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Palladium-Catalyzed Cross-Coupling Reactions with Zinc, Boron, and Indium Exhibiting High Turnover Numbers (TONs): Use of Bidentate Phosphines and Other Critical Factors in Achieving High TONs[†]

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Summary: Palladium-catalyzed reactions of unsaturated organozincs with aryl or alkenyl iodides can exhibit turnover numbers (TONs) over 10^5 *(>70% product yields). Under the conditions employed, Zn, B, and In appear to be the three most favorable metals, followed by Al(Zn) and Zr(Zn), whereas TONs observable with Sn, Cu, and Mn have been significantly lower.*

Palladium-catalyzed cross-coupling has emerged as one of the most widely used methods for carbon−carbon bond formation over the past three decades.[1] Until several years ago, however, it had been routinely carried out with 1−5 mol % of Pd catalysts, even though a paper reporting a turnover number (TON hereafter) exceeding 10^3 (ca. 2000) for the reaction of (*E*)-1-octenylzinc chloride with PhI in the presence of 0.05 mol % of $Pd(PPh_3)_4$, for example, appeared as early as 1987.[2] Over the past several years, a number of workers[3,4] have begun reporting high TONs often in the range 10^5−10^6, and even several examples of cross-coupling between arylboronic acids with aryl bromides and chlorides exhibiting TONs over 10^6 are now known.[3] Most of these investigations have dealt primarily with the Pd-catalyzed cross-coupling of arylboronic acids with aryl halides, although some results of modest TONs have also been reported on the Pd-catalyzed reactions of (i) *p*-tolylzinc chloride with *o*-chlorobenzonitrile (TON $\leq 7.6 \times 10^3$),[4d] (ii) alkylmagnesium bromides with aryl and alkenyl bromides,[3e] and (iii) arylboronic acids with benzyl chlorides (TON $< 10^3$).[4g] As the complexity and cost of Pd catalysts increase, catalyst turnover number (TON) will become a critically important factor for expanding the synthetic scope of Pd-catalyzed cross-coupling.

We report herein unprecedentedly high TONs exceeding 1 000 000 observed in the Pd-catalyzed reactions of aryl-, alkenyl-, and alkynylzinc derivatives with aryl and alkenyl iodides.[5] Since the previously reported maximum TONs observed with organozincs[2,4d] were in the 10^3−10^4 range, these TONs exceeding 10^5 have significantly elevated the TON level.[6] The results summarized in Table 1 indicate the following. (1) All six classes of Pd-catalyzed cross-coupling reactions examined in this study can exhibit TONs exceeding 10^5 (entries 1-ii, 2-ii, 3-ii, 4-ii, 5-ii, and 6-ii). Many of the yield and TON figures represent averages of two or more runs. Moreover, each cross-coupling reaction was run at three or more catalyst concentration levels (5−10^{-5} mol %) and monitored at various reaction times until no further progress was observed. Of course, the TON is a function of the product yield, and it can be stretched considerably at the expense of the latter. As product yields exceeding 60−70% are generally considered to be practically acceptable, only those TONs accompanied by product yields exceeding 60% are considered for determining the maximum attainable TONs under given sets

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[†] This paper is dedicated to Professor Iwao Ojima of SUNY at Stony Brook on the occasion of his 60th birthday.

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(5) **4-Methylbiphenyl. Representative Procedure**: to iodobenzene (245 mg, 1.2 mmol) in THF (2 mL) cooled to −78 °C was added *t*-BuLi (1.41 mL, 1.7 M in hexane, 2.4 mmol). The resultant solution was stirred for 30 min at −78 °C, followed by addition of a solution of dry $ZnBr_2$ (270 mg, 1.2 mmol) in THF (1 mL). After the mixture thus obtained had been stirred for 5 min at −78 °C and warmed to 0 °C over 30 min, *p*-iodotoluene (218 mg, 1 mmol) and $Pd(dppf)Cl_2$ (1×10^{-4} M, 100 uL, 1×10^{-5} mmol in THF) were added at 23 °C. The resultant mixture was stirred at 23 °C and monitored by GLC analysis. After 20 h, GLC analysis indicated that the starting material had been completely consumed and that the title compound was formed in 97% GLC yield (average of two independent runs). The reaction mixture was quenched with 1 M HCl, extracted with ether, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel, hexane) afforded 162 mg (96%) of the title compound (Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963).

