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Reactivity of mixed organozinc and mixed organocopper reagents: 11. Nickel-catalyzed atom-economic aryl–allyl coupling of mixed (n-alkyl)(aryl)zincs[†,‡]

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Group selectivity in the allylation of mixed (n-butyl)(phenyl)zinc reagent can be controlled by changing reaction parameters. CuCN-catalyzed allylation in tetrahydrofuran (THF)–hexamethylphosphoric triamide is n-butyl selective and also γ-selective in the presence of MgCl₂, whereas CuI-catalyzed allylation in THF in the presence of n-Bu₃P takes place with a n-butyl transfer:phenyl transfer ratio of 23:77 and an α:γ transfer ratio of phenyl of 76:24. NiCl₂(Ph₃P)₂-catalyzed allylation in the presence of LiCl is phenyl selective with an α:γ ratio of 65:35. The reaction of methyl- or n-butyl(aryl)zinc reagents with an allylic electrophile in THF at room temperature in the presence of NiCl₂(Ph₃P)₂ catalyst and LiCl as an additive provides an atom-economic alternative to aryl–allyl coupling using diarylzincs. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: alkylarylzincs; mixed diorganozincs; allylation; Ni catalyst

Introduction

Transition metal-catalyzed reactions of organozinc reagents RZnX and R₂Zn are commonly used in organic synthesis due to their high tolerance to functional groups and efficiency toward many electrophiles.[1–3] Diorganozincs, R₂Zn, are more reactive than monoorganozincs, RZnX; however, R₂Zn reagents are not atom-economic and they transfer only one of the R groups efficiently to an electrophile. The problem has been solved by developing mixed diorganozincs, R^1R^2Zn, in which the R^2 group has a lower transfer rate than the R^1 group.[4–18]

Recently, mixed diorganozincs, R_RR_TZn, which have one transferable group R_T together with the residual group R_R, have been developed for synthetic purposes.[19,20] Whereas mixed diorganozincs, R_RR_TZn, have found widespread use in asymmetric 1,2-addition[19–22] and 1,4-addition reactions,[23–26] their C–C[27–29] and C–heteroatom coupling reactions[9] are rare. Mixed alkylzinc-derived zinc cuprate reagents were also used.[27]

The widely accepted hypothesis for the group selectivity of mixed cuprates R^1R^2CuLi is that the group in R^1R^2CuLi that has a stronger bond to Cu acts as the group of lower selectivity.[30–33] However, theoretical studies of Yamanaka and Nakamura on the substitution[34] and 1,4-addition reactions[35] of R(X)CuLi reagents (X = tert-Bu, alkynyl, CN, RS) showed that the group selectivity is controlled by several factors, such as thermodynamic stability and kinetic reactivity of the triorganocopper(III) intermediates formed in these reactions. Peculiar properties of R_R groups in R_RR_TCuLi reagents in the formation of π-complexes of cuprates in their 1,4-addition reactions have been also reported by Bertz et al.[36]

However, Erdik and co-workers in their serial work[37–46] on the reactivity and group selectivity of mixed organometallics reported that the group selectivity of mixed diorganozincs R^1R^2Zn,[37–39,41–43,45] mixed diorganocuprates R^1R^2CuM (M = MgBr,[40,44,45] ZnCl[46]) and Cu-catalyzed mixed triorganozincates $R^1(R^2)_2ZnMgBr$[41,45] depends

on the reaction parameters, such as solvent and catalyst. They also developed new atom-economic procedures for C–alkyl,[40–42,44,45] C–N[39] and C–acyl[37,38,45,46] coupling reactions using mixed diorganozincs R_RR_TZn.

In connection with these studies, we focused our interest on exploring the effect of reaction parameters on the group selectivity and regioselectivity in the reactions of mixed alkylarylzincs with allylic halides, and also on developing an atom-economic procedure for aryl–allyl coupling using mixed arylzincs.

Transition metal-catalyzed allylic substitution is one of the most valuable methods for the formation of C—C bonds.[47] Until now, great progress has been made in controlling the regiochemistry and enantioselectivity of copper-catalyzed alkylzinc–allyl coupling reactions. Alkylzinc reagents undergo exclusively γ-selective allylation in the presence of a Cu catalyst whereas α-selective allylation is observed in the presence of a Ni or Pd catalyst. However, less attention has been given to the regioselective and enantioselective allylic substitution of arylzinc reagents.

Recently, in our kinetic study of the reaction of diorganozincs with allyl bromide in THF at 25°C, it was observed[43] that the reaction with n-BuPhZn results in quantitative yield with a ratio of 13:87 for n-Bu transfer:Ph transfer, and allylation of n-Bu₂Zn and Ph₂Zn respectively gives the corresponding allylated products in a quantitative total yield.

Herein, successful results on the control of group selectivity and regioselectivity in the allylation of alkylarylzinc reagents allowing an atom-economic allylic coupling of alkylarylzincs are reported.

