New Preparation and Reactions of Arylaluminum Reagents Using Barbier Conditions

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Abstract: The reaction of various aryl bromides with magnesium turnings, LiCl and R_2AICl (R = Et, *i*-Bu) provides at room temperature arylaluminum reagents in high yields. These organometallic species undergo readily 1,4-additions, acylations, allylations, and Pd-catalyzed cross-couplings with various aryl iodides and bromides.

Key words: organoaluminum, cross-coupling, 1,4-addition, acylation, Barbier reaction

The preparation of main-group organometallics for applications in organic synthesis is one of the most active research areas in organic chemistry since these organometallics readily form new carbon-carbon bonds. Previously unrecognized high chemoselectivity of zinc and magnesium reagents led to an increased research activity in this field.¹ The preparation of organoaluminum derivatives is of special interest due to the potentially broad functionalgroup tolerance of organoalanes, the low cost of aluminum reagents, and their low toxicity. Surprisingly, general preparations of arylaluminum reagents are rare.² The most important syntheses of arylaluminum compounds are directed aluminations,^{3,4} transmetalation reactions.⁵ Most transmetalations from highly reactive organolithium reagents have to be performed at low temperature.⁵ Recently, we have found that the insertion of various metals (Zn,⁶ In, Mg^8) is dramatically accelerated by the addition of LiCl. Also, the use of Barbier reaction conditions allows to generate sensitive organozinc reagents via reactive intermediate magnesium reagents which are trapped in situ with ZnCl₂.⁸ Using a similar approach, we wish to report herein a new preparation method of arylaluminum reagents of type 1 (Scheme 1) which proceeds at room temperature via an in situ generated organomagnesium species of type 2 obtained by the reaction of aryl bromides 3 with magnesium turnings in the presence of LiCl and a dialkylaluminum chloride (R_2 AlCl; **4a**: R = Et; **4b**: R = i-Bu).

ArBr 3	Mg (2.5 equiv) LiCl (1.25 equiv)		R ₂ AICI (4a , b)
	25 °C, 1–3 h	2	1 (R = Et or <i>i</i> -Bu)
Scher	ne 1		

SYNLETT 2009, No. 8, pp 1321–1325 Advanced online publication: 08.04.2009 DOI: 10.1055/s-0028-1088127; Art ID: G02309ST © Georg Thieme Verlag Stuttgart · New York Thus, the treatment of 4-bromoanisole (1.0 equiv) with magnesium turnings (2.5 equiv) activated with DIBAL-H (1%),⁹ LiCl (1.25 equiv), and Et₂AlCl (1.0 M solution in hexane, 1.1 equiv) at 25 °C provides the corresponding arylaluminum reagent **1a** within 3 hours as indicated by GC analysis of hydrolyzed reaction aliquots. The crude arylaluminum reagent is cannulated to a solution of CuCN·2LiCl (0.1 equiv)⁹ at -10 °C followed by cyclohex-2-enone (0.6 equiv) and TMSCl (1.1 equiv).^{5b} After acidic workup, the 3-arylated cyclohexanone 4a is isolated in 72% yield (entry 1 of Table 1). This Michael addition was extended to arylaluminum reagents bearing a chlorine substituent (1b,c, entries 2 and 3) leading to the 3-substituted cyclohexanones **4b**,**c** in 71–77% yield. The ortho-tolylaluminum species 1d also reacts smoothly with cyclohex-2-enone affording the 1,4-adduct 4d in 76% yield (entry 4). Finally, amino-substituted arylaluminum species such as 1e can be readily prepared with our method providing after the addition to ethyl acrylate the β -arylated ester 4e in 66% yield (entry 5). The competitive transfer of an ethyl group was never observed in these copper-catalyzed 1,4-additions. However, this was the case for Pd-catalyzed cross-couplings. Therefore, in these cases, $Et_AlCl(4a)$ was replaced by *i*-Bu₂AlCl(4b) which transfer only the aryl moiety to the organic electrophile. A range of Pd-catalyzed cross-couplings could be performed with various aryl bromides or iodides of type 6 using PEPPSI-*i*-Pr (7) as the catalyst (2 mol%).¹⁰ In all cases, the arylaluminum reagents 1 undergo directly the desired cross-coupling without the need of a further transmetalation.¹¹ Thus, the reaction of the aluminum reagent 4-MeOC₆H₄Al*i*-Bu₂ (1f) with 4-BrC₆H₄CO₂Et (0.8 equiv, 25 °C, 4 h) in the presence of PEPPSI-*i*-Pr (7) provides the biphenyl derivative 8a in 89% yield (entry 1 of Table 2). The cross-coupling with 2-BrC₆H₄CO₂Et is complete within one hour at 25 °C and furnishes the biphenyl ester (8b) in 95% yield (entry 2). Chlorine- and methyl-substituted arylaluminum reagents 1g and 1h react with the aryl bromides **6b** and **6c** leading to the biphenyls **8c** and **8d** in 81-83% yield (entries 3 and 4). Amino-substituted arylaluminum reagents, such as 1i and 1j, react smoothly with aryl bromides 6c and 6d (1 h, 25 °C) affording the biphenyls 8e and 8f in 68–91% yield (entries 5 and 6). Further CF₃-, MeO-, and trimethoxy-substituted arylaluminums 1k-m undergo cross-couplings under similar reaction conditions in 76–87% yield (entries 7–9). Finally, thiomethyl-substituted arylaluminums (1n and 10) give the

