross-linking units or copolymerization agents, the siloxane loading of the polymer was reasoned to be nearly identical to the molarity of the monomer, namely 3.9 mmol/g, with each polymer chain having a relative length of 200-mers, the latter based on the ratio of monomer **4** to the Grubbs catalyst (200:1). Importantly, PSTA-I_{200} is soluble in most organic solvents and insoluble in CH_3CN and H_2O.

To evaluate PSTA-I_{200} as a viable CCR transfer agent, we employed conditions similar to those previously reported for solution CCRs.[2] As illustrated in Table 1 (entry 1), the use of 2.0 equiv of PSTA-I_{200} at a concentration of 15 mg/mL led to cross-coupling product **6** with PhLi and 4-iodoanisole. A significant amount of starting aryl iodide however remained, in conjunction with formation of a small amount of homocoupled product **7**. Increasing the equivalents of PhLi and PSTA-I_{200} to 2.5 and 3.0, respectively, with the polymer concentration at 15 mg/mL greatly improved the efficiency of the process, providing **6** as the major product (entry 2). Lowering the polymer concentration to 10 mg/mL led to complete conversion of **5** within 2 h, furnishing **6** in 98% isolated yield (entry 3). Attempts to reduce the amount of either PhLi or the siloxane polymer required to consume the starting aryl halide, without leading to homocoupled products, proved unsuccessful (entries 4–6). Finally, inefficient cross-coupling in conjunction with significant homocoupled product resulted in the absence of PSTA-I_{200} (entry 7). The latter is characteristic of the early Murahashi CCR of aryl lithiums with aryl halides promoted by Pd catalysis.[8]

Having identified the optimal conditions for CCR with PSTA-I_{200}, we examined the effect of the polymer structure vis-à-vis the ability to serve as a transfer agent for CCRs (Table 2). By varying the amount of Grubbs catalyst during the ROMP process, we could readily adjust the number of repeating siloxane units on each polymer chain. To date siloxane transfer agent PSTA-I_{200} provides the best results (entry 1). Reducing the relative length of polymer chain to 20-mer led to significant homocoupling (entry 2). Moreover, enlarging the two substituents on the Si atom from methyl to ethyl, unlike that reported for the corresponding monomer under solution phase CCRs,[10]

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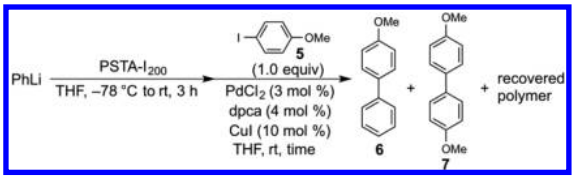
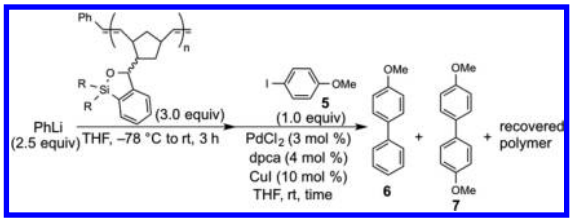
Table 1. Optimization of CCR Employing PSTA[a]



entry	equiv PhLi	equiv STA-I_{200}	concd STA-I_{200}	time	^{1}H NMR results[b] (**6**:**5**:**7**)
1[c]	1.5	2.0	15 mg/mL	25 h	57:40:3
2[d]	2.5	3.0	15 mg/mL	15 h	90:5:5
3[e]	2.5	3.0	10 mg/mL	2 h	100:nd:<1
4	1.5	3.0	10 mg/mL	15 h	84:11:5
5	2.0	3.0	10 mg/mL	2 h	72:18:<1
6	2.0	2.5	10 mg/mL	2 h	88:9:3
7[f]	2.5	–	–	2 h	14:77:9

[a] All reactions were performed on 0.3 mmol scale. [b] Determined by ^{1}H NMR analysis of the reaction mixture following an aqueous workup, extraction with Et_2O, and polymer removal via precipitation in CH_3CN. [c] Part of recovered polymer remained insoluble in THF. [d] Small amount of the recovered polymer remained insoluble in THF; 82% yield of **6**. [e] Polymer was recovered quantitatively and reuseable; 98% yield of **6**. [f] Reaction was run in the absence of siloxane polymer.