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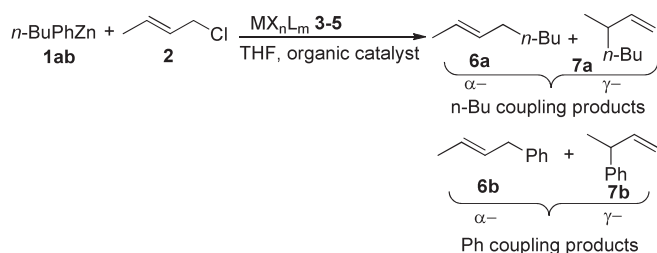
Scheme 1. Group selective allylation of n-BuPhZn reagent (**1ab**) with (E)-crotyl chloride **2** in THF.

Results and Discussion

As a model reaction, allylation of (n-butyl)(phenyl)zinc (**1ab**) with (E)-crotyl chloride (**2**) in THF was selected. Firstly, the effect of reaction parameters on the group selectivity and regioselectivity in the reaction was investigated (Scheme 1).

Magnesium-based organozinc reagents, i.e. n-butyl- and phenylmagnesium bromides to be transmetallated, were used.[37] Phenylzinc chloride prepared by transmetallation of phenyl-magnesium bromide with $ZnCl_2$ was allowed to react with n-butylmagnesium bromide and this one-pot successive procedure leads to formation of (n-Bu)(Ph)Zn. The same procedure can be also applied by reacting n-butylzinc bromide with phenylmagnesium bromide. Mixing equimolar amounts of $n\text{-}Bu_2Zn$ (**1a₂**) and Ph_2Zn (**1b₂**) also favors the formation of **1ab**. However, it was already

Table 1. Group selectivity and regioselectivity in the allylation of n-butylphenylzinc reagent n-BuPhZn (**1**) with (E)-crotyl chloride (**2**) in THF in the presence of Cu, Pd and Ni catalysts[a]

Entry	Catalyst (mol%)	Coupling yield (%)[b]	Group selectivity[c] n-Bu coupling:Ph coupling	Regioselectivity	
				6a:7a[d]	**6b:7b**[e]
1	CuI (5)	98	42:58	5:95	53:47
2	CuI (10)	81	42:58	6:94	43:57
3	CuI (20)	93	44:56	5:95	46:54
4	CuI (100)[f]	99	48:52	4:96	29:71
5	CuCN (5)	96	61:39	3:97	42:58
6	CuCN (100)[f]	92	57:43	4:96	35:65
7	CuX (5)[g]	85–88	40:60 to 44:56	5:95	48:52
8	CuOAc (5)	96	40:60	0:100	55:45
9	CuX₂ (5)[h]	92–97	39:61 to 45:55	3:97	55:45
10	CuBr.Me₂S (5)	~100	42:58	0:100	56:44
11	CuCN.2LiCl (5)	~100	62:38	3:97	42:58
12	CuOTf.C₆H₆ (5)	99	48:52	4:96	51:49
13	CuI (5), n-Bu₃P (5)	~100	23:77	5:95	76:24
14	CuI (5), Ph₃P (5)	~100	32:68	6:94	66:34
15	CuCN (5), n-Bu₃P (5)	90	52:48	2:98	56:44
16	CuCN (5), Ph₃P (5)	98	39:61	8:92	70:30
17	Pd(OAc)₂ (5)	24	0:100	—	67:33
18	NiCl₂ (5)	45	0:100	—	58:42
19	NiCl₂ (5), Ph₃P (5)	82	0:100	—	56:44
20	NiCl₂(Ph₃P)₂ (2.5)	76	0:100	—	59:41

[a]All the data are the average of at least two experiments. The reactions were carried out on a 2 mmol scale according to the conditions indicated by the above equation, unless otherwise specified. Molar ratio of **1ab:2** was optimized to be 1.1:1.
[b]The sum of GC yields of n-Bu coupling products (**6a** and **7a**) and Ph coupling products (**6b** and **7b**).
[c]The ratio of GC yields of (**6a** + **7a**) and (**6b** + **7b**).
[d]The ratio of GC yields of **6a** and **7a**.
[e]The ratio of GC yields of **6b** and **7b**.
[f]Stoichiometric cuprate reagent derived from n-BuPhZn and CuI (or CuCN) was prepared in situ.
[g]X = Cl, Br and SCN.
[h]X = Cl, OAc, OTf and acac.

found that one-pot successive Mg to Zn transmetallation reactions are more practical for the preparation of magnesium-based diorganozincs.[37] In addition, the group originally attached to Zn, which is n-Bu or Ph, does not change the relative transfer ability of these groups. The reaction was carried out by adding allylic substrate **2** to the organozinc reagent **1ab** in THF in the presence of a transition metal catalyst and/or organic catalyst. α-Selective and γ-selective transfer abilities of n-Bu and Ph groups were determined by finding the GC yields of coupled products **6a**, **7a**, **6b** and **7b**. The reaction temperature and time were optimized to be room temperature and 1 h, respectively. As transition metal catalysts, the mostly used Cu, Ni and Pd catalysts for organozinc reagents were studied. Donor solvents were used as co-solvents and some Lewis base and Lewis acid reagents were also tested as additives.[37,45,48]