Table 1 Copper-Catalyzed Michael Additions of Arylaluminum Reagents 1 to Enones

		ArAIEt ₂ TM CuCN 1 -1	(0.6 equiv) SCI (1.1 equiv) -10 -2 LiCI (0.1 equiv) 0 °C to r.t., 4 h FHF, hexane	AcOH to 25 °C, 15 min	Ar 4	
Entry	Arylalum	ninum reagent	Enone	Product 4		Yield (%) ^a
1	1a	4-MeOC ₆ H ₄ AlEt ₂	cyclohex-2-enone	4a	OMe	72
2	1b	3-ClC ₆ H ₄ AlEt ₂	cyclohex-2-enone	4b	CI	77
3	1c	4-ClC ₆ H ₄ AlEt ₂	cyclohex-2-enone	4c	CI	71
4	1d	2-MeC ₆ H ₄ AlEt ₂	cyclohex-2-enone	4d	Me	76
5	1e	3-Me ₂ NC ₆ H ₄ AlEt ₂	ethyl acrylate	4e	CO ₂ Et	66

^a Isolated yields of analytically pure products.

cross-couplings with aryl iodides (**6g** and **6h**) affording the desired biphenyls in 83–84% yield (entries 10 and 11).

The arylaluminum reagents of type 1 undergo also smooth copper(I)-catalyzed acylations with acid chlorides of type 10 leading to aryl ketones of type 11. The reaction of 4- $MeOC_6H_4Ali-Bu_2$ (1f) with benzoyl chloride (10a, 0.8) equiv) between -10 °C to 25 °C in the presence of CuCN·2LiCl⁹ (0.1 equiv) furnishes the desired benzophenone (11a) in 72% yield (entry 1 of Table 3). Similarly, the substituted arylaluminum reagents 1h, 1n, 1p, and 1g react in the presence of CuCN·2LiCl (0.1 equiv) with pivaloyl chloride (10b), benzoyl chloride (10a), or 4-bromobenzoyl chloride (10c) within 3 hours providing the ketones **11b–d** in 77–87% yield (entries 2–4). The reaction of $3-F_3CC_6H_4Ali-Bu_2$ (1k) with ethyl 2-(bromomethyl)acrylate¹² in the presence of CuCN·2LiCl⁹ (0.1 equiv) furnishes the allylation product 12 in 85% yield (Scheme 2). Thus, a copper-catalyzed allylation can be also realized conveniently with the arylaluminum reagents.13-16





In summary, we have shown that the generation of arylaluminums (ArAlR₂) prepared from aryl bromides using magnesium turnings in the presence of LiCl and R₂AlCl (R = Et or *i*-Bu) can tolerate several functional groups. However, a ketone, a nitrile, or an ester group are not compatible with this procedure. The aluminum reagents of type **1** were shown to undergo smooth Pd-catalyzed cross-couplings and Cu-catalyzed Michael additions, acylations, and allylations. Further reactivity studies of these arylaluminum derivatives and extension of this method are currently under way in our laboratory.

