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Iron−Phosphine, −Phosphite, −Arsine, and −Carbene Catalysts for the Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents

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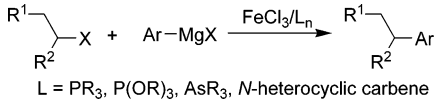
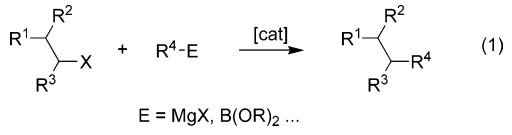


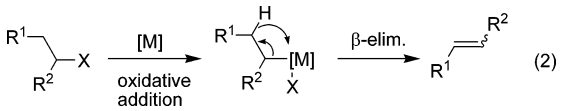
Simple catalysts formed in situ from iron chloride and a wide range of monodentate and bidentate phosphines and arsines have been screened in the coupling of alkyl halides bearing β-hydrogens with aryl Grignard reagents. The best of these show excellent activity, as do catalysts formed in situ with monodentate trialkyl and triaryl phosphite ligands. *N*-heterocyclic carbene-based precatalysts, either preformed or made in situ, also show excellent performance.

Introduction

Coupling reactions leading to the formation of new C−C bonds, typically catalyzed by ubiquitous palladium complexes, form the bedrock of many contemporary syntheses.[1] Despite the undoubted usefulness of such processes, there are still holes in the general methodologies available currently that can limit applicability. Intense research is focused on addressing these shortcomings, and the past few years have seen substantial advances. One major class of substrate that has proved particularly problematic in cross-coupling reactions are primary and secondary alkyl halides bearing β-hydrogens (eq 1).



The uncatalyzed reactions are difficult or impossible due to the exacting requirements of nucleophilic substitution versus elimination, whereas the catalyzed reactions are plagued by β-elimination (eq 2), which tends to give only the corresponding alkene.[2]



Recent studies show that the problem of β-elimination is surmountable. For instance Ni and Pd complexes have been shown to catalyze the coupling of primary alkyl halide substrates with appropriate nucleophilic coupling partners,[2] while Co,[3] Ni,[4] and Fe[5,6] catalysts have all recently shown activity in coupling reactions of both primary and secondary alkyl substrates, typically without the formation of large amounts of β-eliminated byproduct. Building on the seminal observations of Kochi that iron catalysts can be employed in cross-coupling reactions,[7] there

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(1) Reviews: (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (b) *Cross-Coupling Reactions*; Miyaura, N., Ed.; Topics in Current Chemistry Vol. 219; Springer: New York, 2002.

(2) For reviews see: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (b) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (c) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384. (d) Luh, T.-Y.; Leung, M.-k.; Wong, K. T. *Chem. Rev.* **2000**, *100*, 3187.

(3) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137.

(4) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

(5) Nagano, T.;. Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.

(6) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686.

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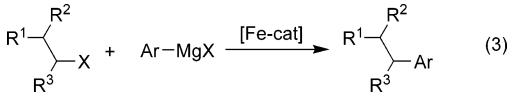
TABLE 1. Coupling of 4-Tolylmagnesium Bromide with Cyclohexyl Bromide Catalyzed by Iron Catalysts with Monodentate Phosphines, Phosphites, and Arsines[a]

			conversion to given compound[b] (%)				
entry	iron chloride	ligand (2 equiv)	**1**	**2**	**3**	**4**	**5**
1	$FeCl_3$	PPh_3	72	2	0	1	6
2	$FeCl_2$		81	3	0	7	7
3	$FeCl_3$	PCy_3	87	6	0	3	8
4	$FeCl_2$		68	0	0	3	16
5	$FeCl_3$	P(*o*-tolyl)$_3$	53	1	0	0	6
6		PCy_2(*o*-biphenyl)	27	2	0	0	26
7		P^tBu_2(*o*-biphenyl)	35	3	0	1	14
8		$AsPh_3$	82	0	1	0	8
9		$P(OPh)_3$	67	10	0	8	16
10		$P(OC_6H_3\text{-}2,4\text{-}^tBu_2)_3$	82	7	0	3	8
11		$P(OMe)_3$	83	0	0	1	13
12		$P(OEt)_3$	69	5	0	6	9
13		$P(O^iPr)_3$	83	4	0	2	8

[a] Conditions: $FeCl_3$ (0.05 mmol); ligand (0.2 mmol); CyBr (1.0 mmol); MeC_6H_4MgBr (2.0 mmol); Et_2O; reflux, 30 min. [b] Conversion to products **1**−**5** determined by GC (mesitylene internal standard).

are several particularly notable reports of the use of iron precatalysts in the cross-coupling of both primary and secondary alkyl halides with aryl Grignard reagents (eq 3).