Uncatalyzed allylation of **1ab** with **2** in THF at 25°C resulted in a yield lower than 20%. The effects of Cu, Ni and Pd catalysts on the group selectivities and regioselectivities of the allylation are summarized in Table 1. With the optimized 5 mol% of CuI catalyst (entry 1), quantitative yield of coupling was obtained. The group selectivity, i.e. n-Bu transfer:Ph transfer ratio, is around 40:60 and regioselectivities, i.e. α:γ ratios for n-Bu transfer and Ph transfer, are 5:95 and 53:47, respectively. As expected, coupling of n-Bu group gives preferential γ-selectivity even with the use of the mixed **1ab**. Using one equiv. CuI, i.e. preparation in situ of cuprate, did not lead to any change in the total coupling yield, and in the group selectivity and also in the regioselectivity of n-Bu transfer. However, Ph transfer results in a quite lower α:γ ratio (entry 4).

The source of copper has been reported to have a strong effect on the reactivity and regioselectivity of catalyst in Cu-catalyzed allylic alkylation with organometallic reagents.[49] So a number of Cu(I) and Cu(II) salts (entries 5–9) and Cu(I) catalysts complexed with a Lewis base such as CuBr.Me$_2$S (entry 10) or in the presence of a Lewis acid such as LiCl (entry 11) or a Lewis base such as R$_3$P (entries 13–16) were also examined as Cu catalysts.

The use of CuCN in catalytic and stoichiometric amounts could drive the allylation of **1ab** quantitatively (entries 5 and 6) and gave somewhat better group selectivity (n-Bu transfer:Ph transfer ratio = 61:39). Other CuX catalysts (X = Cl, Br, SCN) (entry 7) did not markedly change either group selectivity or regioselectivities; however, CuOAc gave quantitative yield for total coupling (entry 8). CuX$_2$ catalysts (X = Cl, OAc, OTf, acac) (entry 9) led to quantitative total coupling yields with n-Bu transfer:Ph transfer ratios and also regioselectivities being identical to those obtained with CuX catalysts. Allylation of **1ab** with CuBr.Me$_2$S (entry 10), with CuCN.2LiCl (entry 11) or with CuOTf.C$_6$H$_6$ (entry 12) resulted in quantitative total coupling with no marked change in the n-Bu transfer:Ph transfer ratios compared to the ratios obtained with non-coordinated catalysts CuCN and CuX (entries 5 and 7). It is noteworthy that, in the presence of CuI and n-Bu$_3$P or Ph$_3$P as an additive, **1ab** can be allylated with a higher Ph transfer (n-Bu transfer:Ph transfer ratio = 23:77 or 32:68) and with a better regioselectivity in the Ph transfer (α:γ ratio = 76:24 or 66:34) (entries 13 and 14). Similar results were obtained when using n-Bu$_3$P or Ph$_3$P as additives in the CuCN-catalyzed allylation (entries 15 and 16).

Table 2. Effect of N- and O-donor co-solvents and Lewis bases on selectivity and regioselectivity in the allylation of n-BuPhZn (**1**) with (E)-crotyl chloride (**2**) in the presence of CuI or CuCN catalyst[a]

n-BuPhZn (**1ab**) + [CH$_3$CH=CHCH$_2$—Cl] (**2**) →[5 mol% Cu catalyst; THF:cosolvent (4:1); 25°C, 1h] → **6a** (n-Bu) + **7a** (n-Bu) + **6b** (Ph) + **7b** (Ph)

Entry	Catalyst	Solvent[b]	Coupling yield (%)[c]	Group selectivity[d] n-Bu coupling:Ph coupling	Regioselectivity 6a:7a[e]	Regioselectivity 6b:7b[f]
1	CuI	THF–NMP	89	72:28	8:92	80:20
2	CuI	THF–HMPA	95	82:18	7:93	63:37
3	CuI	THF–DMPU	84	74:26	7:93	67:33
4	CuI	THF–diglyme	88	80:20	7:93	47:53
5	CuI	THF–DMF	100	48:52	6:94	79:21
6	CuI	THF–DMSO	96	44:56	5:95	74:26
7	CuI	THF–TMEDA	12	58:42	0:100	100:0
8	CuI	THF and 2,2-bipyridyl[g]	87	39:61	3:97	58:42
9	CuI	THF and urotropine[g]	84	32:68	4:96	82:18
10	CuCN	THF–NMP	79	80:20	8:92	65:35
11	CuCN	THF–HMPA	84	85:15	7:93	62:38

[a]Molar ratio of **1ab**:**2** is 1.1:1.
[b]THF–co-solvent volume ratio was optimized to be 4:1. In the case of HMPA, decreasing this ratio to 2:1 decreased the coupling to 71%.
[c]The sum of GC yields of n-Bu coupling products (**6a** and **7a**) and Ph coupling products (**6b** and **7b**).
[d]The ratio of GC yields of (**6a** + **7a**) and (**6b** + **7b**).
[e]The ratio of GC yields of **6a** and **7a**.
[f]The ratio of GC yields of **6b** and **7b**.
[g]1 mol equiv. vs. **2** was used.

