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Palladium-Catalyzed Allyl Cross-Coupling Reactions with In Situ Generated Organoindium Reagents

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Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

Abstract: Inter- and intramolecular palladium-catalyzed allyl cross-coupling reactions, using allylindium generated in situ from allyl halides and indium, is demonstrated. Allylindium compounds may be effective nucleophilic coupling partners in palladium-catalyzed cross-coupling reactions. A variety of allyl halides, such as allyl iodide, allyl bromide, crotyl bromide, prenyl bromide, geranyl bromide, and 3-bromocyclohexene afforded the allylic cross-coupling products in good to excellent yields. Stereochemistry of the double bond is retained in the allylic cross-coupling reactions. Electrophilic cross-coupling partners, such as aryl and vinyl halides, dibromoolefin, alkynyl iodide, and aryl and vinyl triflates participate in these reactions. The presence of various substituents, such as *n*-butyl, ketal, acetyl, ethoxycarbonyl, nitrile, *N*-phenylamido, nitro, and chloride groups on the aromatic ring of electrophilic coupling partners showed little effect on the efficiency of the reactions. The present conditions work equally well for not only intermolecular but also intramolecular palladium-catalyzed cross-coupling reactions. These methods provide an efficient synthetic method for the introduction of an allyl group, which can be easily further functionalized to afford an sp^2- and *sp*-hybridized carbon. The present method complements existing synthetic methods as a result of advantageous features such as easy preparation and handling, thermal stability, high reactivity and selectivity, operational simplicity, and low toxicity of allylindium reagents.

Keywords: allylation · allylindium · cross-coupling · indium · palladium

Introduction

The development of efficient synthetic methods for C–C bond formation is an important continuing research subject in organic synthesis. Transition-metal-catalyzed cross-coupling reactions of organometallic reagents with a wide range of electrophilic coupling partners represent one of the most useful methods to form C–C bonds.[1] Especially, Palladium-catalyzed cross-coupling reactions have been the central focus of transition-metal chemistry during the past three decades.[1g] Recently, the synthetic scope of cross-coupling reactions has been continuously expanded by development and application of new catalysts, electrophilic coupling partners, and nucleophilic coupling partners. Among these, reactions using organoindium reagents have become a favorite owing to their reactivity and selectivity, thermal stability, ease of preparation and handling, operational simplicity, and low toxicity.[2] On the basis of these properties, palladium-catalyzed cross-coupling reactions using tri(organo)indiums have been reported.[3] Also, a wide range of indium-mediated cross-coupling reactions have been investigated.[4] Recently, we reported palladium-catalyzed cross-coupling reactions of allylindiums,[5] allenylindiums,[6] 1,3-butadien-2-ylindiums,[7] vinyl indium,[8] tetra(organo)indates,[9] indium tri(organothiolates),[10] and tri(naphthyl)indium[11] with a variety of electrophiles. Moreover, we have described palladium-catalyzed carbonylative cross-coupling reactions of tri(organo)indiums[12] and tetra(organo)indates with electrophiles.[13] It was found that palladium-catalyzed inter- and intramolecular cross-coupling reactions of aryl and vinyl halides were mediated by indium.[14]

Further functionalization of the allyl group allows its introduction into organic compounds.[15] Therefore, many allylation methods, such as Friedel–Crafts reaction,[16] Claisen

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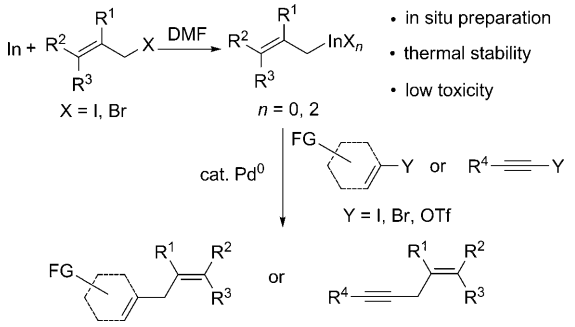
rearrangement,[17] and substitution reactions of allyl halides with organometallic reagents,[18] have been investigated. Moreover, palladium-catalyzed cross-coupling reactions have attracted much attention in allylation methods.[19] One of the most frequently used methods for allyl cross-coupling reactions is the Stille cross-coupling reaction, in which allylstannanes have been used as nucleophilic coupling partners. These reagents have attracted much attention owing to their availability, air- and moisture-stability, and their compatibility with a variety of functional groups.[20] However, the Stille cross-coupling reaction has some limitations, such as difficulties associated with preparation of regiochemically defined allylstannanes, their tendency to undergo allylic isomerization, tin removal from the product, tin toxicity, and excess use of organostannanes arising from dummy ligands. Although allylstannanes are generally accessible from organometallic reagents, such procedures are sometimes inadequate and the requisite allylmetals are difficult to obtain. Allylmetals must ideally be prepared in situ from the reaction of metals with allyl halides. The advantage of allylmagnesium halide and allyllithium as a nucleophilic coupling partner is their availability.[21] However, these reagents show low functional group tolerance. In this sense, development of new allylmetals as coupling partners is necessary to overcome these difficulties. Our interest, both in overcoming the limitations of allyl cross-coupling reactions using allylmetals and applying indium metal to organic synthesis,[22,2b] have led us to investigate the participation of organoindium reagents in metal-catalyzed reactions.[23] Moreover, tri(allyl)indium could not be prepared by the reaction of excess allylmagnesium bromide with indium(III) trihalide or indium(I) iodide.[3c,24] Lloyd-Jones and co-workers reported that reaction of iodobenzene or benzenediazonium tetrafluoroborate with allylindium in the presence of various palladium and nickel complexes did not proceed.[25] Herein, we report in full the novel intermolecular and intramolecular palladium-catalyzed cross-coupling reactions of a wide range of allylindium reagents generated in situ from allyl halides and indium with organic electrophiles, such as aryl and vinyl halides and aryl and vinyl triflates (Scheme 1). Also, stereoselectivity, chemoselectivity, and relative reactivity of allylindium reagents in cross-coupling reactions will be discussed.



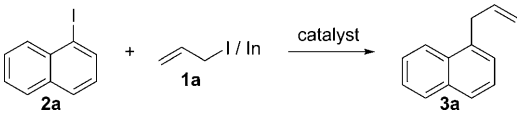
Scheme 1. Palladium-catalyzed allyl cross-coupling reactions. DMF = *N*,*N*-dimethylformamide.