(6) To the best of our knowledge, Pd-catalyzed cross-coupling reactions exhibiting $> 10^4$ TON appear to be unprecedented, with the exception of those observed in the aryl−aryl coupling reactions with arylboronic acids.[3,4]

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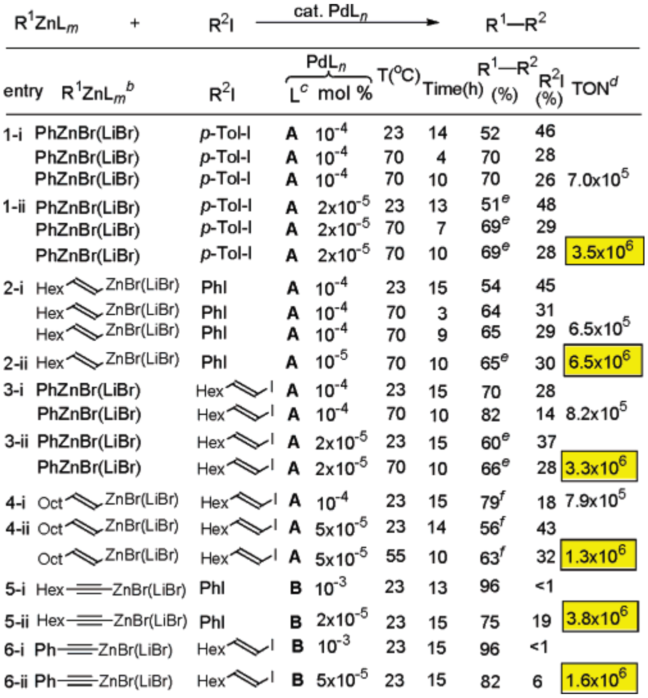
Table 1. Reaction of Aryl-, Alkenyl-, and Alkynylzinc Derivatives with Aryl and Alkenyl Iodides in the Presence of Pd−Phosphine Catalysts[a]



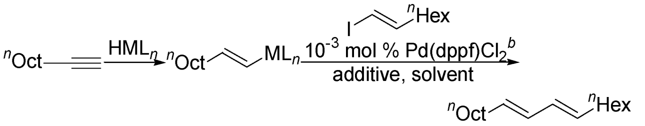
$$R^1ZnL_m + R^2I \xrightarrow{\text{cat. }PdL_n} R^1—R^2$$

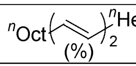
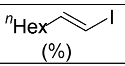
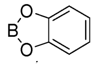
entry	R^1ZnL_m[b]	R^2I	PdL_n		T(°C)	Time(h)	$R^1—R^2$ (%)	R^2I (%)	TON[d]
			L[c]	mol %					
1-i	PhZnBr(LiBr)	p-Tol-I	A	10^{-4}	23	14	52	46	
	PhZnBr(LiBr)	p-Tol-I	A	10^{-4}	70	4	70	28	
	PhZnBr(LiBr)	p-Tol-I	A	10^{-4}	70	10	70	26	7.0×10^5
1-ii	PhZnBr(LiBr)	p-Tol-I	A	2×10^{-5}	23	13	51[e]	48	
	PhZnBr(LiBr)	p-Tol-I	A	2×10^{-5}	70	7	69[e]	29	
	PhZnBr(LiBr)	p-Tol-I	A	2×10^{-5}	70	10	69[e]	28	3.5×10^6
2-i	Hex∕∖ZnBr(LiBr)	PhI	A	10^{-4}	23	15	54	45	
	Hex∕∖ZnBr(LiBr)	PhI	A	10^{-4}	70	3	64	31	
	Hex∕∖ZnBr(LiBr)	PhI	A	10^{-4}	70	9	65	29	6.5×10^5
2-ii	Hex∕∖ZnBr(LiBr)	PhI	A	10^{-5}	70	10	65[e]	30	6.5×10^6
3-i	PhZnBr(LiBr)	Hex∕∖I	A	10^{-4}	23	15	70	28	
	PhZnBr(LiBr)	Hex∕∖I	A	10^{-4}	70	10	82	14	8.2×10^5
3-ii	PhZnBr(LiBr)	Hex∕∖I	A	2×10^{-5}	23	15	60[e]	37	
	PhZnBr(LiBr)	Hex∕∖I	A	2×10^{-5}	70	10	66[e]	28	3.3×10^6
4-i	Oct∕∖ZnBr(LiBr)	Hex∕∖I	A	10^{-4}	23	15	79[f]	18	7.9×10^5
4-ii	Oct∕∖ZnBr(LiBr)	Hex∕∖I	A	5×10^{-5}	23	14	56[f]	43	
	Oct∕∖ZnBr(LiBr)	Hex∕∖I	A	5×10^{-5}	55	10	63[f]	32	1.3×10^6
5-i	Hex—≡—ZnBr(LiBr)	PhI	B	10^{-3}	23	13	96	<1	
5-ii	Hex—≡—ZnBr(LiBr)	PhI	B	2×10^{-5}	23	15	75	19	3.8×10^6
6-i	Ph—≡—ZnBr(LiBr)	Hex∕∖I	B	10^{-3}	23	15	96	<1	
6-ii	Ph—≡—ZnBr(LiBr)	Hex∕∖I	B	5×10^{-5}	23	15	82	6	1.6×10^6