As seen, all Cu catalysts are unsuccessful in group selective allylation of **1ab** with **2**. The highest n-Bu transfer was obtained in the presence of CuCN catalyst (n-Bu transfer:Ph transfer ratio = 61:39) (entry 5). The highest Ph transfer was observed in the presence of CuI catalyst with n-Bu$_3$P as an additive (n-Bu transfer:Ph transfer ratio = 23:77) (entry 13).

Allylation of **1ab** with **2** in THF in the presence of Pd(Ph$_3$P)$_4$, PdCl$_2$ or PEPPSI–IPr catalysts under the optimized conditions did not proceed to completion with a yield higher than 7%. Use of Pd(OAc)$_2$ as catalyst also gave quite a low yield; however, Ph selective coupling was observed (entry 17). Allylation of **1ab** with Ni catalysis provided a surprising result. The use of NiCl$_2$ (entry 18), NiCl$_2$ and Ph$_3$P (entry 19) or NiCl$_2$(Ph$_3$P)$_2$ (entry 20) as catalysts resulted in Ph selective allylation with moderate to high yields, but with a pretty low α:γ ratio of around 60:40.
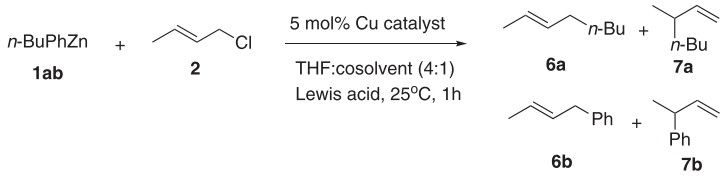
CuI-catalyzed allylation of **1ab** with **2** in THF was also carried out in the presence of N- and O-donor solvents and Lewis base reagents as additives (Table 2). Screening of N-methyl-2-pyrrolidone (NMP), hexamethylphosphoric triamide (HMPA), N,N-dimethylpropylene urea (DMPU), N,N-dimethylformamide (DMF), diethyleneglycol dimethyl ether (diglyme) and dimethylsulfoxide (DMSO) as co-solvents (entries 1–6) in the optimized THF–co-solvent ratio of 4:1 led to the finding that n-Bu transfer is improved in a coordinating solvent except DMF and DMSO (entries 5 and 6). HMPA, being the solvent of choice, gave total coupling with a yield of 95% and n-Bu transfer: Ph transfer ratio of 82:18. As observed in the reaction of **1ab** with allyl bromide,[45] N,N,N',N'-tetramethylethylenediamine (TMEDA) decreased both the total coupling yield and n-Bu transfer (entry

7). 2,2'-Bipyridyl and urotropine were also tested (entries 8 and 9) as Lewis bases in optimized equimolar amounts to allylic substrate **2**. It was interesting to see that urotropine, in contrast to donor solvents, increased Ph transfer selectivity. All Lewis bases resulted in a higher α:γ ratio in Ph transfer. Additional screening of HMPA and NMP in the presence of CuCN catalyst (entries 10 and 11) led to similar group selective and regioselective outcomes of the reaction as obtained in the presence of CuI. Non-coordinating solvents such as toluene as a co-solvent (2:1) did not change the total coupling (95%) and n-Bu transfer:Ph transfer ratio (33:67).

The effect of MgCl$_2$ and LiCl as Lewis catalysts was also investigated in the CuI- and CuCN-catalyzed allylation of **1ab** in THF (Table 3). In fact, the reaction medium is not Mg-free, but Li-free. Under the optimized conditions, MgCl$_2$ or LiCl were used in equivalent amounts vs. substrate in the presence of donor solvents. As seen, in the CuI-catalyzed allylation, the addition of MgCl$_2$ increases the n-Bu transfer:Ph transfer ratio from 42:58 (Table 1, entry 1) to 67:33 (Table 3, entry 1). In the presence of NMP or HMPA and MgCl$_2$, the n-Bu transfer:Ph transfer ratio reached 87:13 (entries 2 and 3). The addition of LiCl did not result in a group selectivity higher (entries 4–6) than those obtained in the presence of MgCl$_2$. Meanwhile, CuCN-catalyzed allylation was completed with the highest n-Bu transfer:Ph transfer ratio using NMP (or HMPA) and MgCl$_2$, i.e. 98:2 (entries 8 and 9, respectively), or using HMPA and LiCl, i.e. 86:14 (entry 12).