Results and Discussion

Optimization of Cross-Coupling Reactions of In Situ Generated Allylindium Reagent with 1-Iodonaphthalene

Our initial study focused on palladium-catalyzed cross-coupling reactions of 1-iodonaphthalene with allylindium reagent generated in situ from a reaction of allyl iodide and indium.[26] The catalytic activity of several palladium complexes was examined and the results are summarized in Table 1. Among the catalysts screened, $[Pd_2(dba)_3]CHCl_3$ (2 mol%) and $[Pd(PPh_3)_4]$ (4 mol%) showed high catalytic activity (Table 1, entries 4 and 21). Other palladium complexes, such as $PdCl_2$, $Pd(OAc)_2$, $[Pd(CH_3CN)_2Cl_2]$, and $[Pd(PhCN)_2Cl_2]$, produced 1-allylnaphthalene in good yields (Table 1, entries 14–17). Among the ligands tested, triphenylphosphine gave the best results (Table 1, entry 4). The use of lithium halide as an additive is critically important for

Table 1. Reaction optimization of 1-iodonaphthalene with allylindium.[a]



Entry	Catalyst	Solvent	Additive	*t* [h]	Yield [%][b]
1	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	–	1	0
2	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	LiCl	16	46[c]
3	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	LiCl	16	50[d]
4	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	LiCl	1	93
5	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	LiCl	1	64[e]
6	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	LiCl	1	27[f]
7	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	LiBr	1	90
8	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	LiI	1	91
9	$[Pd_2(dba)_3]CHCl_3/Ph_3P$	DMF	nBu_4NCl	16	67 (5)[g]
10	$[Pd_2(dba)_3]CHCl_3$/ $[2,6\text{-}(MeO)_2C_6H_3]_3P$	DMF	LiCl	21	10
11	$[Pd_2(dba)_3]CHCl_3$/(*o*-Tolyl)$_3$P	DMF	LiCl	21	11
12	$[Pd_2(dba)_3]CHCl_3/As_3P$	DMF	LiCl	20	11
13	$[Pd_2(dba)_3]CHCl_3$/(2-Furyl)$_3$P	DMF	LiCl	3	75
14	$PdCl_2/Ph_3P$	DMF	LiCl	1	86
15	$Pd(OAc)_2/Ph_3P$	DMF	LiCl	1	86
16	$[Pd(CH_3CN)_2Cl_2]/Ph_3P$	DMF	LiCl	3	70
17	$[Pd(PhCN)_2Cl_2]/Ph_3P$	DMF	LiCl	1	87
18	$[Pd(PPh_3)_4]$	Benzene	LiCl	4	0
19	$[Pd(PPh_3)_4]$	Toluene	LiCl	4	0
20	$[Pd(PPh_3)_4]$	THF	LiCl	18	58
21	$[Pd(PPh_3)_4]$	DMF	LiCl	1	91
22	$[Pd(PPh_3)_4]$[h]	DMF/ H_2O[i]	LiCl	20	0
23	$[Pd(PPh_3)_4]$[h]	THF/ H_2O[j]	LiCl	20	0
24	$[Pd_2(dba)_3]CHCl_3$/P(2-Furyl)$_3$	DMF/ H_2O[i]	LiCl	20	0

[a] Reactions performed with $[Pd_2(dba)_3]CHCl_3$ (2 mol%)/ligand (16 mol%) or $[Pd(PPh_3)_4]$ (4 mol%) in the presence of additive (3.0 equivalents) in DMF at 100°C unless otherwise noted. Allylindium was obtained from the reaction of indium (1 equiv) with allyl iodide (1.5 equiv). [b] Yield of isolated product. [c] In/allyl iodide = 0.66:1. [d] In/allyl iodide = 1:1. [e] LiCl (2 equiv) was used. [f] LiCl (1 equivalent) was used. [g] 1-Iodonaphthalene. [h] PPh_3 (2 mol%) was added. [i] DMF/H_2O = 6:1. [j] THF/H_2O = 6:1.

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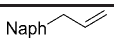
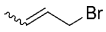
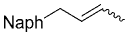
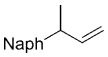
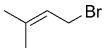
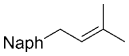
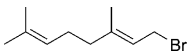
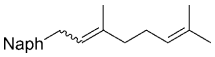
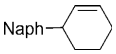
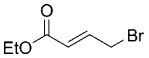
a successful reaction (Table 1, entries 1 and 4). The cross-coupling reactions did not proceed without lithium chloride (Table 1, entry 1). Use of 3 equivalents of lithium chloride gave the best results (Table 1, entries 4–6). Although lithium bromide and lithium iodide gave similar results as lithium chloride (Table 1, entries 7 and 8), lithium chloride was used owing to molecular weight and price. In the case of tetra-*n*-butylammonium chloride, 1-allylnaphthalene was obtained in 67% yield (Table 1, entry 9). *N*,*N*-Dimethylformamide was the best solvent among several reaction media (benzene, toluene, THF, DMF, DMF–H_2O, and THF–H_2O) that were examined (Table 1, entries 18–24). Allylindium reagent generated in situ from the reaction of indium (1 equiv) with allyl iodide (1.5 equiv) gave the best result as a nucleophilic coupling partner. Use of indium in less than 1 equivalent and allyl iodide in less than 1.5 equivalents resulted in a sluggish reaction and gave lower yields as well as longer reaction times (Table 1, entries 2 and 3). Of the catalytic systems examined, the best results were obtained with [$Pd_2(dba)_3CHCl_3$] (2 mol%)/Ph_3P (16 mol%) or [$Pd(PPh_3)_4$] (4 mol%) in the presence of LiCl (3 equiv) in *N*,*N*-dimethylformamide at 100°C for 1 hour under nitrogen atmosphere (Table 1, entries 4 and 21).