[a] All reactions were initially run at 23 °C. In cases where substantial amounts of R^2I remained unreacted after 10−15 h, the reaction mixtures were then refluxed. Regardless of the amount of residual R^2I, the reactions were judged to be over if no detectable progress was observed during 24 h. In each case, the results of the final analysis by GLC are presented. [b] $R^1ZnX(LiX)$ indicates that it was generated in situ by treating R^1Li with dry ZnX_2. [c] Legend: **A** = dppf = 1,1′-bis(diphenylphosphino)ferrocene; **B** = DPEphos = bis(o-(diphenylphosphino)phenyl) ether. Other Pd−phosphine complexes, such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $Pd(TFP)_2Cl_2$, were also examined, but the results obtained with them were uniformly inferior to or at best comparable with those reported. [d] Listed only for those cases where the yield of $R^1−R^2$ exceeds 60%. [e] Only THF was used as the solvent, whereas THF−Hex mixed solvent was used in all the other entries. [f] Only DMF was used as solvent.

of parameters and conditions. (2) One notable and intuitively expected finding is that certain bidentate phosphines, specifically dppf (1,1′-bis(diphenylphosphino)ferrocene)[7] and DPEphos (bis(o-(diphenylphosphino)phenyl) ether),[8] are consistently superior to some of the widely used monodentate phosphines, including PPh_3 and TFP (tris(o-furyl)phosphine),[9] at low catalyst loading levels.[10] Although not listed in Table 1, all catalysts containing any of the above-mentioned phosphines led to ≥90−95% product yields for all six reactions in Table 1 at the 1−5 mol % catalyst loading level. (3) Effects of solvents on product yield−TON are also noticeable. It was necessary in some cases to evaporate THF−hexane, the latter of which was introduced as a solution of ^{t}BuLi in hexane, and use pure THF for observing $>10^6$ TONs accompanied by >60% product yields. Although not listed in Table 1, the use of $Ni(PPh_3)_2Cl_2$ in the reaction of PhZnBr(LiBr) with p-Tol-I was also briefly investigated.[11] The desired biaryl was obtained in 98% yield with 1 mol % of the Ni catalyst. However, the yield decreased to 49% (24 h at 70 °C) at the 0.1 mol % level.

Table 2. High Turnover Numbers Observed in Hydrometalation−Cross-Coupling Tandem Reactions Producing Conjugated (E,E)-Dienes[a]



entry	ML_n	additive	solvent	 (%)	 (%)	TON
1		2 CsF	toluene	65	28	6.5×10^4
2	Al^iBu_2	$ZnBr_2$	THF-Hex.	62	28	6.2×10^4
3	$ZrCp_2Cl$	$ZnBr_2$	THF-Hex.	60	34	6.0×10^4

[a] Little or no further reaction was observed during the 15−24 h period in each case. [b] dppf = 1,1′-bis(diphenylphosphino)ferrocene.

