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Unification of Anion Relay Chemistry with the Takeda and Hiyama Cross-Coupling Reactions: Identification of an Effective Silicon-Based Transfer Agent

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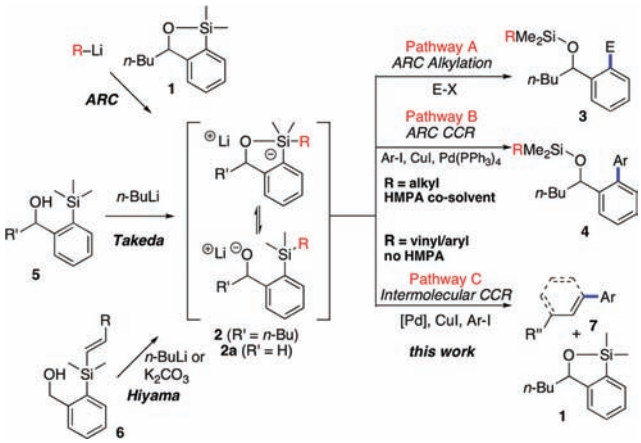
Supporting Information

ABSTRACT: The unification of Anion Relay Chemistry (ARC) with the Takeda and Hiyama palladium-mediated cross-coupling processes to provide aryl−aryl, alkenyl−aryl, and alkenyl−alkenyl coupled products by exploiting a common silicon-based transfer agent has been achieved. These results provide a practical solution for intermolecular cross-coupling of organolithium reagents without the problematic lithium−halogen exchange and/or undesired homocoupling that has kept organolithium cross-couplings from achieving the same level of utility as other palladium-mediated methods (e.g., Suzuki organoboron, Negishi organozinc, Stille organotin, Kumada organomagnesium, etc.).

Cross-coupling reactions (CCRs) of organometallic/main-group reagents with organic halides, which permit facile construction of a wide variety of carbon−carbon bonds, constitute one of the most important reaction types discovered and developed over the past 50 years. As such, CCRs have evolved into the mainstay of modern drug development, complex molecule synthesis, and material science programs. Early in the annals of CCRs (cf. 1974), Murahashi and co-workers reported the palladium-catalyzed cross-coupling of readily available organolithium compounds with aryl halides.[1] Although it is a highly atom-efficient process, limitations of the Murahashi CCR include the required use of preformed arylpalladium complexes and/or extremely slow addition of the aryllithiums in order to limit formation of homocoupled products resulting from rapid lithium−halogen exchange prior to the Pd-catalyzed C−C bond-formation event. Thus, CCRs that intrinsically avoid homocoupling (i.e., use of Suzuki organoboron,[2] Stille organotin,[3] Negishi organozinc,[4] and Hiyama[5]/Denmark[6] organosilicon reagents) have gained in popularity and now are the gold standards of CCR methods despite the requirement in many cases of an additional synthetic manipulation and possible isolation of a suitable nucleophilic coupling partner, the latter frequently accessed via the corresponding organolithium species.

In connection with the evolution of Anion Relay Chemistry (ARC),[7] we recently demonstrated that 1-oxa-2-silacyclopentene **1** is a competent alternative substrate for accessing the type-II ARC manifold,[8] now recognized to entail an alkoxide intermediate,[9] via addition of an alkyl- or aryllithium (Scheme 1). Subsequent addition of a polar solvent such as hexamethylphosphoramide (HMPA) triggers a "Brook-like" rearrangement[10−12] that in the presence of an alkyl or aryl halide furnishes,

Scheme 1. Silicon-Mediated Reaction Pathways



respectively, alkylation products (**3**; pathway A) or ARC/CCR adducts (**4**; pathway B), the latter process requiring 3 mol % $Pd(PPh_3)_4$.[11]

To document the concept of common reactive intermediates between known silicon-mediated processes (Scheme 1), we demonstrate in Table 1 that identical biaryl cross-coupling products **4** can be accessed via either the aforementioned ARC/CCR pathway or the Takeda pathway,[10] employing different starting materials. Following the ARC precedent, addition of an initiating nucleophile (MeLi) to **1** followed by exposure to CuI in a polar solvent (HMPA) leads to Si−C bond cleavage. Palladium-catalyzed cross-coupling of the resultant arylcopper species then provides **4a−c** (entries 1, 3, and 5). Alternatively, **4a−c** could be formed via deprotonation of **8** with MeLi and similar exposure to CuI in HMPA to promote C → O silyl migration, followed by Pd-catalyzed cross-coupling with the corresponding aryl iodide (entries 2, 4, and 6). Depending on the initiating nucleophile and workup conditions, the resulting silyl ether can be retained to provide a customizable protecting group in addition to the newly formed C−C bond (entry 7). In addition to aryl halides, alkenyl halide **9d** proved to be a compatible coupling partner in the process, providing styrene **4d** in 45% yield.

