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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 ROMP polymer supporting siloxane transfer agents have been achieved that permit efficient palladium-catalyzed cross-coupling reactions. The solubility properties of the polymer not only facilitate product purification, but also 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 carbon-carbon and carbon-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 Negishi³ and Stille⁴ CCRs, respectively), as well as the manipulation and purification steps required by the Hiyama,⁵ Denmark⁶ and Suzuki⁷ CCRs to access the nucleophilic coupling partners. Importantly, the use of siloxane transfer agents holds promise for a solution to the intrinsic limitation of Murahashi⁸ and the recent Feringa⁹ 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 was recently addressed by careful redesign with incorporation of Brønsted bases.¹⁰ Nonetheless, the development of a solid-supported siloxane transfer agent would further simplify both product purification and siloxane recycle, thereby facilitating the use of 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 both to 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 palladium-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. CH₃CN or H₂O) 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 Me₂SiHCl and treatment with H₂O led to a mixture of benzyl alcohol **3b** and siloxane **4** (¹H-NMR), which in turn was treated with catalytic KO^tBu¹⁴ 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-I₂₀₀ can be achieved on multigram-scale. The residual Ru was removed by treatment with an aqueous solution of P(CH₂OH)₃.¹⁶ Precipitation via dropwise addition of the concentrated reaction mixture into CH₃CN afforded the desired polymer-supported siloxane transfer agent PSTA-I₂₀₀ as a white solid. Given that the polymer was obtained in near quantitative yield, without use of cross-linking units or co-polymerization 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-I₂₀₀ is soluble in most organic solvents and insoluble in CH₃CN and H₂O.

To evaluate PSTA-I₂₀₀ 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-I₂₀₀ 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 equiv of PhLi and PSTA-I₂₀₀ 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, furnished CCR product **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, 5 and 6). Finally, and as expected, inefficient cross-coupling in conjunction with significant homocoupled product resulted in the absence of PSTA-I₂₀₀ (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-I₂₀₀, 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-I₂₀₀ 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 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 turned to explore the scope of Pd-catalyzed CCRs employing PSTA-I₂₀₀ (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, 8, and 9). In all cases, the reaction mixtures were quenched with saturated aqueous NH₄Cl, followed by extraction with Et₂O. The resultant organic solution was then concentrated, the siloxane polymer precipitated with CH₃CN, and removed from the cross-coupling product by filtration. Importantly, the CCRs employing PSTA-I₂₀₀ are as rapid and high-yielding as those employing the originally reported siloxane transfer agent (**1**) in solution, of course, with the added advantage of product isolation.

Attention was next directed towards the structural stability of PSTA-I₂₀₀ upon CCRs. We first examined the ability of PSTA-I₂₀₀ to retain CCR activity through multiple cycles, using the same nucleophile for each transformation (Table 4). Here, PhLi and 4-iodoanisole 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 ¹H-NMR. Pleasingly, the polymer can be reused for at least 3 cycles, providing excellent to good yield 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 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 4¹⁸). Although unconfirmed, we reason that the increase in the *M_n* is likely due to polymer cross-linking, in which the 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 small decrease in solubility in organic solvents after each cycle supports this hypothesis. The ¹H-NMR and IR of PSTA-I₂₀₀ however did not reveal a significant difference. A similar increase in molecular weight of recovered polymer was also observed when the saturated polymer (PSTA-I'₂₀) was employed in iterative cycles (see supporting information), thus eliminating the unsaturation in the polymer backbone as responsible for increase in *M_n*.

Finally, we explored the possibility of cross-contamination of the nucleophile in the CCR product, upon repeated recycle of PSTA-I₂₀₀ (Table 5). Interestingly, 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 cross-over 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 activity through multiple cycles. The ability to simplify product purification, coupled with high level of atom-economy, mild reaction conditions and 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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18. See supporting information for plotted Gel Permeation Chromatograms of recovered polymers.

Scheme 1.
CCRs Using Siloxane Transfer Agent

Scheme 2.
Synthesis of PSTA

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 ¹H-NMR analysis of the reaction mixture following an aqueous workup, extraction with Et₂O and polymer removal via precipitation in CH₃CN.

^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 re-useable; 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 ¹H-NMR analysis of the reaction mixture following an aqueous workup, extraction with Et₂O and polymer removal via precipitation in CH₃CN.

^c 98% yield of **6**.

^d The insoluble polymer was stirred heterogeneously in reaction mixture. nd = not detected.

Table 3

Substrate-Scope Study of CCR Employing PSTA

entry	R ¹ -Li	R ² -X	time	product	yield ^a
1	PhLi		2 h		98%
2	PhLi		2 h		91%
3	PhLi		2 h		93%
4	PhLi		24 h		7%
5	PhLi		12 h		89%
6			2 h		98%
7			2 h		71%
8			17 h		70%
9			15 h		72% ^b

^a Isolated yield.

^b After polymer removal, the product mixture was treated with TBAF to remove the silyl group prior to purification.

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)	
1 st	98%	98% (M _n = 73000, PDI = 1.6)	100:nd:<1
2 nd	91%	99% (M _n = 104400, PDI = 2.3)	97:nd:3
3 rd	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		
1 st			R ² -I	R ² -R ²
	(C ₇ H ₁₃ -Li)	78	20	2
2 nd	PhLi	Ph-R ²	R ² -R ²	
		91	5	4
3 rd	PhLi	Ph-R ²	R ² -I	
		75	22	2
				1

^aDetermined by ¹H-NMR analysis of the reaction mixture following an aqueous workup, extraction with Et₂O and polymer removal.