Having adopted a practical procedure for determining product yield−TON, which provide a more sensitive and meaningful means of comparing various protocols of Pd- or Ni-catalyzed cross-coupling than mere comparison of product yields, we then compared various metal countercations in (i) aryl−aryl coupling, (ii) alkenyl−alkenyl coupling, and (iii) alkynyl−alkenyl coupling. For each metal countercation, efforts were made to choose the most favorable additives and solvents known in the literature.[1] For the reaction of phenylmetals with p-Tol-I, the three most widely used metals, i.e., Zn, B, and Sn, as well as Mg were screened and compared. At the catalyst loading level of 1 mol %, all reactions except that of PhMgCl[12] produced the desired biaryl in ≥95% yields with PPh_3, dppf, and DPEphos as phosphine ligands. Thus, they all appeared comparably effective. At the lower catalyst loading levels, however, effects of phosphines, additives, and solvents on product yield−TON were noticeable. In the reaction of $PhSnBu_3$ with p-Tol-I, addition of CsF and use of DMF are effective for achieving higher product yield−TON, and dppf is superior to PPh_3. Under the conditions employed, however, the TON for this reaction was limited to below 5.0×10^3. The reaction of $PhB(OH)_2$ was considerably more favorable than that of $PhSnBu_3$. Using $Pd(dppf)Cl_2$, CsF, and toluene, a TON of 6.8×10^4 was observed. As in many other reactions discussed in this paper, the sum of the desired product and the remaining p-Tol-I exceeded 90%. It is therefore entirely possible that further optimization of ligands, additives, and solvents might lead to higher TONs. In the cross-coupling between (E)-1-decenylmetals and (E)-1-octenyl iodide, it was hoped to observe high product yield−TON in the hydrometalation−cross-coupling tandem processes. We therefore examined B, Al, and Zr, and the results are summarized in Table 2.

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(10) Use of bidentate and tetradentate phosphines for observing high TON has been previously reported.[3c−e]

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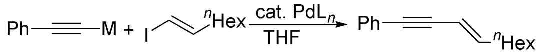
(12) The yield observed with PhMgCl was 83%.

Table 3. Comparison of Metal Countercations in the Pd-Catalyzed Reaction of (Phenylethynyl)metals with (*E*)-1-Octenyl Iodide[a]



entry	M of PhC≡CM	amt of PdL_n[b] (mol %)	temp (°C)	time (h)	product (%)	iodide (%)	TON[c]
1-i	H(CuI)[d]	10^{-1}	23	10	92	<1	9.2×10^2
1-ii	H(CuI)[d]	10^{-3}	reflux	24	32	65	
1-iii	H(CuI)[e]	10^{-3}	reflux	24	56	40	
2-i	$SnBu_3$	5	23	10	85	<1	1.7×10
2-ii	$SnBu_3$	10^{-1}	reflux	24	67	9	6.7×10^2
2-iii	$SnBu_3$	10^{-2}	reflux	24	26	58	
3-i	MnCl	5	23	4	92	<1	1.8×10
3-ii	MnCl	10^{-1}	reflux	24	69	17	6.9×10^2
3-iii	MnCl	10^{-2}	reflux	24	48	35	
4-i	MgBr	10^{-1}	23	10	85	<1	8.5×10^2
4-ii	MgBr	10^{-3}	reflux	24	55	40	
5-i	BL_n[f]	10^{-1}	reflux	24	93	1	9.3×10^2
5-ii	BL_n[f]	10^{-3}	reflux	24	81	10	8.1×10^4
6-i	In	10^{-1}	23	10	93	<1	9.3×10^2
6-ii	In	10^{-3}	reflux	24	84	1	8.4×10^4

[a] See footnote *a* in Table 1. [b] PdL_n = $Pd(DPEphos)Cl_2$, where DPEphos is bis(*o*-(diphenylphosphino)phenyl) ether. [c] See footnote *d* in Table 1. [d] Et_2NH used as solvent. [e] Cs_2CO_3 used as an additive. [f] BL_n = *B*-MeO-9-BBN.