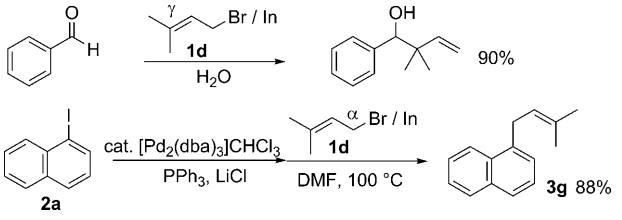
Cross-Coupling Reactions of In Situ Generated Allylindium Reagents with Halonaphthalenes

To demonstrate the efficiency and scope of the present method, we applied a variety of in situ generated allylindium reagents in cross-coupling reactions. The results are summarized in Table 2. Aryl iodide was more reactive than aryl bromide toward allylindium. Thus, a slightly higher yield of cross-coupling product from 1-iodonaphthalene was obtained (Table 2, entries 1 and 2). The reaction of allylindium obtained from allyl iodide with 1- or 2-bromonaphthalene gave the desired products in 88% and 80% yields, respectively (Table 2, entries 2 and 4). Under the optimum reaction conditions, treatment of 1-iodonaphthalene with allylindium derived from allyl bromide gave 1-allylnaphthalene in 87% yield (Table 2, entry 5). The presence of various alkyl substituents at the α- and γ-position exhibited little effect on both the reaction rates and product yields. The reaction of **2a** with crotyl bromide (**1c**, *cis*/*trans* = 1:5) in the presence of indium provided a 1:3.2 mixture of α-attack (*cis*/*trans* = 1.5:1, **3c**) and γ-attack products (**3d**), but the product resulting from γ-attack predominates (Table 2, entry 6). Benzaldehyde reacted with prenyl bromide and indium, producing 2,2-dimethyl-1-phenyl-3-buten-1-ol in 90% yield, which was the γ-attacked product, in water (Scheme 2).[26c] However, 1-iodonaphthalene was treated with prenylindium to afford exclusively 1-prenylnaphthalene (**3g**), which was the α-at-

Table 2. Palladium-catalyzed allyl cross-coupling reactions of allylindiums with halonaphthalenes.[a]

Entry	Allyl Halide		Naph-X	*t* [h]	Product		Yield [%][b]
1		**1a**	1-I (**2a**)	1		**3a**	93
2			1-Br (**2b**)	3		**3a**	88
3			1-Cl (**2c**)	3		**3a**	0
4			2-Br (**2d**)	3		**3b**	80
5		**1b**	1-I (**2a**)	11		**3a**	87
6		**1c**[c]	1-I (**2a**)	24		**3c 3e**	86 (1[f]:3.2)[g]
7			1-Br (**2b**)	27		**3d 3f**	61 (1[h]:4)[g]
8			2-Br (**2d**)	7			61 (1[h]:4.1)[i]
9		**1d**	1-I (**2a**)	25		**3g**[d]	88
10			1-Br (**2b**)	20		**3g**[d]	72
11			2-Br (**2d**)	6		**3h**[e]	84
12		**1e**	1-I (**2a**)	24		**3i**	71 (1:2)[j]
13		**1f**	1-I (**2a**)	3		**3j**[d]	66
14			1-Br (**2b**)	22		**3j**[d]	80
15			2-Br (**2d**)	4		**3k**[e]	50
16		**1g**	1-I (**2a**)	22			0

[a] Reactions performed with [$Pd_2(dba)_3$]$CHCl_3$ (2 mol%)/ligand (16 mol%) and LiCl (3 equiv) in DMF at 100°C. Allylindium was obtained from the reaction of indium (1 equiv) with allyl iodide (1.5 equiv). Naph = naphthalene. [b] Yield of isolated product. [c] *cis*/*trans* = 1:5. [d] 1-Allyl substituted naphthalenes. [e] 2-Allyl substituted naphthalenes. [f] *cis*/*trans* = 1.5:1. [g] **3c**/**3d** ratio. [h] *cis*/*trans* = 1:1. [i] **3e**/**3f** ratio. [j] *cis*/*trans* ratio.



Scheme 2. γ-Attack in addition to carbonyl compound and α-attack in palladium-catalyzed cross-coupling reaction of prenylindium. THF = tetrahydrofuran, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

tacked product, in 88% yield under the present conditions (Table 2, entry 9). Reaction of benzaldehyde with organoindium reagent obtained from prenyl bromide and indium in water proceeded through cyclic transition states, all with the carbonyl oxygen coordinated with indium, producing the γ-attack product selectively. Regioselectivity appears to be governed by the steric size of the γ-substituent, but not by the degree of substitution. Therefore, the palladium-catalyzed cross-coupling reaction of prenylindium with 1-iodonaphthalene might be governed by the steric size owing to the absence of a carbonyl oxygen, selectively producing the α-attack product. In the case of crotyl bromide, the results are complicated owing to the isomer mixture (*cis*/*trans* = 1:5) of crotyl bromide and an ambiguous steric effect.

The reaction of **2a** with in situ generated geranylindium from indium and geranyl bromide gave cross-coupling product **3i** in 71% yield (*cis*/*trans* = 1:2) (Table 2, entry 12). In the case of 3-bromocyclohexene, the desired products were obtained in moderate to good yields (Table 2, entries 13–15). However, use of allylindium reagents derived from ethyl 4-bromocrotonate and indium did not afford the desired product (Table 2, entry 16).

Intermolecular Cross-Coupling Reactions of In Situ Generated Allylindium Reagents with Electrophilic Coupling Partners

Next, we applied this catalytic system to a variety of aryl and vinyl halides and aryl and vinyl triflates. For a vast number of aryl iodides, the presence of various substituents, such as *n*-butyl, ketal, acetyl, ethoxycarbonyl, nitrile, *N*-phenylamido, nitro, and chloride groups on the aromatic ring, showed little effect on the efficiency of the reactions. The results are summarized in Table 3.

Palladium-catalyzed cross-coupling reactions of 4-*n*-butyliodobenzene with a variety of allyl halide (**1a**–**1d** and **1f**) and indium gave the desired products in good yields (Table 3, entries 1–5). It should be mentioned that 4-iodoacetophenone, having a labile keto group toward allylindium, provided allylic cross-coupling products in good yields (Table 3, entries 8–12). In the case of ethyl iodobenzoate, yield and selectivity of cross-coupling reactions are independent on electronic and steric effect (Table 3, entries 13–17). 4-Iodobenzonitrile was treated with prenylindium to give 4-prenylbenzonitrile in 86% yield (Table 3, entry 20).