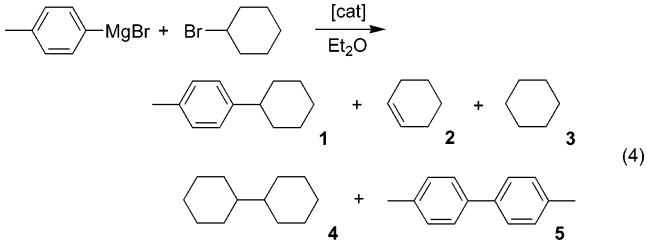
(3)

Nagano and Hayashi showed that $[Fe(acac)_3]$ can be used to good effect,[5] while Martin and Fürstner showed the ferrate complex $[Li(tmeda)_2][Fe(C_2H_4)_4]$ (tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) to be an effective precursor in the coupling of a large range of alkyl halides with diverse functionality.[8] We found that simple iron−salen type complexes can also be exploited.[9] Nakamura and co-workers demonstrated that iron(III) chloride can be employed in the presence of appropriate amines, typically tmeda.[6] While this latter method is particularly attractive due to the simplicity and low cost of the catalyst and the excellent results obtained, as reported it suffered from three major limitations. First, a greater than stoichiometric amount of amine is required, which needs to be added with the Grignard reagent. Second, the Grignard/amine mixture must be added very slowly via the use of a syringe pump and, third, the reactions must be cooled to low temperatures. We subsequently found that all these problems are surmountable: amines can be used in catalytic quantities, the reactions can be performed at elevated temperatures, and there is no requirement for slow addition of the Grignard reagent.[10] The data we obtained with a variety of amines under our conditions provide a significant contrast with the work of Nakamura and co-workers, strongly suggesting that *different catalytic manifolds are operative*, despite the apparent similarity in precatalyst composition.

Nakamura et al. reported that phosphine ligands proved ineffective under their conditions.[6] Given the significant changes in performance observed with the same amine ligands under different reaction conditions, we wondered whether phosphine ligands may actually prove effective under a modified protocol. This indeed turns out to be the case, and we report below the use of simple iron−phosphine, −phosphite, −arsine, and −carbene precatalysts for the coupling of primary and secondary alkyl halides bearing β-hydrogens with aryl Grignard reagents.

Results and Discussion

Phosphine, Phosphite, and Arsine Ligands. For the initial screening of catalyst performance, we chose the reaction outlined in eq 4 as a typical example of aryl Grignard−secondary alkyl coupling. Table 1 shows the conversions to the desired coupled product **1** along with the formation of the β-elimination product, cyclohexene (**2**); the hydrodehalogenated product, cyclohexane (**3**); and the two homo-coupled products, dicyclohexane (**4**) and 4,4′-bitolyl (**5**) with a range of monodentate phosphine and phosphite ligands with both iron(III) and iron(II) chloride. The iron chloride and ligand were mixed in dichloromethane for 2 min before addition to the reaction flask.[11] The solvent was then removed in vacuo, and diethyl ether was added as the solvent for the catalytic reaction.



(4)

Comparing entries 1 and 2, it can be seen that iron(II) chloride gives a slightly higher conversion to the coupled product than iron(III), but at the expense of selectivity; greater relative amounts of homocoupled products **4** and **5** are produced. With tricyclohexylphosphine the iron(III) chloride shows better performance than iron(II) (entries 3 and 4), both in terms of conversion to the desired product and relative amounts of side products formed. For these reasons the rest of the studies with in situ formed catalysts were performed using iron(III) chloride. Tri-*o*-tolylphosphine (entry 5) is less effective then either PPh_3 or PCy_3. The dialkyl *o*-biphenylphosphine ligands tested did not prove to be particularly effective (entries 6 and 7); indeed

(7) Selected reviews: (a) Kochi, J. K. *J. Organomet. Chem.* **2002**, *653*, 11. (b) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351.

