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

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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 coupling products, exploiting a common silicon-based transfer agent, has been achieved. These results provide a practical solution to the intermolecular cross-coupling of organolithium reagents without 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 organoborn, Negishi organozinc, Sille organotin, Kumada organomagnesium, etc.).

Cross-Coupling Reactions (CCRs) of organometallic/main group reagents with organic halides, that permit facile construction of a wide variety of carbon-carbon bonds, comprises 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 coworkers reported the palladium-catalyzed cross-coupling of readily available organolithium compounds with aryl halides.[1] Although 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 that derive via 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 to access the Type II ARC manifold,[8] now recognized to entail an alkoxide intermediate,[9] via addition of an alkyl- or aryl-lithium (Scheme 1). Subsequent addition of a polar solvent (cf. HMPA) triggers a “Brook-like” rearrangement[10,11,12] that in the presence of an alkyl or aryl halide

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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.

furnishes, respectively, alkylation products (**3**; Pathway A) or ARC/CCR adducts (**4**; Pathway B), the latter process requiring 3 mol% of $Pd(PPh_3)_4$.[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 either via the aforementioned ARC/CCR or the Takeda reaction pathways,[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 aryl copper species then provides **4a–c** (Entries 1, 3 and 5). Alternatively, **4a–c** could be formed via deprotonation of **1** 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 to provide styrene **4d** in 45% yield.

Based on our initial results with 1-oxa-2-silacyclopentenes,[8] we were struck with the similarities between both the ARC and Takeda alkylation/CCR reaction pathways[10] and the reactive 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, exploiting a silicon-based “transfer agent.” To the best of our knowledge, there exists only a single report of utilizing a silicon-based transfer agent 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-silaindan.[13]

We began evaluating this hypothesis by subjecting the proposed alkoxide intermediate **2**, derived from the reaction between PhLi and **1**, to conditions similar to those reported by Hiyama with 4-iodobenzonitrile as the electrophile.[5d] As illustrated in Table 3 (Entry 1), the ARC CCR process was favored to furnish **4b** as the major product when a polar solvent (DMSO) was used, consistent with our previous ARC study using HMPA.[8] However, when THF was employed as the solvent only cross-coupled biaryl **10b** was observed (Entry 2). Best results (96%) were observed when 2.1 equivalents of PhLi were 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 ^1H NMR due to the diagnostic methyl aryl ether signals of the various components. A series of reaction conditions were explored. Changing the catalyst system to $PdCl_2(PPh_3)_2$ and dppp led to inconsistent results with a significant amount of homocoupled **12a** (not shown). 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 led to extremely poor conversion of **9a** (not shown).

A significant increase in the efficiency of the process was observed when the catalyst system ($PdCl_2$, dpca (**11**) and CuI) was allowed to pre-mix for 30 min in THF at room temperature prior to introduction of the aryl halide, followed by immediate addition, via cannula, of a mixture of PhLi and **1** in THF (Entry 4). Employing this protocol, in conjunction with 2.0

equivalents of transfer agent **1**, led to complete conversion of **9a** with no detectable homocoupled product. However, the use of 1.2 equivalents of PhLi did not serve to consume fully 4-iodoanisole (Entry 9). Importantly, and as expected, in the absence of the transfer agent (**1**) significant homocoupling and catalyst decomposition was observed, consistent with Murahashi's early observations that comprise the major limitation of known organolithium cross-coupling processes.[1] Additional experimentation identified 1.8 equiv. of **1** and 1.5 equiv. of PhLi as the optimal conditions to consume completely 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 amino-heterocycles), providing the biaryl compounds (**10a**–**l**) in yields ranging from 67 to 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 **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, cross-couplings using alkenyl substrates were explored (Table 5). Vinyllithiums **9i**–**k** were competent coupling partners with **13a** to generate styrenes **14a–c** with retention of alkene geometry (Entries 1, 3 and 5). Importantly, the roles of the coupling partners could be reversed by using the corresponding aryllithium and alkenyl halide to access identical coupling products in comparable yields, demonstrating the flexibility that this cross-coupling protocol offers with respect to the choice of nucleophilic and electrophilic component (Entries 2, 4 and 6). Geminal and vicinal substitution patterns were tolerated in the transfer process from silicon, providing coupled products **14c** and **14d**. Also noteworthy, we achieved the successful vinyl-vinyl coupling between **13f** and **9l**, as well as **13g** and (+)-**9m** to provide dienes **14f** and (+)-**14g**.