Table 3. Palladium-catalyzed allyl cross-coupling reactions of allylindiums with aryl halides.[a]

Entry	Allyl Halide	FG	*t* [h]	Product	Yield [%][b]
1	**1a**	4-*n*Bu (**4a**)	1	**5a**	75
2	**1b**		22	**5a**	60
3	**1c**		21	**5b**[c] **5c**[d]	71 (4.8[e]:1)[f]
4	**1d**		15	**5d**	50
5	**1f**		3	**5e**	70
6	**1a**	4-CCH_3 (OCH_2CH_2O) (**4b**)	3	**5f**	93
7	**1f**		3	**5g**	89
8	**1a**	4-Ac (**4c**)	1	**5h**	88
9	**1b**		9	**5h**	70
10	**1c**		4	**5i**[c] **5j**[d]	60 (1[g]:1)[f]
11	**1d**		15	**5k**	72
12	**1f**		3	**5l**	66
13	**1a**	2-EtO_2C (**4d**)	1	**5m**	96
14	**1d**		1	**5n**	76
15	**1a**	3-EtO_2C (**4e**)	2	**5o**	84 (7)[h]
16	**1a**	4-EtO_2C (**4f**)	2	**5p**	84
17	**1f**		2	**5q**	75
18	**1a**	4-NC (**4g**)	7	**5r**	73
19	**1a**		7	**5r**	71[i] (4:1)[j]
20	**1d**		8	**5s**	86
21	**1d**		8	**5s**	81[i]
22	**1a**	4-BnNHCO (**4h**)	6	**5t**	76
23	**1a**		6	**5t**	71[i]
24	**1a**	3-O_2N (**4i**)	3	**5u**	94
25	**1c**		9	**5v**[c] **5w**[d]	89 (1[k]:1.2)[f]
26	**1d**		9	**5x**	88
27	**1e**		9	**5y**	88 (1:2)[l]
28	**1f**		9	**5z**	81
29	**1e**	4-Cl (**4j**)	6	**5a′**	65 (1:3)[l] (21)[m]

[a] Reactions performed in the presence of $[Pd_2(dba)_3]CHCl_3$ (2 mol%)/PPh_3 (16 mol%) and LiCl (3.0 equiv) in DMF at 100 °C. Allylindium was obtained from the reaction of indium (1 equivalent) with allyl iodide (1.5 equiv). Aryl iodides were used unless otherwise noted. [b] Yield of isolated product. [c] α-Attack product. [d] γ-Attack product. [e] *cis*/*trans* = 1:1.5. [f] Ratio of α-attack and γ-attack product. [g] *cis*/*trans* = 1:1. [h] Ethyl benzoate. [i] Aryl bromide was used. [j] Ratio of 4-allylbenzonitrile and 4-*trans*-(1-propenyl)-benzonitrile. $[Pd(PPh_3)_4]$ (4 mol%) was used. [k] *cis*/*trans* = 1:1.5. [l] *cis*/*trans* ratio. [m] 4,4′-Dichlorobiphenyl.

Subjecting 4-bromobenzonitrile and *N*-benzyl-4-bromobenzamide to prenylindium and allylindium afforded the desired products in 81% and 71% yields, respectively (Table 3, entries 21 and 23). In the case of 1-iodo-3-nitrobenzene, the desired products were obtained in good to excellent yields from a wide range of allylindium reagents (Table 3, entries 24–28). In general, yields of the cross-coupling products were increased for aryl iodides possessing an electron withdrawing group. These results can be understood on the basis of the fact that an electron withdrawing group on aryl halides generally enhances the rate of oxidative addition of the palladium center to this substrate.[27] Reaction of 4-iodoanisole with allylindium did not proceed.

Although 1-iodonaphthalene reacted with allylmagnesium bromide in the presence of $[Pd_2(dba)_3]CHCl_3$ (2 mol%)/dppf (8 mol%, THF, 25 °C, 7 h) to afford 1-allylnaphthalene

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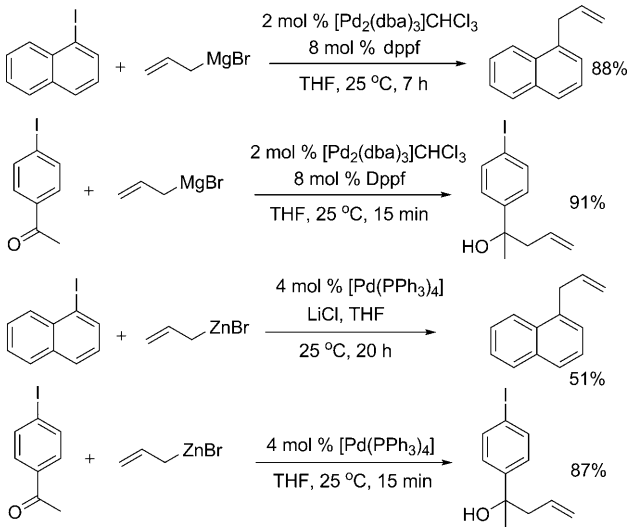
in 88% yield, reaction of 4-iodoacetophenone with allylmagnesium bromide gave rise to 1-(4-iodophenyl)-1-methyl-3-buten-1-ol (91%) obtained from the addition of allylmagnesium bromide to the ketone group (THF, 25°C, 15 min). This result indicates that the allylindium reagent shows better chemoselectivity than allylmagnesium bromide in the cross-coupling reactions and also has more covalent character than allylmagnesium bromide (Scheme 3). Treatment of

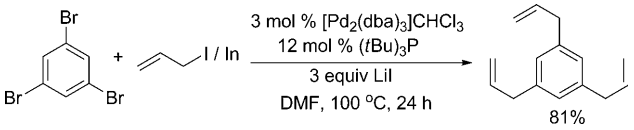


Scheme 3. Reactivity comparison between allylmagnesium bromide, allylzinc bromide, and allylindium reagent.

1-iodonaphthalene with allylzinc bromide[28] obtained from allyl bromide and zinc afforded 1-allylnaphthalene and 1,1′-bi(naphthyl) in 51% and 21% yields, respectively, in the presence of $[Pd(PPh_3)_4]$ (4 mol%) and LiCl (3 equiv) (THF, 25°C, 20 h). 1-(4-Iodophenyl)-1-methyl-3-buten-1-ol was obtained in 87% yield from reaction of 4-iodoacetophenone with allylzinc bromide in the presence of $[Pd(PPh_3)_4]$ (4 mol%) (THF, 25°C, 15 min).