All three hydrometalation−cross-coupling tandem reactions involving B, Al, and Zr produced the desired conjugated diene (>98% *E,E*) in 92−95% yields at the catalyst loading level of 10^{-1} mol %. Even at the 10^{-3} mol % catalyst loading level, all of these metals exhibited TONs of (6.0−6.5) × 10^4 accompanied by 60−65% product yields (Table 2).

In the case of alkynyl−alkenyl coupling, the previously reported inability of Li to serve as a satisfactory countercation under the catalytic conditions[14] was confirmed for the reaction of PhC≡CLi with (*E*)-ⁿHexCH=CHI in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ or $Pd(DPEphos)Cl_2$ (≤5% yields). Six metal countercations, including the widely used Cu (used as a cocatalyst in the Sonogashira reaction[15]), Mg,[14,16] B,[14,16] and Sn[14,16] as well as the recently introduced In[13] and Mn,[17] were compared with Zn in the reaction of PhC≡CM with (*E*)-ⁿHexCH=CHI. All six metals were shown to be very satisfactory at the catalyst loading level of 1−5 mol % (>85−95% product yields). As summarized in Table 3, the Sonogashira coupling[15] can proceed very satisfactorily at the catalyst loading level of 0.1 mol % (entry 1-i).

Table 4. Pd-Catalyzed Reaction of Phenylmetals Containing Zn and Mg with *p*-Tolyl Iodide and Bromide in THF[a]

entry	M of PhM[b]	X of *p*-TolX	L_n of PdL_nCl_2	mol %	temp (°C)	product (%)	*p*-TolX (%)	TON
1	ZnBr(LiBr)	I	dppf	10^{-1}	23	99	<1	9.9×10^2
2-i	ZnBr(MgClBr)	I	dppf	10^{-1}	23	98	1	9.8×10^2
2-ii	ZnBr(MgClBr)	I	dppf	10^{-3}	reflux	65	30	6.5×10^4
3-i	ZnBr(LiBr)	Br	$(PPh_3)_2$	5	reflux	95	2	19
3-ii	ZnBr(LiBr)	Br	$(PPh_3)_2$	10^{-1}	reflux	21	75	
4	ZnBr(LiBr)	Br	dppf	10^{-1}	reflux	25	70	
5-i	ZnBr(MgClBr)	Br	dppf	10^{-1}	23	96	1	9.6×10^2
5-ii	ZnBr(MgClBr)	Br	dppf	10^{-2}	reflux	83	7	8.3×10^3
5-iii	ZnBr(MgClBr)	Br	dppf	10^{-3}	reflux	26	70	−
6-i	MgCl	Br	DPEphos	10^{-1}	23	96	2	9.6×10^2
6-ii	MgCl	Br	DPEphos	10^{-2}	reflux	61	34	6.1×10^3
7	MgCl	Br	dppf	10^{-2}	reflux	61	34	6.1×10^3
8-i	MgCl	I	DPEphos	5	23	83	7	17
8-ii	MgCl	I	DPEphos	10^{-1}	reflux	22	38	
8-iii	MgCl	I	dppf	10^{-1}	reflux	29	50	

[a] All reactions were initially run at 23 °C for 20 h. In cases where >5% of the starting aryl halide remained unreacted, the reaction mixture was refluxed for up to 24 h. The yields were determined by GLC with a hydrocarbon internal standard. [b] $PhLi + ZnBr_2 \rightarrow PhZnBr(LiBr)$; $PhMgCl + ZnBr_2 \rightarrow PhZnBr(MgClBr)$.

However, satisfactory results could not be observed at the level of 10^{-3} mol % (entries 1-ii and 1-iii). Even less satisfactory was the reaction of $PhC{\equiv}CSnBu_3$, in which the maximum TON was limited to 670 (entry 2-ii). Similar results were obtained with PhC≡CMnCl(MgBrCl) (entries 3-i−3-iii). Despite its intrinsic limitation associated with low chemoselectivity, Mg was somewhat more satisfactory than Cu, Sn, and Mn at the 10^{-3} mol % level (entries 4-i and 4-ii). In contrast with these metals, both B (entries 5-i and 5-ii, TON = 8.1×10^4) and In (entries 6-i and 6-ii, TON = 8.4×10^4) proved to be satisfactory. Although no further attempts were made, the maximum TONs accompanied by >70% product yields observable in these reactions should surpass 10^5.