In summary, we have demonstrated that siloxane **1** comprises a competent silicon-based "transfer agent" for intermolecular cross-coupling reactions of aryl and alkenyl organolithium reagents, and in turn have confirmed 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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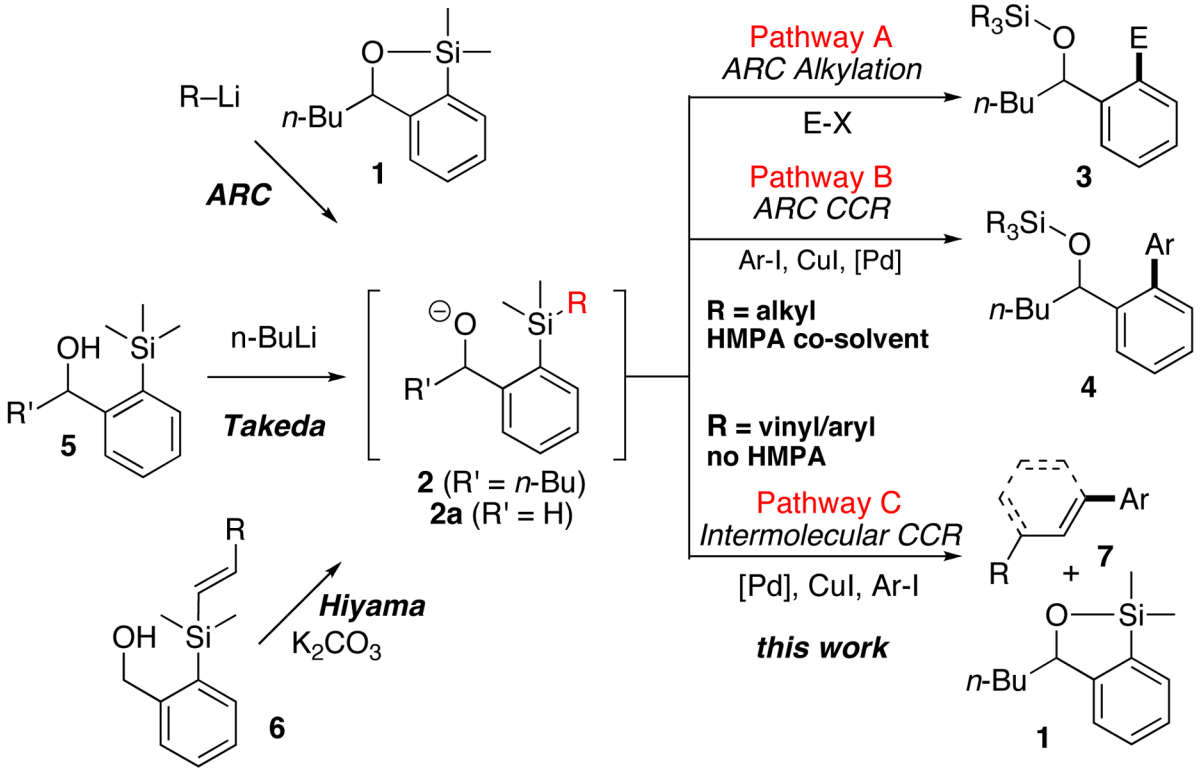
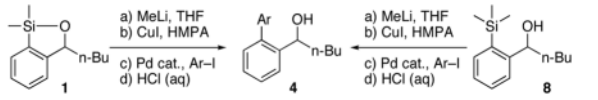
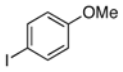
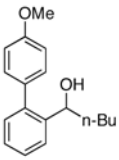
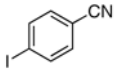
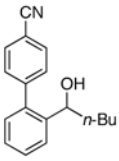
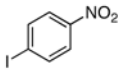
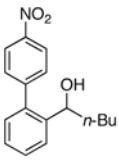
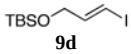
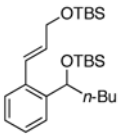


Scheme 1.
Silicon-mediated reaction pathways

Table 1

Alternate access to CCR products 4.



Entry	Starting Material	Ar-I	Product	Yield[a]
1[b]	1	 **9a**	 **4a**	55%
2[b]	8	9a	4a	50%
3[c]	1	 **9b**	 **4b**	69%
4[c]	8	9b	4b	60%
5[c]	1	 **9c**	 **4c**	57%
6[c]	8	9c	4c	64%
7[c,d]	1	 **9d**	 **4d**	45%

[a] Isolated yields;

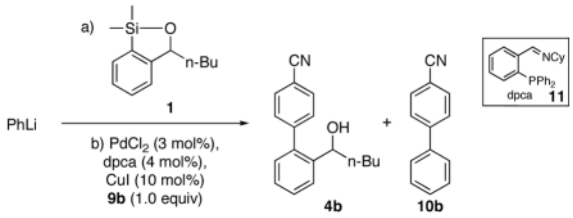
[b] PdCl2(dppf) (3 mol%) and PPh3 (6 mol%) was used as the catalyst;

[c] Pd(PPh3)4 (3 mol%) used as the catalyst;

[d] *t*-BuLi used in place of PhLi as the initiating nucleophile and HCl was omitted to preserve the resulting silyl ether.