Allylation of stoichiometric iodozinc n-butyl phenylcuprates, n-BuPhCuZnI, prepared from 1 equiv. n-BuPhZn and 1 equiv. CuI in THF, was also carried out to prove the formation of catalytic

Table 3. Optimization of conditions in the CuI- and CuCN-catalyzed allylation of n-BuPhZn (**1**) with (E)-crotyl chloride (**2**) in THF in the presence of a co-solvent and/or Lewis acid[a]

Entry	Catalyst	Co-solvent, Lewis acid[b]	Coupling yield (%)[c]	Group selectivity[d] n-Bu coupling:Ph coupling	Regioselectivity	
					6a:7a[e]	6b:7b[f]
1	CuI	—, MgCl$_2$	93	67:33	6:94	39:61
2	CuI	NMP, MgCl$_2$	87	87:13	7:93	55:45
3	CuI	HMPA, MgCl$_2$	89	87:13	6:94	50:50
4	CuI	—, LiCl	96	67:33	6:94	56:44
5	CuI	NMP, LiCl	83	82:18	6:94	60:40
6	CuI	HMPA, LiCl	89	87:13	6:94	50:50
7	CuCN	—, MgCl$_2$	93	76:24	8:92	27:73
8	CuCN	NMP, MgCl$_2$	71	97:3	7:93	50:50
9	CuCN	HMPA, MgCl$_2$	81	98:2	6:94	50:50
10	CuCN	—, LiCl	88	76:24	6:94	48:52
11	CuCN	NMP, LiCl	89	81:19	6:94	53:47
12	CuCN	HMPA, LiCl	94	86:14	7:93	38:62

[a]Molar ratio of **1ab**:**2** is 1.1:1.
[b]1 mol equiv. to **2** was used.
[c]The sum of GC yields of n-Bu coupling products (**6a** and **7a**) and Ph coupling products (**6b** and **7b**).
[d]The ratio of GC yields of (**6a** + **7a**) and (**6b** + **7b**).
[e]The ratio of GC yields of **6a** and **7a**.
[f]The ratio of GC yields of **6b** and **7b**.

cuprates as intermediates in the CuI-catalyzed allylations of **1ab** reagents. The stoichiometric cuprate afforded 94% total coupling with a ratio of 51:49 for *n*-Bu transfer:Ph transfer and γ-selective *n*-Bu transfer. The use of LiCl as an additive increased the *n*-Bu transfer:Ph transfer ratio to 73:27 and the use of HMPA as a co-solvent and LiCl resulted in exclusively *n*-Bu transfer (91:9). Similarity of these results to the data in Table 1 (entry 1), Table 2 (entry 2) and Table 3 (entry 6), which were obtained in the allylation of *n*-BuCuZn in the presence of CuI catalyst, provides a proof for the expected *in situ* formation of catalytic mixed cuprates.

Donor solvents, Lewis base and Lewis acid additives were also used in the Ni-catalyzed Ph selective allylation of **1ab** with **2** with the aim of finding better coupling yield and/or better regioselectivity (Table 4). The use of donor solvents (entries 1–4) such as NMP, HMPA, DMPU, diglyme, DMF and DMSO is ineffective in altering the Ph coupling yield; however, using HMPA, DMF or DMSO resulted in a small increase in the α:γ ratio (entries 1, 3 and 4). Urotropine and MgCl$_2$ decreased the coupling yield (entries 6 and 7). The use of LiCl resulted in the highest coupling yield, i.e. 83%, for Ph transfer with an α:γ ratio of 65:35 (entry 8). In the presence of HMPA and LiCl, the α:γ ratio increased to 73:27; however, this increase in regioselectivity is within the limit of experimental error.

Optimization of the effects of reaction parameters to control the group selectivity and regioselectivity in the Cu- and Ni-catalyzed allylation of **1ab** with **2** has revealed the following points:

(i) The allylation is *n*-Bu group-selective in the presence of CuCN (5 mol%) catalyst in THF–HMPA (4:1) and MgCl$_2$ or LiCl (1 equiv. vs. **2**). Total coupling yield is 81% and 94% and *n*-butyl transfer:Ph transfer ratio is 98:2 and 86:14, respectively (Table 3, entries 9 and 12). The *n*-butyl transfer takes place with γ-selectivity.

(ii) The allylation in the presence of CuI (5 mol%) catalyst and *n*-Bu$_3$P (5 mol%) (Table 1, entry 13) or urotropine (1 mol equiv.) (Table 2, entry 9) in THF takes place with a total coupling yield of *ca* 100% and 84% and with a *n*-Bu transfer:Ph transfer ratio of 23:77 and 32:68, respectively. Phenyl transfer results in moderate α-selectivity (α:γ = 76:24 and 82:18, respectively).

(iii) The allylation takes place with complete Ph transfer in the presence of NiCl$_2$(Ph$_3$P)$_2$ (2.5 mol%) catalyst in THF with a yield of 76% and an α:γ ratio of 59:41 (Table 1, entry 20). Using LiCl (1 equiv. vs. **2**) increases the coupling yield to 83% and the α:γ ratio to 65:35 (Table 4, entry11).