Selectivity in the allyl cross-coupling reaction between aryl halide, aldehyde, and ketone groups was examined (Scheme 4). Although 4-iodobenzaldehyde reacted with allylindium to give 1-(4-iodophenyl)-3-buten-1-ol and 1-(4-allylphenyl)-3-buten-1-ol in 63% yield and 15% yields, respectively, 4-iodoacetophenone selectively produced 4-allylacetophenone in 88% yield. Moreover, treatment of 4-bromoacetophenone with allylindium afforded 1-(4-bromo-phenyl)-1-methyl-3-buten-1-ol in 50% yield as a major compound, indicating that selectivity of these functional groups for allylindium is benzaldehyde > iodobenzene > acetophenone > bromobenzene.

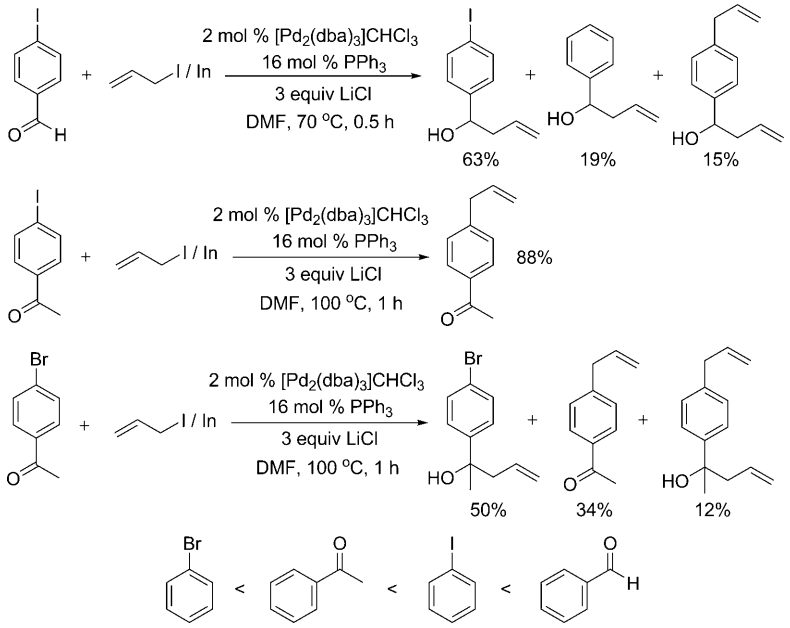
We then applied the present method to 1,3,5-tribromobenzene to obtain 1,3,5-tri(allyl)benzene, which can be used effectively in material and polymer sciences. Reaction of 1,3,5-tribromobenzene with 6 equivalents of allyl iodide and 4 equivalents of indium in the presence of $[Pd_2(dba)_3]CHCl_3$ (3 mol%) and $(tBu)_3P$ (3 mol%) produced 1,3,5-tri(allyl)benzene in 81% yield (DMF, 100°C, 24 h, Scheme 5).



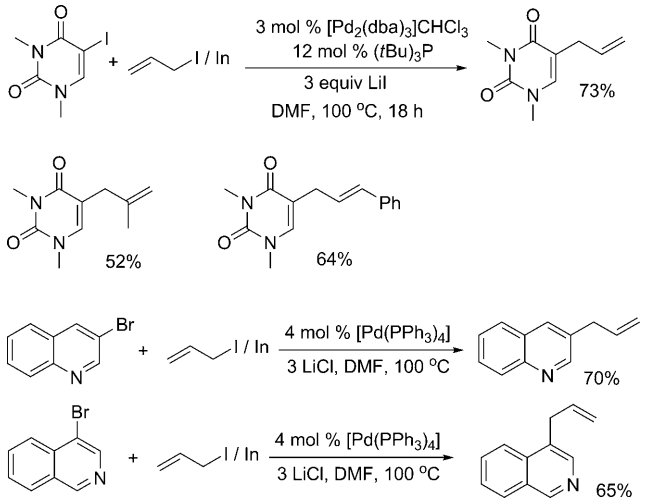
Scheme 5. Palladium-catalyzed allyl cross-coupling reaction of allylindium with 1,3,5-tribromobenzene.

Heteroatoms turned out to be compatible with the employed reaction conditions. Treatment of allylindium with 5-iodo-1,3-dimethyl-1*H*-pyrimidine-2,4-dione under the optimum conditions gave the desired compound in 73% yield (Scheme 6). The reaction worked equally well with 3-bromo-2-methylpropene and *trans*-cinnamy bromide. Moreover, reaction of 3-bromoquinoline and 4-bromoisoquinoline with allylindium afforded the corresponding allylic cross-coupling products in 70% and 65% yields, respectively.

Encouraged by these results, palladium-catalyzed cross-coupling reactions of allylindium with vinyl halides, dibromoolefin, and alkynyl iodide were examined. The results are summarized in Table 4. α-Bromostyrene was treated with allylindium to give 2-phenyl-1,4-pentadiene (**7a**) and *trans*-1-



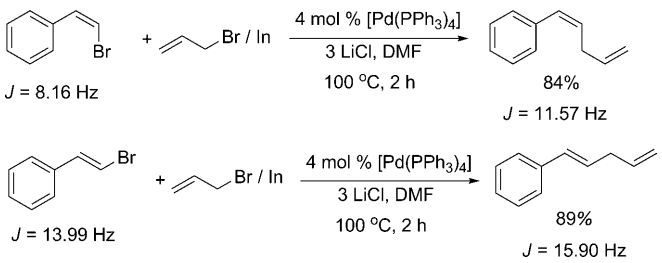
Scheme 4. Selectivity between aryl halide, aldehyde, and ketone groups.



Scheme 6. Palladium-catalyzed allyl cross-coupling reaction of allylindium with haloheterocycles.

phenyl-1,4-pentadiene (**7b**) in 65% and 32% yields, respectively (Table 4, entry 1). Although the mechanism of formation of **7b** is not clear, we believe that 1,4-diene **7b** might be produced by oxidative addition of palladium to α-bromostyrene, dehydropalladation owing to a steric effect to produce phenylacetylene, and then hydropalladation to phenylacetylene followed by an allyl cross-coupling reaction.[29] In the case of 2-bromo-5-phenyl-1-pentene (**6b**), 4-(3-phenylpropyl)-1,4-pentadiene (**7g**) was produced in 86% yield (Table 4, entry 5). This result supports the mechanism of formation of **7b** mentioned above. The reaction of α-bromostyrene with crotyl bromide (*cis*/*trans* = 1:5) in the presence of indium produced a 1.9:1 mixture of α-attack (*cis*/*trans* = 1:1, **7c**) and γ-attack products (**7d**) (Table 4, entry 2). Treatment of **6a** with geranylindium produced the desired product **7e** in 97% yield (Table 4, entry 3). In case of β,β-dibromostyrene (**6d**),[30] the twofold cross-coupling product **7i** was obtained in 92% yield with 2 equivalents of allylindium (Table 4, entry 7). Treatment of iodophenylacetylene[31] with prenylindium regioselectively produced 5-methyl-1-phenyl-4-hexen-1-yne (**7n**) in 82% yield (Table 4, entry 12).