Table 2	Pd-Catalyzed Cross-Couplings of Arylaluminum Reagents 1 with Aryl Bromides and Iodides of Type 6 Leading to Biphenyls of
Type 8	

				Ar ² X (6 , 0.8 equiv) PEPPSI <i>i</i> -Pr (7 ; 2 mol%)		. 1 . 2	
		Ą	r ¹ Al(<i>i</i> -Bu) ₂ 1	25 °C, 1–12 h THF, heptane		Ar'–Ar ² 8	
Entry	Arylalu	iminum reagent	Ar ¹ X		Produ	uct 8	Yield (%) ^a
1	1f	4-MeOC ₆ H ₄ Al <i>i</i> -Bu ₂	6a	4-BrC ₆ H ₄ CO ₂ Et	8a	MeO CO ₂ Et	89
2	1f	4-MeOC ₆ H ₄ Al <i>i</i> -Bu ₂	6b	2-BrC ₆ H ₄ CO ₂ Et	8b	MeO-EtO ₂ C	95
3	1g	3-ClC ₆ H ₄ Al <i>i</i> -Bu ₂	6b	2-BrC ₆ H ₄ CO ₂ Et	8c	CI	81
4	1h	2-MeC ₆ H ₄ Al <i>i</i> -Bu ₂	6с	2-BrC ₆ H₄OMe	8d	Me	83
5	1i	3-Me ₂ NC ₆ H ₄ -Al <i>i</i> Bu ₂	6d	4-BrC ₆ H₄OMe	8e	NMe ₂	68
6	1j	4-Me ₂ NC ₆ H ₄ Al <i>i</i> -Bu ₂	6e	4-BrC ₆ H₄Cl	8f	Mean	91
7	1k	3-F ₃ CC ₆ H ₄ -Al <i>i</i> -Bu ₂	6a	4-BrC ₆ H ₄ CO ₂ Et	8g	CF ₃ CO ₂ Et	76
8	11	2-MeOC ₆ H ₄ -Al <i>i</i> -Bu ₂	6f	2-BrC ₆ H₄Me	8d		87
9	1m	3,4,5-(MeO) ₃ C ₆ H ₂ Al <i>i</i> -	Bu ₂ 6a	4-BrC ₆ H ₄ CO ₂ Et	8h	MeO MeO	79
10	1n	4-MeSC ₆ H ₄ Al <i>i</i> -Bu ₂	6g	2-IC ₆ H ₄ CO ₂ Et	8i	OMe MeS EtO ₂ C	84
11	10	2-MeSC ₆ H ₄ Al <i>i</i> -Bu ₂	6h	4-IC ₆ H ₄ CO ₂ Et	8j	SMe CO ₂ Et	83

^a Isolated yields of analytically pure products.

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 Table 3
 Copper(I)-Catalyzed Acylations of Arylaluminum Reagents 1 with Acid Chlorides of Type 10 Leading to Aryl Ketones of Type 11