On the basis of our initial results with 1-oxa-2-silacyclopentenes,[8] we were struck with the similarities between both the ARC and Takeda alkylation/CCR pathways[10] and the reactive

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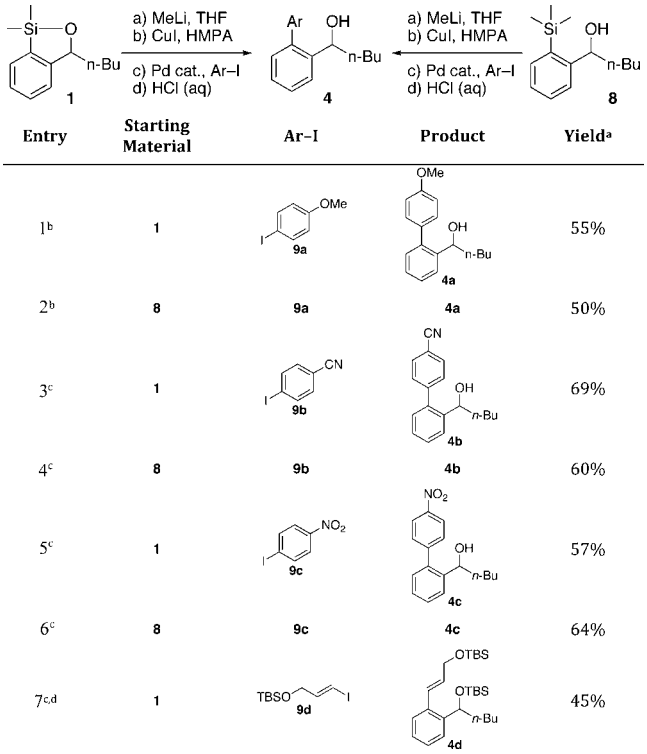
Table 1. Alternate Access to CCR Products 4



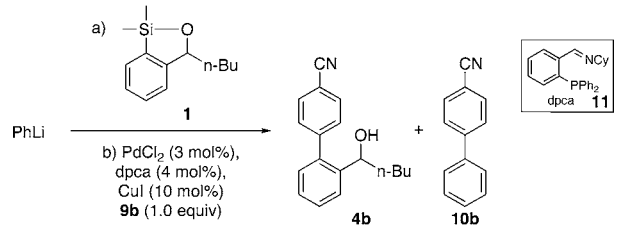
[a]Isolated yields. [b]$PdCl_2(dppf)$ (3 mol %) and PPh_3 (6 mol %) were used as the catalyst. [c]$Pd(PPh_3)_4$ (3 mol %) was used as the catalyst. [d]*t*-BuLi was used in place of PhLi as the initiating nucleophile, and HCl was omitted to preserve the resulting silyl ether.

intermediates of the Hiyama CCR[5,6] (Scheme 1, pathway C). We thus reasoned that we could intersect the latter cross-coupling reaction manifold via 1-oxa-2-silacyclopentene and related congeners. Success would provide a valuable and, ideally, practical method for the direct cross-coupling of organolithium reagents with aryl and alkenyl halides without the advent of homocoupling by exploiting a silicon-based "transfer agent." To the best of our knowledge, there exists only a single report in which a silicon-based transfer agent was utilized to achieve the Pd-catalyzed CCR of aryllithium reagents to form biaryl products, in which Tamao and co-workers employed a regioisomeric 1-oxa-2-silaindane.[13]

We began evaluating this hypothesis by subjecting the proposed alkoxide intermediate **2** (Scheme 1), derived from the reaction between PhLi and **1**, to conditions similar to those reported by Hiyama using 4-iodobenzonitrile as the electrophile.[5d] As illustrated in Table 2, entry 1, the ARC CCR process was favored, furnishing **4b** as the major product, when the polar solvent dimethyl sulfoxide (DMSO) was used, consistent with our previous ARC study using the polar solvent HMPA.[8] However, when tetrahydrofuran (THF) was employed as the solvent, only cross-coupled biaryl **10b** was observed (entry 2). The best results (96%) were observed when 2.1 equiv of PhLi was employed (entry 3). Taken together, these results support the unified reaction pathway hypothesis.