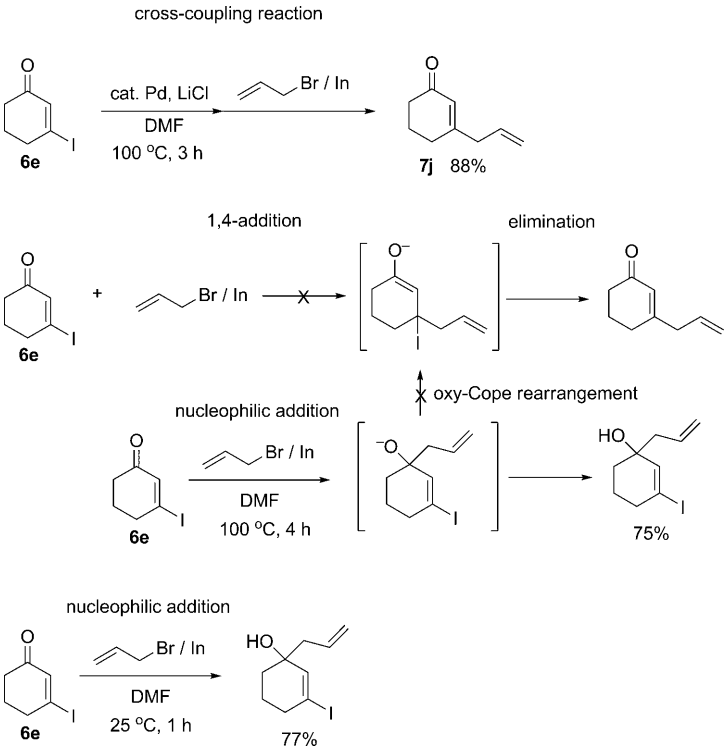
Stereochemistry in cross-coupling reactions using an allylindium reagent was examined (Scheme 7). The reaction of β-bromostyrene (*cis*/*trans* = 1:4) with allylindium gave cross-coupling product 1-phenyl-1,4-pentadiene (*cis*/*trans* = 1:4,



Scheme 7. Stereochemistry in reaction of *cis*- and *trans*-β-bromostyrene with allylindium.

7h) in 96% yield (Table 4, entry 6). Under the optimum reaction conditions, reaction of *cis*- and *trans*-β-bromostyrene with allylindium afforded selectively *cis*- and *trans*-1-phenyl-1,4-pentadiene in 84% and 89% yields, respectively, indicating that stereochemistry of the double bond is retained in the allylic cross-coupling reaction.

It should be noted that 3- or 2-iodo-2-cyclohexen-1-one having labile ketone group toward allylindium provided the desired products **7j**, **7k**, **7l**, and **7m** in good yields (Table 4, entries 8–11), respectively. 1,2-Addition product (1-allyl-3-iodo-2-cyclohexen-1-ol) from reaction of **6e** with allylindium was obtained in 77% yield in the absence of palladium catalyst. Although reaction of **6e** with allylindium reagent was carried out in *N*,*N*-dimethylformamide at 100 °C for 4 hours, the 1,2-addition product was only obtained in 75% yield. Therefore, formation of **7j** through 1,2-addition followed by oxy-Cope rearrangement was excluded. With these results in hand, the present reaction proceeded definitely through a palladium-catalyzed cross-coupling reaction (Scheme 8).



Scheme 8. Reaction mechanism of allylindium with 3-iodo-2-cyclohexene-1-one.

As an extension of this work, we applied this catalytic system in a variety of aryl and vinyl triflates. The results are summarized in Table 5. Reactivity of naphthyl triflates derived from 1- and 2-naphthtol is similar to that of 1-halonaphthalene. Under the optimized conditions, **8a** reacted with allyl iodide and indium to produce **3a** in 92% yield (Table 5, entry 1). Whereas addition reaction of prenylindium to benzaldehyde usually gave the product resulting from γ-attack (Scheme 2),[26] reaction of **8a** with prenylindium re-

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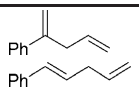
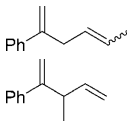
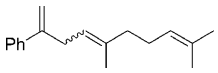
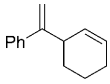
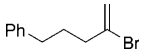
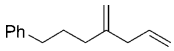
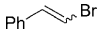
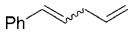
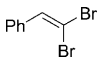
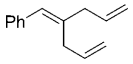
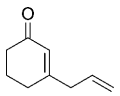
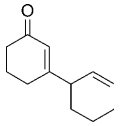
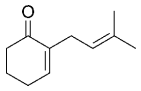
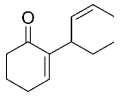
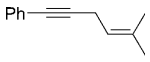
Table 4. Palladium-catalyzed allyl cross-coupling reactions of allylindiums with vinyl halides and alkynyl iodide.[a]

Entry	Allyl Halide	Vinyl Halide		*t* [h]	Product		Yield [%][b]
1	**1a**		**6a**	3.5		**7a** **7b**	97 (2:1)[c]
2	**1c**[d]		**6a**	5		**7c** **7d**	89 (1.9[e]:1)[f]
3	**1e**		**6a**	6.5		**7e**	97 (1:1)[g]
4	**1f**		**6a**	3		**7f**	91
5	**1a**		**6b**	5		**7g**	86[h]
6	**1a**		**6c**[i]	2.5		**7h**	96 (1:4)[g]
7	**1a**		**6d**	3		**7i**	92[j,k]
8	**1a**		**6e**	3		**7j**	88
9	**1b**		**6e**	3		**7k**	96
10	**1d**		**6f**	1		**7l**	84
11	**1f**		**6f**	1		**7m**	89
12	**1d**		**6g**	1		**7n**	82[j]