(8) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955.

(9) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822.

(10) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161.

(11) We have found that adding the catalysts as a dichloromethane solution can lead to an enhancement in activity, even for preformed catalysts. See ref 9.

TABLE 2. Coupling of 4-Tolylmagnesium Bromide with Cyclohexyl Bromide Catalyzed by Iron Catalysts with Bidentate Phosphine and Arsine Ligands[a]

		conversion to given compound[b] (%)				
entry	ligand (1 equiv)	**1**	**2**	**3**	**4**	**5**
1	$Ph_2PCH_2PPh_2$	60	2	0	2	4
2	$Ph_2P(CH_2)_2PPh_2$	66	1	0	1	5
3	$Ph_2P(CH_2)_3PPh_2$	88	4	0	1	7
4	$Ph_2P(CH_2)_4PPh_2$	75	4	0	0	5
5	$Ph_2P(CH_2)_5PPh_2$	87	2	0	0	2
6	$Ph_2P(CH_2)_6PPh_2$	91	2	0	0	8
7	*cis*-$Ph_2P(CH{=}CH)PPh_2$	82	7	0	5	14
8	*trans*-$Ph_2P(CH{=}CH)PPh_2$	30	6	0	7	17
9	$Ph_2AsCH_2AsPh_2$	82	2	0	0	10
10	DPPF[c]	0	0	0	0	5

[a] Conditions: As in Table 1. [b] Conversion to products **1**−**5** determined by GC (mesitylene internal standard). [c] DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

the activity is lower than that obtained with iron(III) chloride in the absence of added ligand, which gives 39% conversion to the desired product **1**.[10] Interestingly, triphenylarsine performs better than triphenylphosphine under identical conditions (compare entries 1 and 8). Looking across the data for all the monodentate phosphine and arsine donors, there does not seem to be a specific trend obvious from electronic or steric perspectives.

Phosphite ligands can also be employed to good effect. Comparing entries 9 and 10, it can be seen that increasing the bulk of triaryl phosphite ligand has a beneficial effect on both activity and selectivity. By contrast there does not appear to be such a trend with trialkyl phosphites; while both trimethyl phosphite and triisopropyl phosphite perform well, lower performance is seen with triethyl phosphite (entries 11−13).

Table 2 summarizes the data obtained for the coupling outlined in eq 4 using bis-phosphine and arsine ligands. As can be seen, increasing the chain length of the alkyl spacer in the bidentate phosphines $Ph_2P(CH_2)_nPPh_2$ (n = 1−6) leads to a general increase in conversion to the desired coupled product (entries 1−6), although 1,3-bis(diphenylphosphino)propane shows higher activity than anticipated from the trend. The structurally rigid ligand *cis*-$Ph_2P(CH{=}CH)PPh_2$ shows greater activity than its more flexible alkyl counterpart $Ph_2P(CH_2)_2PPh_2$ (compare entries 2 and 7) but at the expense of selectivity. Perhaps unsurprisingly, given its inability to form chelates, the alternate isomer *trans*-$Ph_2P(CH{=}CH)PPh_2$ performs particularly badly (entry 8). Again the activity here is lower than that observed in the absence of added ligand.[10] Interestingly, the bidentate arsine ligand $Ph_2AsCH_2AsPh_2$ fares somewhat better than its phosphine counterpart (compare entries 1 and 9) in line with the result obtained with triphenylarsine.

The catalyst formed in situ from $FeCl_3$ and DPPF (1,1′-bis(diphenylphosphino)ferrocene) shows no activity (entry 10). It is interesting to note that while all of the other reactions turn very dark brown to black on addition of the Grignard, there is no significant color change in this case, other than a slight darkening of the yellow color obtained on mixing the ligand and the iron chloride. The lack of activity with DPPF is perhaps surprising considering that this ligand is particularly effective in the palladium- and nickel-catalyzed coupling of aryl Grignard reagents with aryl halides.[12] This inactivity may be a consequence of the fact that in this case coupling probably proceeds via a radical pathway rather than a classical oxidative−addition/reductive elimination manifold (vide infra); the presence of two potentially interacting redox centers may conceivably act to switch off such a process.