			ArAl(<i>i</i> -Bu) ₂	RCOCI (10; 0.8 equiv) 0.1 CuCN·2 LiCI -10 to 25 °C , 3 h THF, heptane	•	Ar R	
Entry	Arylalun	ninum reagent	RCOCI		Produc	et 11	Yield (%) ^a
1	1f	4-MeOC ₆ H ₄ Al <i>i</i> -B	u ₂ 10a	PhCOC1	11a	MeO-COPh	72
2	1h	2-MeC ₆ H ₄ Al <i>i</i> -Bu ₂	2 10b	t-BuCOCl	11b	Me CO <i>t</i> -Bu	77
3	1n	4-MeSC ₆ H ₄ Al <i>i</i> -B	u ₂ 10a	PhCOCl	11c	MeS-COPh	87
4	1p	2-F ₃ CC ₆ H ₄ Al <i>i</i> -Bu	₂ 10a	PhCOCl	11d	CF ₃ COPh	85
5	1g	3-ClC ₆ H ₄ Al <i>i</i> -Bu ₂	10c	4-BrC ₆ H ₄ COCl	11e		85

^a Isolated yields of analytically pure products.

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- (13) Typical Procedure: Preparation of Aluminum Reagent 1f
 - A dry argon-flushed Schlenk flask equipped with a magnetic stirrer and a rubber septum was charged with anhyd LiCl (106 mg, 2.5 mmol), and the flask was dried with a heating gun for 3–5 min on high vacuum (1 mbar). To this flask was added the magnesium turnings (122 mg, 5.0 mmol), and the flask was evacuated and refilled with argon. After the addition of freshly distilled THF (3 mL), magnesium turnings were activated with DIBAL-H (0.2 mL, 0.1 M solution in THF, 0.02 mmol). After heating for about 1 min and then cooling to 25 °C, *i*-Bu₂AlCl soln (2.2 mmol, 0.8 M in heptane) was added. Finally, 4-bromoanisole (374 mg, 2.0 mmol) was added in one portion at 25 °C. After 3 h at this temperature, the reaction mixture was cannulated to a new Schlenk flask for the trapping reaction with an electrophile.
- (14) The ²⁷Al NMR spectra of **1a** obtained by our method and by the reaction of *p*-lithioanisole and **4a** give the same chemical shift ($\delta = 178.16$ ppm, in THF and Et₂O).

(15) Typical Procedure: Preparation of 3-(4-Methoxyphenyl)cyclohexanone (4a)

The freshly made aluminum reagent 1a was cannulated into a dry argon-flushed Schlenk flask equipped with a magnetic stirrer and a rubber septum at -10 °C. To this was added CuCN·2LiCl (0.2 mL, 1 M in THF, 0.2 mmol), and the reaction mixture was stirred for 5 min. After the addition of cyclohex-2-enone (115 mg, 1.2 mmol) and then TMSCl (239 mg, 2.2 mmol), the cooling bath was removed and the mixture was stirred for 4 h at 25 °C. The reaction was quenched with AcOH (360 mg, 6.0 mmol) at -30 °C and then kept at 25 °C for 15 min. The mixture was extracted three times with EtOAc, washed with aq sat. NaHCO₃, H₂O, and sat. NaCl soln. The combined organic layers were dried over Na₂SO₄, and the solvents were removed under reduced pressure to furnish the crude product, which was further purified by column chromatography (SiO₂) to obtain a light yellow oil (72% yield, 176 mg).

(16) Typical Procedure: Preparation of Ethyl 4'-Methoxybiphenyl-2-carboxylate (8b)

A dry Schlenk flask equipped with a magnetic stirrer and a rubber septum was charged with ethyl 2-bromobenzoate (366 mg, 1.6 mmol), PEPPSIi-Pr (13.6 mg, 2 mol%). The flask was thoroughly flushed with argon, and freshly distilled THF (0.5 mL) was added to it through the rubber septum. The resultant mixture was stirred at 25 °C for 5 min before the aluminum reagent 1f was slowly cannulated into the flask. After 1 h, the reaction was quenched with aq 2 N HCl at -30 °C and then kept at 25 °C for 10 min. The mixture was extracted three times with EtOAc, washed with aq sat. NaHCO₃, H₂O, and sat. NaCl soln. The combined organic layers were dried over Na2SO4, and the solvents were removed under reduced pressure to furnish the crude product, which was further purified by column chromatography (SiO₂) to obtain a light yellow oil (95% yield, 389 mg).

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