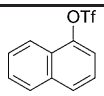
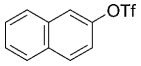
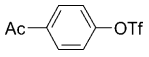
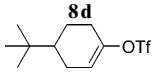
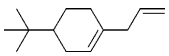
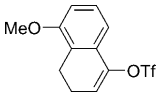
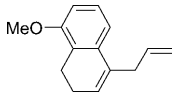
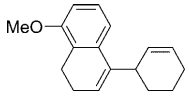
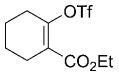
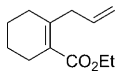
[a] Reactions performed in the presence of $[Pd(PPh_3)_4]$ (4 mol%) and LiCl (3 equiv) in DMF at 100°C. [b] Yield of isolated product. [c] Ratio of **7a** and **7b**. [d] *cis*/*trans* = 1:5. [e] Isomeric ratio of **7c**: *cis*/*trans* = 1:1. [f] **7c**(α)/**7d**(γ) ratio. [g] *cis*/*trans* ratio. [h] $[Pd_2(dba)_3]CHCl_3$ (4 mol%)/PPh_3 (32 mol%) was used as catalyst. [i] *cis*/*trans* = 1:4. [j] $[Pd_2(dba)_3]CHCl_3$ (2 mol%)/PPh_3 (16 mol%) was used as catalyst. [k] In (2 equiv) and allyl iodide (3 equiv) was used.

gioselectively produced **3g** in 87% yield resulting from α-attack (Table 5, entry 2). Reaction of **8b** with 3-bromocyclohexene in the presence of indium afforded 2-(cyclohex-2-enyl)naphthalene in 86% yield (Table 5, entry 6). In the case of triflate (**8c**) of 4-hydroxyacetophenone, the cross-coupling product (**5h**) and homoallyl alcohol were produced in 30% and 55% yields, respectively (Table 5, entry 7). Subjecting vinyl triflates (**8d**, **8e**, **8f**, and **8g**) to in situ generated allylindium produced the corresponding allylic compounds in good to excellent yields (Table 5, entries 8–12).

Intramolecular Cross-Coupling Reactions Using In Situ Generated Allylindium Reagents

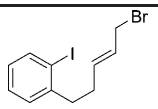
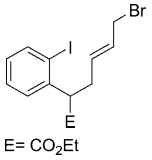
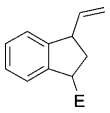
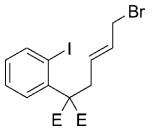
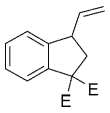
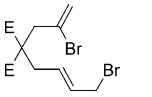
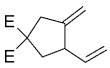
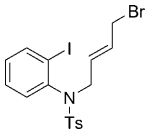
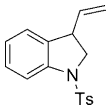
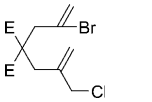
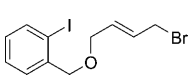
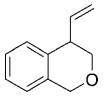
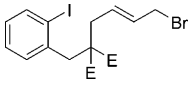
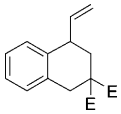
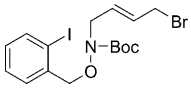
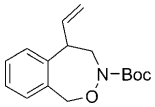
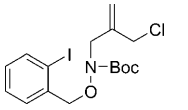
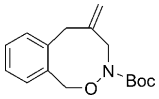
On the basis of above results, intramolecular cross-coupling reactions were investigated. The results are summarized in Table 6. Intramolecular cross-coupling reaction of **10c** was selected for initial examination as it was expected that cyclization of this substrate would be facilitated by a Thorpe–Ingold effect.[32] Subjecting **10c** to the optimum conditions gave the desired compound **11c** in 78% yield (Table 6, entry 3). Compound **10b**, having one ethoxycarbonyl group on the backbone chain, was cyclized to produce **11b** in 75% yield (Table 6, entry 2). Also, iodobenzene having allyl bromide **10a** was smoothly cyclized to give 1-vinylindane in 69% yield under the optimum reaction conditions (Table 6, entry 1), indicating that presence of a geminal Thorpe–Ingold buttressing is helpful but not a prerequisite for successful cyclization, as **10a** partakes in the reaction. Exposure of **10d**, containing a moiety of vinyl bromide and allyl bromide, to indium (1 equivalent) and lithium iodide (3 equiv) (DMF, 100°C, 1 h) in the presence of $[Pd(PPh_3)_4]$ (4 mol%) provided the desired product (**11d**) in 82% yield (Table 6, entry 4). Iodobenzene derivative (**10e**), having a nitrogen

Table 5. Palladium-catalyzed allyl cross-coupling reactions of allylindiums with aryl and vinyl triflates.[a]

Entry	Allyl Halide	Triflate	t [h]	Product	Yield [%][b]
1	**1a**	 **8a**	2	**3a**	92[c]
2	**1d**	**8a**	15	**3g**	87[c]
3	**1f**	**8a**	7	**3j**	85[c]
4	**1a**	 **8b**	20	**3b**	92
5	**1d**	**8b**	21	**3h**	83
6	**1f**	**8b**	3	**3k**	86
7	**1a**	 **8c**	3	**5h**	30 (55)[d]
8	**1a**	 **8d**	2	**7a**	62
9	**1a**	 **8e**	21	 **9a**	93[c]
10	**1a**	 **8f**	16	 **9b**	84
11	**1f**	**8f**	8	 **9c**	73
12	**1a**	 **8g**	2	 **9d**	82

[a] Reactions performed in the presence of $[Pd_2(dba)_3]CHCl_3$ (2 mol%)/PPh_3 (4 mol%) and LiCl (3 equiv) in DMF at 100°C. [b] Yield of isolated product. [c] $[Pd(PPh_3)_4]$ (4 mol%) was used. [d] 4-(1-Hydroxy-1-methylbut-3-enyl)phenyl trifluoromethanesulfonate.