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%

nd = not detected.

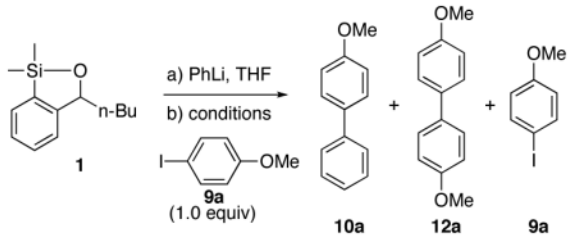
[a] Isolated yields;

[b] **1** (1.2 equiv) and PhLi (1.26 equiv) used;

[c] **1** (2.0 equiv) and PhLi (2.1 equiv) used.

Table 3

Intermolecular CCR optimization



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

All reactions performed on 0.45 mmol scale with 4-iodoanisole as the limiting reagent. nd = not detected by ^{1}H NMR.

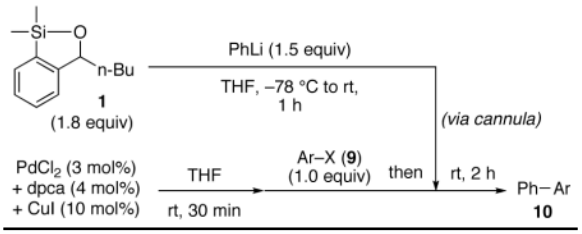
[a] Analysis of the crude mixture of reaction products following aqueous workup and extraction (Et_2O);

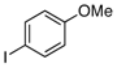
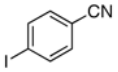
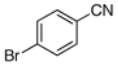
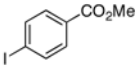
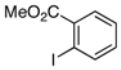
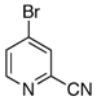
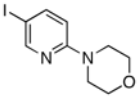
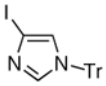
[b] $PdCl_2$ (3 mol%), dpca (4 mol%) and CuI (10 mol%) were premixed for 30 min in THF prior to the addition of 4-iodoanisole followed by introduction of the PhLi/**1** reaction mixture via cannula;

[c] No 1-oxa-2-silacyclopentene was used in the reaction; a solution of PhLi in THF was used as a substitute.

Table 4

Intermolecular CCR to form biaryl products



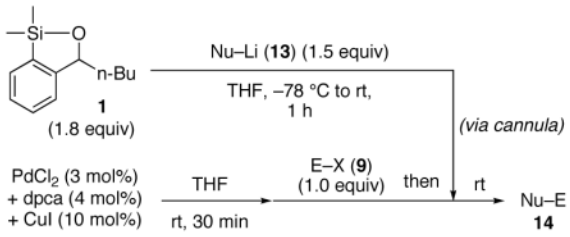
Entry	Ar-X	Yield[a]
1	 **9a**	96% (**10a**)
2	 **9b**	92% (**10b**)
3[b]	 **9c**	92% (**10b**)
4	 **9e**	75% (**10c**)
5	 **9f**	76% (**10d**)
6[b]	 **9g**	85% (**10e**)
7	 **9h**	95% (**10f**)
8	 **9i**	67% (**10g**)

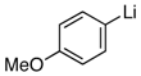
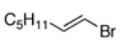
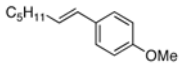
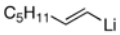
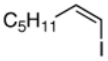
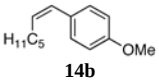
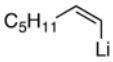
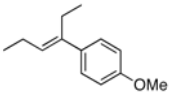
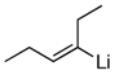
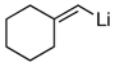
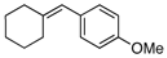
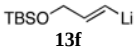
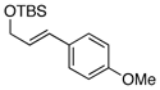
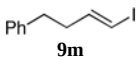
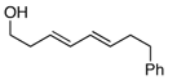
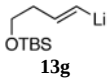
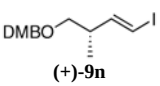
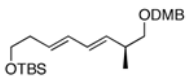
[a] Isolated yields;

[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.