Table 2. Structure–Activity Study of Siloxane Polymers in CCR[a]



entry	siloxane polymer	time	^{1}H NMR results[b] (**6**:**5**:**7**)
1	**PSTA-I_{200}**: R = Me, n = 200, unsaturated backbone	2 h	100:nd:<1[c]
2	**PSTA-I_{20}**: R = Me, n = 20, unsaturated backbone	2 h	80:nd:20
3	**PSTA-II_{200}**: R = Et, n = 200, unsaturated backbone	50 h	1:99:nd
4	**PSTA-II_{20}**: R = Et, n = 20, unsaturated backbone	20 h	42:33:25
5[d]	**PSTA-I'_{200}**: R = Me, n = 200, saturated backbone	20 h	6:94:nd
6	**PSTA-I'_{20}**: R = Me, n = 20, saturated backbone	2 h	83:nd:17

[a] All reactions were performed on 0.3 mmol scale. [b] Determined by ^{1}H NMR analysis of the reaction mixture following an aqueous workup, extraction with Et_2O, and polymer removal via precipitation in CH_3CN. [c] 98% yield of **6**. [d] The insoluble polymer was stirred heterogeneously in reaction mixture. nd = not detected.

eliminates near completely the ability of the polymer to serve as a transfer agent, presumably due to increased steric bulk at Si (entries 3 and 4). We also explored the effect of the unsaturation in the polymer chain, given the possible vulnerability of the polymer backbone to chemical degradation. To this end, we prepared the corresponding saturated polymer via a modified tandem ROMP-hydrogenation protocol.[17] Not surprisingly, the saturated 200-mer was not soluble in any organic solvents and only yielded trace amounts of cross-coupling products after 20 h in THF (entry 5). The saturated 20-mer, on the other-hand, displayed similar solubility profiles to the unsaturated polymers. Attempts to use this polymer in CCRs, although resulting in complete consumption of starting aryl halide within 2 h, led to significant homocoupling (entry 6), a result very similar to that obtained when employing the unsaturated 20-mer (entry 2).

We next explored the scope of Pd-catalyzed CCRs employing PSTA-I_{200} (Table 3). Cross-coupling between aryl organolithiums and aryl or alkenyl iodides readily provided the CCR products in excellent yields (entries 1, 2, 3, and 6). Electron-rich and -deficient substrates were well tolerated in the CCRs; even azaheterocycle proceeded well (entry 3). Cross-coupling between PhLi and the electron-rich *p*-methoxyphenyl bromide however proved ineffective (entry 4), but electron-deficient *p*-cyanophenyl bromide proceeded smoothly in excellent yield with PhLi (entry 5). Equally successful, use of alkenyl organolithium reagents as the nucleophilic partner proceeded in good yield with retention of the alkene geometry (entries 7–9). In all cases, the reaction mixtures were quenched with saturated aqueous NH_4Cl, followed by extraction with Et_2O. The resultant organic solution was then concentrated, the siloxane polymer precipitated with CH_3CN, and then the polymer removed from the product by filtration. Importantly, the CCRs employing PSTA-I_{200} are as rapid and high-yielding as those employing the originally reported siloxane transfer agent (**1**) in solution,[2,10] of course, with the added advantage of product isolation.

Attention was next directed toward the structural stability of PSTA-I_{200} upon CCRs. We first examined the ability of PSTA-I_{200} to retain CCR activity through multiple cycles, using the same nucleophile for each transformation (Table 4). Here, PhLi and 4-idodoanisole were used for each experiment. After a 2 h reaction time, the polymer was removed from the reaction products as described above and employed in the subsequent run. The ratio of the products in each cycle was determined by ^{1}H NMR. Pleasingly, the polymer can be reused for at least 3 cycles, providing excellent to good yields of the desired cross-coupling product. In all cases, the polymer was recovered in near quantitative yield. We however noticed a small decrease in CCR efficiency after each cycle.

The small decrease of CCR efficiency led us to explore the molecular weight (MW) of the polymer both before and after several CCR cycles. We observed an increase in the number average molecular weight (M_n) and higher polydispersity index (PDI) of the recovered polymer determined by gel permeation chromatography (Table 4,[18]). Although unconfirmed, we reason that the increase in the M_n is likely due to polymer cross-linking, in which the

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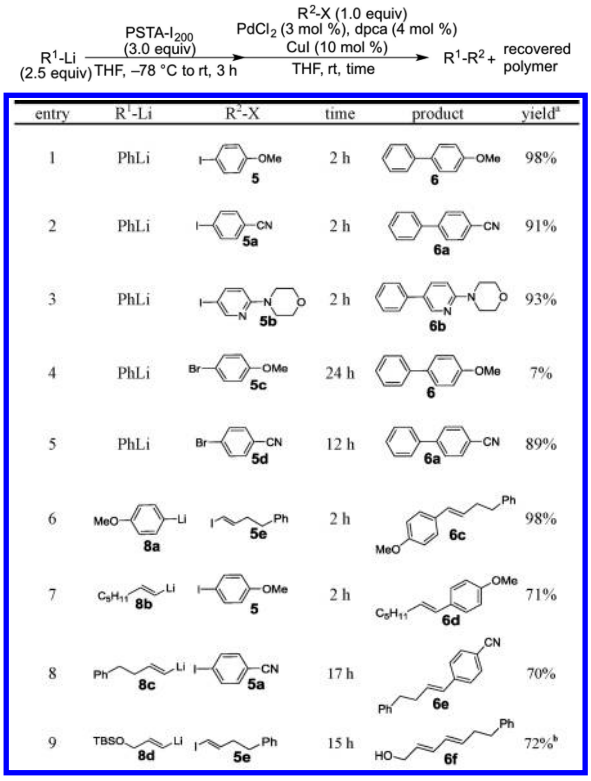
(18) See Supporting Information for plotted Gel Permeation Chromatograms of recovered polymers.