It is interesting to note that we observe essentially no formation of cyclohexane (3) in any of the reactions with phosphine, arsine or phosphite ligands.[13] This is in contrast with the use of either the catalysts formed in situ from $FeCl_3$ with amine ligands or preformed iron(III) salen-type precatalysts.[9,10]

Having established that tricyclohexylphosphine, tris(2,4-di-*tert*-butylphenyl)phosphite, and 1,6-bis(diphenylphosphino)-hexane show essentially the best activity in the test reaction, we next examined their performance in the coupling of a range of primary and secondary alkyl halides with aryl Grignard reagents. The results from this study are summarized in Table 3. In some cases, isolated products could not be obtained pure, even after two consecutive chromatographic separations.

Comparing entries 1−3, it can be seen that better conversion to the desired product is typically obtained when cyclohexyl bromide is used rather than the chloride or iodide counterparts, irrespective of the choice of catalyst. The general trend appears to be Br > I > Cl. This is the same pattern that we have observed previously with Fe−salen systems under similar conditions.[9] Hayashi observed a similar trend using [Fe(acac)$_3$] (acac = acetylacetonato),[5] while the use of Fe−amine systems tends to give the trend I > Br > Cl irrespective of Fe/amine stoichiometry or conditions.[6,10] Increasing the nucleophilicity of the Grignard reagent (entry 4) leads to a slight decrease in conversion; in this case the least electron-donating, triaryl phosphite ligand shows a marked improvement in performance over the other two systems.

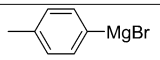
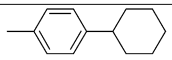
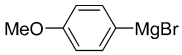
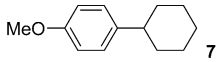
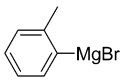
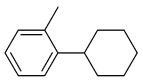
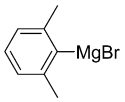
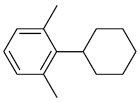
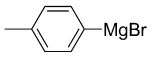
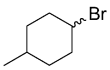
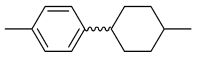
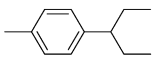
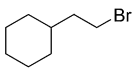
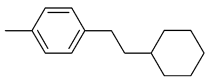
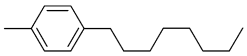
Increasing the steric bulk of the Grignard reagent is deleterious to the reaction with *o*-tolylmagnesium bromide, giving significantly reduced conversion to the coupled product (entry 5). Again the triaryl phosphite ligand proves to be most effective in this instance. When the steric hindrance is increased further by the use of (1,3-dimethylphenyl)magnesium bromide, then no reaction is observed (entry 6). We have previously found both Fe−amine and Fe−salen systems to be ineffective in this reaction,[10,9] and to the best of our knowledge there are no reports of the coupling of such sterically hindered, di-ortho-substituted aryl Grignard reagents with secondary alkyl halides.[14] This is an area that obviously needs further attention in the future.

The coupling of 4-methylcyclohexyl bromide with 4-tolylmagnesium bromide (entry 7) leads to the formation of both cis and trans isomers of the coupled product **10**, with a similar

(12) See, for example: Togni, A.; Hayashi, T. *Ferrocene*−Homogeneous Catalysis, Organic Syntheses and Materials Science; VCH: Weinheim, Germany, 1995; Parts 1 and 2.

(13) At most we see trace amounts by GC, representing much less than 1% conversion.