After having determined the reaction conditions for *n*-alkyl or aryl transfer to an allylic substrate using a mixed *n*-alkylarylzinc reagent, we also found the coupling yields and regioselectivity in the allylation of homodiorganozincs, *n*-Bu$_2$Zn (**1a$_2$**) and Ph$_2$Zn (**1b$_2$**), with **2** under the optimized conditions (Table 5). Uncatalyzed allylation of **1a$_2$** and **1b$_2$** did not take place. Coupling yields of **1a$_2$** in the CuI- or CuCN-catalyzed reactions (entries 1 and 2) are not different from those of **1ab**. Coupling in the presence of a donor solvent resulted in somewhat higher yields (entries 3 and 4). Ni catalyst did not allow an alkyl–allyl coupling (entry 5).

Allylation of **1b$_2$** takes place quantitatively in the presence of both Cu and Ni catalysts (entries 6–8). Carrying out the coupling

Table 4. Effect of Lewis bases and Lewis acids on the group selectivity and regioselectivity in the allylation of *n*-BuPhZn (**1**) with (*E*)-crotyl chloride (**2**) in THF in the presence of NiCl$_2$(Ph$_3$P)$_2$ catalyst[a]: optimization of conditions

n-BuPhZn (**1ab**) + (**2**) Cl → [2.5 mol% NiCl$_2$(Ph$_3$P)$_2$ **5**, THF:cosolvent (4:1), 25°C, 1h] → (**6a**) *n*-Bu + (**7a**) *n*-Bu + (**6b**) Ph + (**7b**) Ph

| Entry	Cosolvent, Lewis acid[b]	Coupling yield (%)[c]	Group selectivity[d] *n*-Bu coupling: Ph coupling	Regioselectivity 6a:7a[e]	Regioselectivity 6b:7b[f]
1	HMPA	77	0:100	—	68:32
2	Diglyme	68	0:100	—	59:41
3	DMF	78	3:97	—	71:29
4	DMSO	68	0:100	—	69:31
5	2,2'-Bipyridyl[b]	74	0:100	—	54:46
6	Urotropine[b]	40	0:100	—	60:40
7	—, MgCl$_2$	35	0:100	—	54:46
8	—, LiCl	83	0:100	—	65:35
9	HMPA, LiCl	72	3:97	—	73:27
10	DMF, LiCl	52	4:96	—	74:26

[a]Molar ratio of **1ab**:**2** is 1.1:1.
[b]1 mol equiv. vs. **2** was used.
[c]The sum of GC yields of *n*-Bu coupling products (**6a** and **7a**) and Ph coupling products (**6b** and **7b**).
[d]The ratio of GC yields of (**6a** + **7a**) and (**6b** + **7b**).
[e]The ratio of GC yields of **6a** and **7a**.
[f]The ratio of GC yields of **6b** and **7b**.

Table 5. Allylation of n-Bu$_2$Zn (**1a$_2$**) and Ph$_2$Zn (**1b$_2$**) with (*E*)-crotyl chloride (**2**) in the presence of Cu or Ni catalyst in THF[a]: effect of co-solvent
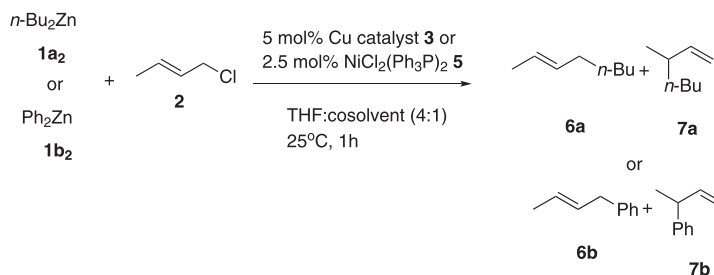
Entry	R$_2$Zn	Catalyst	Co-solvent	Coupling yield (%)[b]	Regioselectivity	
					6a:7a[c]	6b:7b[d]
1	n-Bu$_2$Zn	CuI	—	82	7:93	
2	n-Bu$_2$Zn	CuCN	—	92	7:93	
3	n-Bu$_2$Zn	CuI	HMPA	91	7:93	
4	n-Bu$_2$Zn	CuI	Diglyme	99	6:94	
5	n-Bu$_2$Zn	NiCl$_2$(Ph$_3$P)$_2$	—	—	—	
6	Ph$_2$Zn	CuI	—	100		60:40
7	Ph$_2$Zn	CuCN	—	100		42:58
8	Ph$_2$Zn	NiCl$_2$(Ph$_3$P)$_2$	—	100		56:44
9	Ph$_2$Zn	CuI	HMPA	80		55:45
10	Ph$_2$Zn	CuI	Diglyme	85		75:25

[a]Molar ratio of **1a$_2$:2** and **1b$_2$:2** is 1.1:1.
[b]The sum of GC yields of n-Bu coupling products (**6a** and **7a**) and Ph coupling products (**6b** and **7b**).
[c]The ratio of GC yields of **6a** and **7a**.
[d]The ratio of GC yields of **6b** and **7b**.