Table 6. Intramolecular palladium-catalyzed allyl cross-coupling reactions.[a]

Entry	Reactant		t [h]	Product		Yield [%][b]
1		**10a**	1		**11a**	69
2		**10b**	1		**11b**	75
3		**10c**	1		**11c**	78
4		**10d**	1		**11d**	82
5		**10e**	1		**11e**	71
6		**10f**	1		**11f**	83
7		**10g**	1		**11g**	73
8		**10h**	1		**11h**	84
9		**10i**	1		**11i**	84
10		**10j**	1		**11j**	76

[a] Reactions performed in the presence of $[Pd(PPh_3)_4]$ (4 mol%) and LiI (3 equiv) in DMF at 100°C. [b] Yield of isolated product.

linkage, produced *N*-tosyl-3-vinylindoline (**11e**) in 71% yield (Table 6, entry 5). **10f**, possessing an allyl chloride moiety, was smoothly cyclized to produce **11f** in 83% yield (Table 6, entry 6). Exposure of **10g**, having an ether linkage on the backbone chain, to palladium catalyst and indium gave the tetrahydropyran derivative **11g** in 73% yield (Table 6, entry 7). Next, we applied the present conditions to **10i** and **10j** and the 7- and 8-membered ring compounds (**11i** and **11j**) were obtained in 84% and 76% yields, respectively (Table 6, entries 9 and 10). Although a wide range of allyl acetates was used in the intramolecular palladium-catalyzed allylic cross-coupling reaction, a variety of allyl halides was used in the present reaction.[5f]

Use of LiCl instead of LiI gave rise to **11f** in 10% yield together with the reduced compound in 10% yield. In addition, reaction did not take place without LiI (Scheme 9). The corresponding allyl iodide was quantitatively produced from the reaction of **10f** with LiI (3 equiv) in $[D_7]$*N*,*N*-dimethylformamide. As a result of allyl chlorides being poor substrates for forming allylindium species and indium metal reacts with aryl iodides in the presence of LiCl in DMF to produce aryl or vinyl indium species,[4i] intramolecular cyclization of vinyl bromide or aryl iodides and allyl chlorides (Table 6, entries 6 and 10) might proceed through oxidative addition of palladium(0) to allyl halides to form π-allyl palladium complexes and subsequent reaction of aryl/vinyl indium species with π-allyl palladium complexes. Another possibility is that the allylindium intermediate may be formed from an initial palladium π-allyl complex that subsequently undergoes reductive transmetallation with indium metal.[33]

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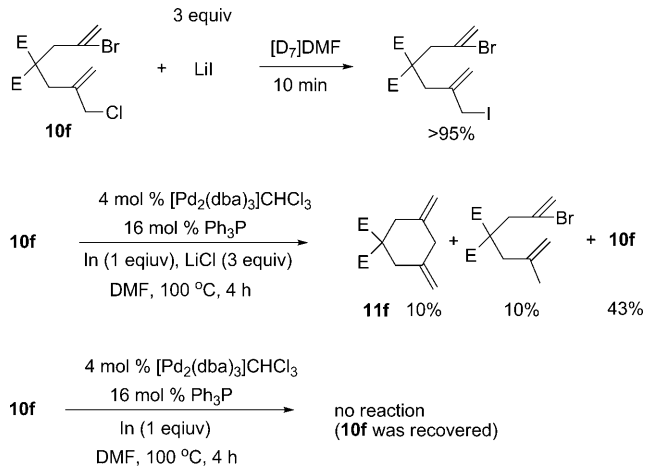
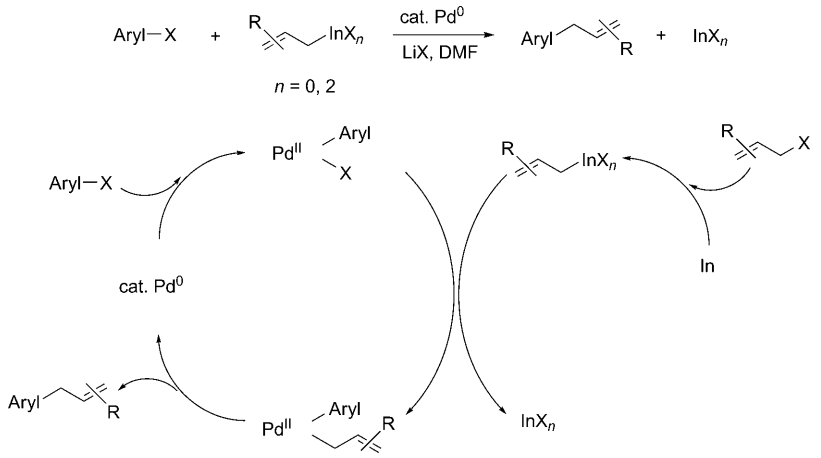


Scheme 9. Effect on LiX in cross-coupling reaction.

Mechanistic Insights

It is stated that allylindium(I) is formed by reaction of allyl iodide and indium in water, but that in *N*,*N*-dimethylformamide, at least two allylindium compounds were formed, one of which is the same as the compound formed in aqueous media.[24] Although the mechanism of reaction of in situ generated allylindium compounds with a variety of electrophilic coupling partners is not clear at the present time, a possible reaction pathway is described in Scheme 10. Oxidative addition of palladium catalyst to electrophile, subsequent transmetallation with allylindium reagent in situ generated from allyl halide (Br and I), and indium, and reductive elimination affords the allylic cross-coupling products. Although the role of lithium chloride in the coupling reaction has not been established, we believe that lithium chloride might accelerate the transmetallation step.



Scheme 10. Mechanism of palladium-catalyzed allyl cross-coupling reactions.

Conclusions

In conclusion, palladium-catalyzed allyl cross-coupling reactions using in situ generated allylindium from allyl halides and indium were successfully demonstrated. In situ generated allylindiums could be effective nucleophilic coupling partners in palladium-catalyzed cross-coupling reactions. A wide range of allyl halides, such as allyl iodide, allyl bromide, crotyl bromide, prenyl bromide, geranyl bromide, and 3-bromocyclohexene in cross-coupling reactions, afforded the corresponding allylic compounds in good to excellent yields. Stereochemistry of the double bond is retained in the allylic cross-coupling reaction. Various electrophilic cross-coupling partners, such as aryl and vinyl halides, dibromoolefin, alkynyl iodide, and aryl and vinyl triflates, participated well in these reactions. The presence of various substituents, such as a *n*-butyl, ketal, acetyl, ethoxycarbonyl, nitrile, *N*-phenylamido, nitro, and chloride group on the aromatic ring of electrophilic coupling partners, showed little effect on the efficiency of the reactions. The present conditions work equally well not only intermolecular but also intramolecular palladium-catalyzed cross-coupling reactions. This method provides an efficient synthetic method for the introduction of an allyl group, which can be easily further functionalized to a sp^2- and *sp*-hybridized carbon. The present method complements existing synthetic methods as a result of advantageous features such as easy preparation and handling, thermal stability, high reactivity and selectivity, operational simplicity, and low toxicity of allylindium reagents. These results should immediately provide more opportunities for the elucidation of efficient new catalytic C–C bond forming reactions.

Acknowledgements

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