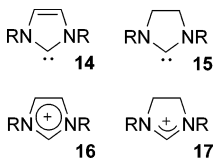
TABLE 3. Coupling of Alkyl Halides with Aryl Grignards Using PR_3 as Ligand[a]

Entry	Aryl Grignard	Alkyl halide	Product	Conversion [b] [isolated yield] [c] (%) with ligand 2 PCy_3	$Ph_2(CH_2)_6PPh_2$	2 $P(OC_6H_3\text{-}2,4\text{-}^tBu_2)_3$
1			 **6**	75	81	85
2				85	85	88
3				63	66 [51]	58
4			 **7**	76	70	88 [74]
5			 **8**	44	31	60 [49] [d]
6			 **9**	0	0	0
7			 **10**	72 (*cis*:*trans* = 32:68)	78 (*cis*:*trans* = 29:71) [72]	70 (*cis*:*trans* = 33:67)
8			 **11**	41	38	47 [43] [e]
9			 **12**	64	64	65 [47] [f]
10		Br−^{n}octyl	 **13**	71 [51]	48	58

[a] Conditions: Alkyl halide (2.0 mmol), ArMgBr (4.0 mmol), $FeCl_3$ (0.1 mmol), ligand (0.1 or 0.2 mmol), Et_2O, reflux. [b] Conversion to coupled product determined by ^1H NMR spectroscopy (mesitylene internal standard). [c] Isolated by column chromatography. [d] Product could not be separated from bicyclohexyl side product. [e] Product contains 2,4-di-*tert*-butylphenol, tris(2,4-di-*tert*-butylphenyl)phosphite, and 3-bromopentane. [f] Contains 2,4-di-*tert*-butylphenol.

ratio in all cases; the trans isomer is the preferred product. The use of open-chain alkyl bromides leads to a decrease in conversion to the desired coupled products, with secondary alkyl bromides faring worse than primary substrates (entries 8−10).

Carbene Ligands. Palladium complexes with *N*-heterocyclic carbene ligands **14** and **15**, have proved useful in palladium-based coupling reactions of alkyl halide substrates.[15] While such catalysts can be preformed, they are often formed in situ by deprotonation of the corresponding imidazolium or related salts (**16** and **17**).



Given the success enjoyed with phosphine, phosphite, and arsine ligands, we were keen to see whether carbene ligands would prove useful in the coupling of alkyl halides with aryl Grignard reagents. The results from a survey of activity with varying carbene ligands in the reaction outlined in eq 4 (above) are collected in Table 4. Preformed carbene adducts of iron−halides remain rare; one recently published example is the "CNC"−pyridyl bis(carbene) pincer complex **18**.[16] This shows excellent activity in the test reaction (entry 1), comparable with some of the best phosphine-, phosphite-, and arsine-containing systems outlined above. The *N*,*N*-dicylcohexyl-substituted carbene formed in situ from the salt **17a** shows a good conversion to the coupled product (entry 2) and the di-*tert*-butyl analogue formed from **17b** displays excellent activity (entry 3). The conversion obtained here is even higher than those obtained using the best phosphine-, phosphite-, and arsine-containing systems. The carbenes formed from the *N*,*N*-diaryl-substituted salts **17c**,**d** show somewhat lower activity (entries 4 and 5) than their alkyl-substituted counterparts.

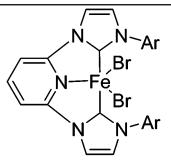
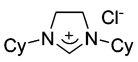
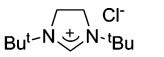
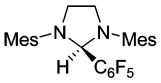
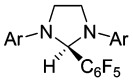
In the examples listed in entries 2−4 we are relying on in situ deprotonation of the ligand precursor to yield the free carbene. We could use the free carbenes themselves, but this can lead to problems with handling due to their air and moisture

(14) Hayashi and co-workers demonstrated that the similarly sized mesitylmagnesium bromide is able to react with a *primary* alkyl halide. See ref 5.

(15) (a) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805. (b) Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 351. (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (d) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642. (e) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403. (f) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945.