Table 6. Ni-catalyzed coupling of n-butylarylzincs or methylarylzincs with allylic substrates in THF in the presence of LiCl[a]

R^1= Me, n-Bu
R^2= C$_6$H$_5$, FG-C$_6$H$_4$
R, A= Me, Cl **2a**, C$_6$H$_5$, Cl **2b**, C$_6$H$_5$, OAc **2c**
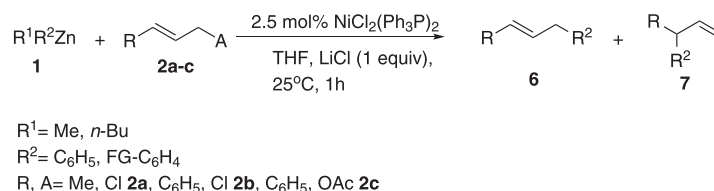
Entry	R^1	R^2	R, A (**2a, 2b, 2c**)	Coupling yield (%)[b]	Regioselectivity 6:7[c]
1	n-Bu	C$_6$H$_5$	Me, Cl	80	72:28
2	n-Bu	4-MeC$_6$H$_4$	Me, Cl	77	75:25
3	Me	3-MeC$_6$H$_4$	Me, Cl	80	66:34
4	n-Bu	4-*tert*-BuC$_6$H$_4$	Me, Cl	76	73:27
5	n-Bu	4-MeOC$_6$H$_4$	Me, Cl	85	71:29
6	n-Bu	3-MeOC$_6$H$_4$	Me, Cl	95	80:20
7	Me	C$_6$H$_5$	C$_6$H$_5$, Cl	69	86:14
8	Me	C$_6$H$_5$	C$_6$H$_5$, OAc	77	76:24
9	Me	4-MeC$_6$H$_4$	C$_6$H$_5$, OAc	82	60:40
10	Me	3-MeC$_6$H$_4$	C$_6$H$_5$, OAc	63	56:44
11	Me	4-MeOC$_6$H$_4$	C$_6$H$_5$, OAc	72	67:33
12	Me	3-MeOC$_6$H$_4$	C$_6$H$_5$, OAc	79	56:44

[a]Reactions were run with a 1.1:1 molar ratio of **1:2**. General reaction conditions: R^{1}R^{2}Zn reagent (10 mmol) in THF, allylic substrate (9 mmol), NiCl$_2$(Ph$_3$P)$_2$ (0.25 mol), LiCl (9 mmol) at room temperature for 1 h. See Experimental section.
[b]Isolated yield of product mixture of **6** and **7**.
[c]The α:γ ratio was determined using 500 MHz ^{1}H NMR analysis and also using GC analysis.

in the presence of a donor solvent led to lower yields (entries 9 and 10) as observed in the yield of Ph transfer of **1ab** reagents.

This study showed that in the Cu-catalyzed allylation of **1ab**, both n-Bu and Ph group are transferred to the allylic substrate **2** in a ratio of ca 1:1 with total quantitative coupling yield. However, reaction parameters (transition metal catalyst, Lewis base and/or Lewis acid) can be adjusted for selective n-butyl transfer or phenyl transfer to take place with moderate to high regioselectivities.

As a result, the use of mixed (n-alkyl)(aryl)Zn reagents in allylation allows coupling of either n-alkyl or aryl group. CuCN (5 mol%)-catalyzed allylation of mixed (n-alkyl)PhZn reagents in THF–HMPA (4:1) with $MgCl_2$ (1 equiv.) at 25°C seems a prominent γ-selective procedure for n-alkyl–allyl coupling (Table 3, entry 9). This protocol provides an atom-economic alternative to allylation using (n-alkyl)$_2$Zn reagents if the n-alkyl group is cost-sensitive.

For the particular interest in developing an atom-economic procedure for aryl–allyl coupling using mixed n-Bu(aryl)zincs, two procedures can be applied: allylation in the presence of CuI (5 mol%) catalyst and n-Bu$_3$P (5 mol%) as an additive in THF (Table 1, entry 13); or allylation in the presence of NiCl$_2$ (Ph$_3$P)$_2$ (2.5 mol%) catalyst and LiCl (1 equiv.) as an additive in THF (Table 4, entry 11). These both give good to high yields. NiCl$_2$(Ph$_3$P)$_2$-catalyzed allylation is more advantageous, being aryl group-selective with an α:γ ratio of 65:35. This protocol provides an atom-economic alternative to allylation using (aryl)$_2$Zn reagents if the aryl group is cost-sensitive.