Table 3. Substrate-Scope Study of CCR Employing PSTA



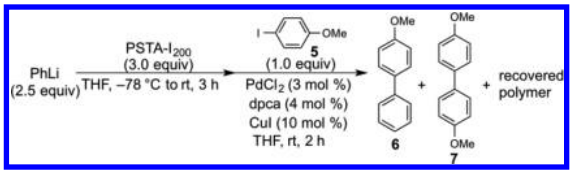
[a] Isolated yield. [b] After polymer removal, the product mixture was treated with TBAF to remove the silyl group prior to purification.

oxyanion formed after the addition of PhLi attacks a nearby silicon atom of another siloxane unit on a different polymer chain. The fact that the recovered polymer appeared to have an increased hardness, in conjunction with a small decrease in solubility in organic solvents after each cycle, supports this hypothesis. The ^{1}H NMR and IR of PSTA-I_{200} however did not reveal a significant difference. A similar increase in MW of the recovered polymer was also observed when the saturated polymer (PSTA-I′$_{20}$) was employed in iterative cycles (see Supporting Information), eliminating the unsaturation in the polymer backbone as being responsible for the increase in M_n.

Finally, we explored the possibility of cross-contamination of the nucleophile in the CCR product, upon repeated recycling of PSTA-I_{200} (Table 5). Even with an excess of vinyl lithium (2.5 equiv) employed in the first CCR cycle, only a trace amount (4%) of the first cross-coupling product was formed in the second cycle when PhLi was employed as the second nucleophile. The crossover vinyl contaminant was further reduced in the third cycle with PhLi, demonstrating the ability to reuse the PSTA in multiple cycles with different nucleophilic coupling partners without significant cross-contamination.

In summary, we have developed and validated a soluble ROMP polymer-supported siloxane transfer agent for use in Pd-catalyzed CCRs. Importantly, the ROMP-generated polymer can be recovered in a simple and efficient manner, with the recovered polymer retaining near complete CCR

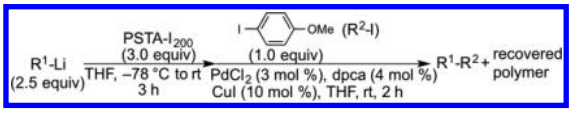
Table 4. Recyclability of Polymer Using the Same Nucleophile



cycle	isolated yield of **6**	polymer recovered[a]	^{1}H NMR results (**6**:**5**:**7**)
0		(M_n = 63500, PDI = 1.2)	
1st	98%	98% (M_n = 73000, PDI = 1.6)	100:nd:<1
2nd	91%	99% (M_n = 104400, PDI = 2.3)	97:nd:3
3rd	81%	99% (M_n = 94600, PDI = 2.6)	86:11:3

[a] Poly(methyl methacrylate) standards were used to determine M_n and PDI values. nd = not detected.

Table 5. Recyclability of Polymer Using Multiple Nucleophiles



cycle	R^1-Li	^{1}H-NMR ratio of products[a]			
1st	C_5H_{11}-Li (C_7H_{13}-Li)	C_7H_{13}-R^2 78	R^2-I 20	R^2-R^2 2	
2nd	PhLi	Ph-R^2 91	R^2-R^2 5	C_7H_{13}-R^2 4	
3rd	PhLi	Ph-R^2 75	R^2-I 22	C_7H_{13}-R^2 2	R^2-R^2 1

[a] Determined by ^{1}H NMR analysis of the reaction mixture following an aqueous workup, extraction with Et_2O, and polymer removal.

activity through multiple cycles. The ability to simplify product purification, coupled with a high level of atom economy, mild reaction conditions, and an operationally convenient protocol, further advances siloxane based CCR and renders this tactic an example of Green Chemistry. Furthermore, the validation of a solid-supported transfer agent holds promise for a variety of applications (e.g., coating of siloxane polymer in flow microreactors). Studies to determine the effect of polymer structure on reactivity, with the possibility of designing a polymer that can be recycled indefinitely, continue in our laboratory.

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

The authors declare no competing financial interest.