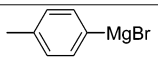
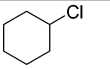
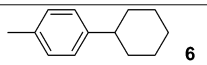
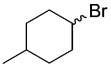
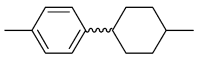
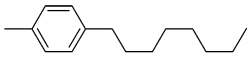
(16) Danopoulos, A. A.; Tsoureas, N.; Wright, J.; Light, M. *Organometallics* **2004**, *23*, 166

TABLE 4. Coupling of 4-Tolylmagnesium Bromide with Cyclohexyl Bromide Catalyzed by Iron Catalysts with Carbene Ligands[a]

Entry	Catalyst	Conversion to 1	2	3	4	5 (%) [b]
1	 **18:** Ar = C_6H_3-2,6-$^iPr_2$	94	0	0	1	10
2	*$FeCl_3$ + 2 equiv of:*  **17a**	87	2	0	1	11
3	 **17b**	97	1	0	1	15
4	 **17c**	45	1	0	1	5
5	 **19a**	67	4	0	6	9
6	 **19b:** Ar = C_6H_3-2,6-$^iPr_2$	94	4	0	1	10

[a] Conditions: As in Table 1. [b] Conversion to products **1**−**5** determined by GC (mesitylene internal standard).

TABLE 5. Coupling of Alkyl Halides with Aryl Grignards Using Carbenes as Ligands[a]

Entry	Aryl Grignard	Alkyl halide	Product	Conversion (%) with catalyst **18**	Conversion (%) with catalyst $FeCl_3$ + 2 **17b**
1			 **6**	-	73
2			 **10**	89 [b]	81 [c]
3		Br-^{n}octyl	 **13**	71	-

[a] Conditions: As for Table 3. [b] Trans:cis = 69:31. [c] Trans:cis = 70:30.

sensitivity. Instead we opted to examine the use of neutral carbene precursors that form carbenes by thermal decomposition under mild conditions rather than deprotonation. Waymouth and co-workers very recently showed that the 2-(pentafluorophenyl)-imidazolidine **19a** can be used as a simple, air-stable precursor for the synthesis of both the free carbene and a carbene adduct of allylpalladium chloride under mild thermolytic conditions, via loss of pentafluorobenzene.[17] Subsequently we showed that both **19a**,**b** can be used to form carbene adducts of phosphite-based palladacycles.[18] The catalysts formed in situ from **19a** show enhanced performance compared with that formed from the salt **17c** (compare entries 4 and 5). Increasing the steric bulk of the *N*-aryl substituent leads to a substantial increase in performance, with **19b** showing excellent activity. Interestingly, it appears that the carbene precursors **19a**,**b** react with iron(III) chloride even at room temperature in dichloromethane; the reactions are accompanied by a very rapid color change from yellow to orange-red.[19]

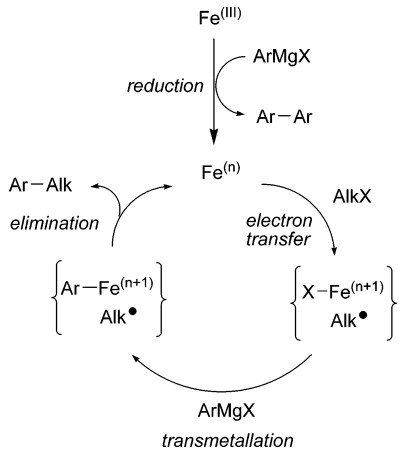
The preformed complex **18** and the catalyst formed in situ from iron(III) chloride and **17b** were then singled out for further brief testing with selected substrates; the results from this study are presented in Table 5. In the coupling of 4-tolylmagnesium bromide with either cyclohexyl chloride or 4-methylcyclohexyl bromide carbene catalysts are significantly more active than the best phosphine or phosphite systems (compare with Table 3),

(17) Nyce, G. W.; Csihony, S.; Waymouth, R. M.; Hedrick, J. L. *Chem. Eur. J.* **2004**, *10*, 4073.

(18) Bedford, R. B.; Betham, M.; Blake, M. E.; Frost, R. M.; Horton, P. N.; Hursthouse, M. B.; López-Nicolás, R.-M. *Dalton Trans.* **2005**, 2774.

(19) Investigations into the structures of the resultant complexes are ongoing within our group.