All results presented above were obtained with aryl and alkenyl iodides. For economic and other reasons, it is desirable to use the corresponding bromides, especially aryl bromides. In general, however, the Pd-catalyzed cross-coupling reactions of organic bromides have been found to be more sluggish and, hence, less favorable than the corresponding reactions of organic iodides.[1] With the ultimate goal of developing high-yield−high-TON reactions of bromides, we first chose to investigate the reaction of phenylzinc halides and phenylmagnesium halides with *p*-tolyl bromide and iodide in some detail and found some striking and unexpected results, which are summarized in Table 4. The following are particularly noteworthy.

(1) With 0.1 mol % of $Pd(dppf)Cl_2$, both PhZnBr(LiBr) derived from PhLi and PhZnBr(MgClBr) derived from PhMgCl reacted cleanly with *p*-TolI to give the desired biaryl in ≥98% yields (entries 1 and 2-i). Whereas PhZnBr(MgClBr) also reacted well with *p*-TolBr (entry 5-i), the maximum product yield observed in the reaction of PhZnBr(LiBr) with *p*-TolBr was ≤25% (entries 3-ii and 4). For the former reaction, a TON of 8.3×10^3 accompanied by 83% yield was observed (entry 5-ii).

(2) At the catalyst loading level of 0.1 mol %, the reaction of PhMgCl with *p*-TolBr is highly satisfactory, producing the desired biaryl in 96% yield (entry 6-i), and the maximum TON of 6.1×10^3 accompanied by 61% product yield with either DPEphos or dppf as a ligand was observed (entries 6-ii and 7). Although the reaction of PhMgCl with *p*-TolI in the presence of 5 mol

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Table 5. Reaction of PhZnBr(LiBr), PhZnBr(MgClBr), and PhMgCl with (*E*)-1-Octenyl Bromide and Iodide in the Presence of 0.1 mol % of Pd(dppf)Cl_2 in THF[a]

entry	M of PhM	X	temp. (°C)	time (h)	prod. (%)	halide (%)	dimer[b] (%)
1	ZnBr(LiBr)	I	23	20	99	0	0
2	ZnBr(LiBr)	Br	reflux	24	14[c]	74	6
3	ZnBr(MgClBr)	I	23	20	96	3	<1
4	ZnBr(MgClBr)	Br	23	20	98	2	0
5	MgCl	I	reflux	24	44[d]	30	16
6	MgCl	Br	23	20	95	2	2

[a] All reactions were initially run at 23 °C for 20 h. In cases where >5% of the starting alkenyl halide remained unreacted, the reaction mixture was refluxed for up to 24 h. The yields were determined by GLC with a hydrocarbon internal standard. [b] dimer = (*E*,*E*)-7,9-hexadecadiene. [c] The product yield after 20 h at 23 °C was 2%, with 98% of the starting bromide remaining unreacted. [d] The yield after 20 h at 23 °C was 40%, the amounts of the starting iodide and the (*E*,*E*)-7,9-hexadecadiene being 38% and 13%, respectively.

% of phosphine was satisfactory (entry 8-i), it was rather unsatisfactory at the 0.1 mol % level, and toluene was a noticeable byproduct (entry 8-ii). The use of dppf led to similarly disappointing results (entry 8-iii).

(3) Those unexpected "mismatch" cases presented above (entries 3-ii and 4 as well as 8-ii and 8-iii) should be clearly noted. Whereas PhZnBr(MgClBr) reacts well with either *p*-Tol-I or *p*-TolBr, PhZnBr(LiBr) and *p*-TolBr as well as PhMgCl and *p*-TolI represented "mismatches" to be avoided. In contrast to the widely held generalization, *p*-TolBr reacts better with PhMgCl than *p*-Tol-I does (entries 6−8).

Although it is still premature to consider those unexpected results and trends shown in Table 4 to be generally observable, the results presented in Table 5 strongly support further the generalization presented above and help delineate the scope of R^1ZnBr(LiBr) − R^2Br and R^1MgCl−R^2I "mismatch" cases to be avoided.

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Supporting Information Available: Text giving detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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