To optimize further the reaction conditions, we turned to 4-iodoanisole as the electrophilic coupling partner (Table 3), which would permit facile analysis of the crude product mixture by ^{1}H NMR spectroscopy because of the diagnostic methyl aryl ether signals of the various components. A series of reaction conditions was explored. Changing the catalyst system to

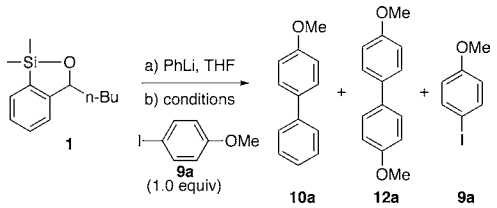
Table 2. Initial Attempts To Promote the Intermolecular CCR over the ARC CCR



Entry	Conditions	Yield (4b : 10b)[a]
1[b]	a) THF, −78 °C then rt, 30 min; b) DMSO, 50 °C, 17 h	36% : nd
2[b]	a) THF, −78 °C then rt, 30 min; b) K_2CO_3 (2.0 equiv), THF, 50 °C, 17 h	nd : 56%
3[c]	a) THF, −78 °C then rt, 30 min, THF; b) THF, rt, 10 min	nd : 96%

[a]Isolated yields. nd = not detected. [b]**1** (1.2 equiv) and PhLi (1.26 equiv) were used. [c]**1** (2.0 equiv) and PhLi (2.1 equiv) were used.

Table 3. Optimization of the Intermolecular CCR[a]



Entry	Solvent	Equiv. 1	Equiv. PhLi	Time (step a)	Time (step b)	^{1}H NMR Results (10a : 12a : 9a)[b]
1	THF	2.0	2.1	0.5 h	2 h	13.4 : 1 : nd
2	THF	1.2	1.1	0.5 h	0.5 h	7.2 : 1.0 : 4.0
3	THF	1.6	1.5	1 h	2 h	17.8 : 1.0 : 2.2
4[c]	THF	1.6	1.5	1 h	2 h	>20 : 1.0 : 2.8
5[c]	THF	2.0	1.5	1 h	2 h	>20 : nd : nd
6[c]	THF	2.0	1.2	1 h	2 h	3.4 : nd : 1.0
7[c]	THF	--	1.5	1 h	2 h	2.5 : 0.6 : 1.0[d]
8[c]	THF	1.8	1.5	1 h	2 h	>20 : nd : nd

[a]All reactions were performed on 0.45 mmol scale with 4-iodoanisole as the limiting reagent. [b]Determined by ^{1}H NMR analysis of the crude mixture of reaction products following aqueous workup and extraction (Et_2O). nd = not detected. [c]$PdCl_2$ (3 mol %), dpca (4 mol %), and CuI (10 mol %) were premixed for 30 min in THF prior to the addition of 4-iodoanisole, after which the PhLi/**1** reaction mixture was introduced via cannula. [d]No 1-oxa-2-silacyclopentene was used in the reaction; a solution of PhLi in THF was used as a substitute.

$PdCl_2(PPh_3)_2$ and dppp (not shown) led to inconsistent results with a significant amount of homocoupled **12a**. Attempts to reduce the amount of PhLi needed to consume fully the starting aryl iodide resulted in **12a** with incomplete consumption of the halide (entry 2). Better conversion of the aryl iodide occurred when steps a and b were allowed to proceed for longer times (entry 3). The use of toluene as the solvent (not shown) led to extremely poor conversion of **9a**.

A significant increase in the efficiency of the process was observed when the catalyst system [$PdCl_2$, dpca (**11**), and CuI] was premixed for 30 min in THF at room temperature prior to introduction of the aryl halide, which was followed by immediate addition of a mixture of PhLi and **1** in THF via cannula (entry 4). Employing this protocol in conjunction with the use of 2.0 equiv of transfer agent **1** led to complete

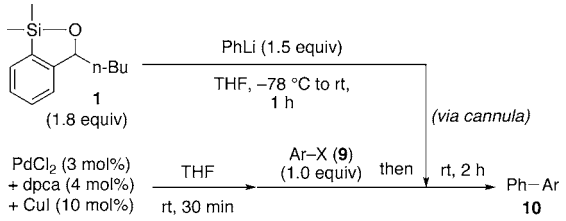
conversion of **9a** with no detectable homocoupled product (entry 5). However, the use of 1.2 equiv of PhLi did not result in complete consumption of 4-iodoanisole (entry 6). Importantly, and as expected, significant homocoupling and catalyst decomposition was observed in the absence of silicon transfer agent **1** (entry 7), consistent with Murahashi's early observations that constitute the major limitation of known organolithium cross-coupling processes.[1] Additional experimentation identified 1.8 equiv of silicon transfer agent **1** and 1.5 equiv of PhLi as the optimal amounts for complete consumption of the limiting aryl iodide while avoiding homocoupling (entry 8).