Thus, with the optimized conditions in hand, potential synthetic transfer of aryl groups of (n-butyl)(aryl)zincs to allylic substrates was investigated. Instead of (n-butyl)(phenyl)zinc, (methyl)(phenyl)zinc was also examined in the allylation, which did not change the outcome of the reaction. So, both n-butyl and methyl groups were used as residual groups in the mixed alkylarylzincs to give aryl–allyl coupling in the presence of NiCl$_2$(Ph$_3$P)$_2$ as catalyst and LiCl. The results are summarized in Table 6. The data are averages of at least two independent experiments.[50] The products were fully characterized using ^{1}H NMR analysis, and the α:γ ratios of the product mixtures were determined using ^{1}H NMR analysis and also by GC analysis. As allylic substrates, (E)-crotyl chloride, (E)-cinnamyl chloride and (E)-cinnamyl acetate were screened. The coupling yields are high (63–95%) and α:γ ratios for the coupling product vary between 56:44 and 86:14 depending on the coupling partners.

Coupling of alkyl- and methoxy-substituted aryl groups with **2** (entries 2–6) and with cinnamyl substrates **2b** and **2c** (entries 8–13) proceeded smoothly and provided the target compounds. Side products, such as methyl- and methoxy-substituted biphenyls could not be completely suppressed. However, coupling of halogeno- and acyl-substituted aryl groups was discouraged due to low yields of products with formation of side products.

Conclusions

A range of reaction parameters were examined with the aim of controlling the group selectivity and regioselectivity in the allylation of (n-butyl)(phenyl)zinc. The following were demonstrated:

(i) In the Cu-catalyzed allylation of mixed (n-butyl)(phenyl)zinc, group selectivity can be controlled by changing the reaction parameters, and either the n-butyl or phenyl group can be transferred to the allylic substrate. These findings also provide another support for Erdik's hypothesis of the dependence

of group selectivity of diorganocuprates on the reaction parameters.

(ii) A new and simple procedure for aryl–allyl coupling using Ni-catalyzed allylation of methyl- or n-butyl(aryl)zincs provides an atom-economic alternative to allylic coupling of diarylzincs.

Further studies are underway with the aim of increasing the functional group tolerance and the regioselectivity in the allylation of mixed arylzincs as well as investigating the mechanism of the organic catalysts in the group selectivity.

Experimental

General

All reactions were carried out in oven-dried glassware under a positive pressure of nitrogen using standard syringe–septum cap techniques.[50] GC analyses were performed using a Thermo Finnigan gas chromatograph equipped with a ZB-5 capillary column packed with phenylpolysiloxane using the internal standard technique. THF was distilled from sodium benzophenonedianion. Alkyl bromides and bromobenzene were obtained commercially and purified using literature procedures. Mg turnings for Grignard reagents were used without further purification. $ZnCl_2$ (Aldrich) was dried under reduced pressure at 100°C for 2 h and used as a THF solution. CuI was purified according to the literature procedure, dried under reduced pressure at 60–90°C for at least 1 h and kept under nitrogen.[51] CuCN was purified according to a published procedure.[52] Ni and Pd catalysts were used without further purification. HMPA, NMP, DMPU, diglyme and TMEDA were distilled under reduced pressure and kept over molecular sieves under nitrogen. Toluene was distilled and kept over sodium under nitrogen. $MgCl_2$ and LiCl were dried under reduced pressure.

Grignard reagents RMgBr (R = n-Bu, C$_6$H$_5$, FG-C$_6$H$_4$ (FG = 3-MeO, 4-MeO, 3-Me, 4-Me, 3-Br, 4-Br)) were prepared in THF by standard methods and their concentrations were found by titration before use.[53] For the preparation of (n-alkyl)(aryl)zinc reagents R^{1}R^{2}Zn (R^1 = Me, n-Bu; R^2 = C$_6$H$_5$, FG-C$_6$H$_4$),[37] arylzinc chlorides R^{2}ZnCl were reacted with n-BuMgBr (or MeMgCl). R^{2}ZnCl were prepared by addition of arylmagnesium bromide (10 mmol) to $ZnCl_2$ (10 mmol) in THF (10 ml) at −20°C with stirring at that temperature for 15 min. To freshly prepared R^{2}ZnCl reagent (10 mmol), n-BuMgBr (or MeMgCl) (10 mmol) in THF was added dropwise and the mixture was stirred at −20°C for another 15 min.

Synthetic Procedure for Ni-Catalyzed Allylation of (Alkyl)(aryl) zincs R^{1}R^{2}Zn in the Presence of LiCl

To the prepared R^{1}R^{2}Zn reagent (10 mmol), NiCl$_2$[(Ph)$_3$P]$_2$ (0.25 mmol, 0.16 g) was added at −20°C and stirred at that temperature for another 15 min. LiCl (9 mmol, 0.425 g) was added and then allylic substrate (9 mmol) was added dropwise at −20°C. The mixture was stirred at room temperature for 1 h. The mixture was hydrolyzed with saturated NH$_4$Cl solution. The aqueous layer was extracted with ether. The organic combined solutions were dried with Na$_2$SO$_4$, concentrated and subjected to silica gel column chromatography with petroleum ether. A mixture of α- and γ-products was obtained as a light yellow liquid. The ratio of α-product to γ-product was determined using GC analysis and also using 500 MHz ^{1}H NMR analysis.

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