Having identified the optimal conditions, the scope of the Pd-catalyzed CCR of PhLi employing transfer agent **1** with various aryl halides was examined (Table 4). Electron-rich and -deficient substrates were well-tolerated in the reaction, as were a variety of common functional groups (esters, nitriles, and azaheterocycles), providing the biaryl compounds (**10a–g**) in yields of 67–96%. In all cases, siloxane **1** emerged from the reaction intact, as observed by ^{1}H NMR analysis of the crude reaction mixtures. For products possessing polarities similar to that of silicon transfer agent **1**, an oxidative Tamao–Fleming workup[12,14] of the initial reaction mixture was employed to convert **1** selectively to the corresponding diol, which could be easily separated by column chromatography.

To extend this protocol further, CCRs using alkenyl substrates were explored (Table 5). Vinyl halides **9j–l** were competent coupling partners with **13a**, generating styrenes **14a–c** with retention of the alkene geometry (entries 1, 3, and 5). Importantly, the roles of the coupling partners could be reversed by using the corresponding vinyllithium and aryl halide to access identical coupling products in comparable yields (entries 2, 4, and 6), demonstrating the flexibility offered by this cross-coupling protocol with respect to the choice of the nucleophilic and electrophilic components. Geminal and vicinal substitution patterns were tolerated in the transfer process from silicon, providing coupled products **14c** and **14d**. Also noteworthy were the successful vinyl–vinyl couplings between **13f** and **9m** and between **13g** and (+)-**9n** to provide dienes **14f** and (+)-**14g**.

In summary, we have demonstrated that siloxane **1** is a competent silicon-based "transfer agent" for intermolecular cross-coupling reactions of aryl and alkenyl organolithium reagents, in turn confirming our initial hypothesis regarding the common reaction manifolds of known silicon cross-coupling processes (e.g., Takeda and Hiyama). Importantly, this synthetic tactic offers a viable solution to the prohibitive issues surrounding the cross-coupling of organolithium compounds, notably lithium–halogen exchange and subsequent homocoupling. Studies to determine the effect of the siloxane structure on reactivity, the possibility of devising a catalytic silicon transfer agent, and the pursuit of sp^3–sp^2 and sp^3–sp^3 couplings continue in our Laboratory.

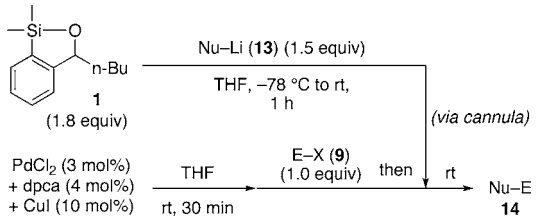
Table 4. Intermolecular CCR To Form Biaryl Products



Entry	Ar–X	Yield[a]	Entry	Ar–X	Yield[a]
1	**9a**	96% (**10a**)	4	**9f**	76% (**10d**)
2	**9b**	92% (**10b**)	5	**9g**	85% (**10e**)
3[b]	**9c**	92% (**10b**)	6[b]	**9h**	95% (**10f**)
4	**9e**	75% (**10c**)	7	**9i**	67% (**10g**)

[a]Isolated yields. [b]The reaction was allowed to proceed for 12 h following cannulation.

Table 5. Intermolecular CCR of Alkenyl Halides



Entry	Nu–Li	E–X	Product	Yield[a]
1	**13a**	**9j**	**14a**	81%
2	**13b**	**9a**	**14a**	82% (*gram-scale*)
3	**13a**	**9k**	**14b**	84%
4	**13c**	**9a**	**14b**	82%
5	**13a**	**9l**	**14c**	79%
6	**13d**	**9a**	**14c**	77%
7	**13e**	**9a**	**14d**	67%
8	**13f**	**9a**	**14e**	81%
9[b]	**13f**	**9m**	**14f**	72%
10	**13g**	(+)-**9n**	(+)-**14g**	78%

[a]Isolated yields. [b]The crude product mixture was treated with TBAF in THF to remove the silyl group prior to purification.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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