SCHEME 1. Simplified Radical Coupling Pathway



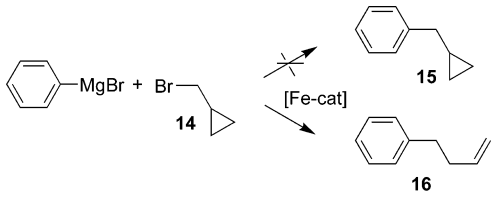
while the activity shown by **18** in the coupling with octyl bromide is comparable with the best phosphine (PCy_3). Interestingly, both the preformed pincer complex and the in situ formed precatalyst show very similar trans selectivities in the coupling of 4-methylcyclohexyl bromide with 4-tolylmagnesium bromide.

Mechanistic Considerations. For the coupling of alkenyl halides and Grignard reagents, Kochi proposed a "classical" coupling cycle based on oxidative addition of the alkenyl halide to an iron(I) center which generates an iron(III) alkenyl species, followed by transmetalation and reductive elimination of the product.[20] More recently Fürstner and co-workers have invoked an Fe(0)/Fe(II) couple in the reaction of aryl halides with Grignard reagents.[21] Hayashi and co-workers also favor a classical coupling mechanism for the coupling of alkyl halides with aryl Grignard reagents,[5] but evidence has been presented by both Nakamura and Fürstner to suggest that in this case the reaction may in fact proceed via a radical process.[6,8] In both cases this includes the observation that the coupling of resolved 2-bromooctane with PhMgBr leads to the formation of racemic product.

Scheme 1 shows a highly simplified representation of a possible radical-based coupling mechanism. The active iron species in oxidation state *n* reacts with the alkyl halide by the transfer of a single electron to generate an alkyl radical (via the intermediate formation of a radical anion) and an $[Fe^{(n+1)}X]$ species. It is possible that the alkyl radical is not free but rather associated with the iron center.[6] Transmetalation with the Grignard reagent generates an iron−aryl complex which is then attacked by the alkyl radical to give the product and active catalyst.

We have previously presented evidence that suggests that the coupling of alkyl halides with aryl Grignard reagents catalyzed by iron−amine-based systems proceeds via a radical pathway. To see whether a similar manifold is adopted by the systems reported here, we examined the use of representative catalysts formed in situ from $FeCl_3$ and PCy_3 or $P(OC_6H_2\text{-}2,4\text{-}{}^tBu_2)_3$ in the coupling of phenylmagnesium bromide with (bromomethyl)-cyclopropane, **14** (Scheme 2). If an oxidative addition pathway is operative, then it would be expected that the simple coupled product **15** would form.[22] However, this is not the case; instead

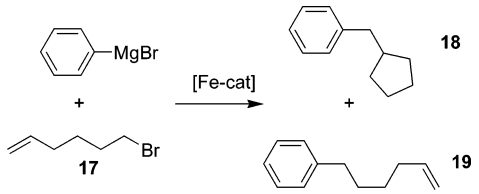
SCHEME 2. Coupling of PhMgBr with 14 Using Representative Catalysts[a]



Catalyst	Conv. to **16**, %[b]
$FeCl_3 + PCy_3$	54
$FeCl_3 + P\{OC_6H_3\text{-}2,4\text{-}{}^tBu_2)_3$	61

[a] Conditions: PhMgBr (4.0 mmol), **14** (2.0 mmol), Fe catalyst (5 mol %), Et_2O/THF (3:2), 45 °C (external temp), 30 min. [b]Conversion to **16** determined by ^1H NMR spectroscopy (mesitylene internal standard).

SCHEME 3. Coupling of PhMgBr with 17 Using Representative Catalysts[a]



Catalyst	Conv. to **18**, **19** %[b]
$FeCl_3 + 2\ PCy_3$	40, 23
$FeCl_3 + 2\ P\{OC_6H_3\text{-}2,4\text{-}{}^tBu_2)$	42, 25

[a] Conditions: PhMgBr (4.0 mmol), **17** (2.0 mmol), Fe catalyst (5 mol %), Et_2O/THF (3:2), 45 °C (external temp), 30 min. [b]Conversion to **18** and **19** determined by ^1H NMR spectroscopy (mesitylene internal standard).

the ring-opened product 4-phenylbutene, **16**, is obtained, lending support to a radical pathway.[23]

Further evidence in favor of an alkyl radical intermediate is provided by the reaction of phenylmagnesium bromide with 6-bromohexene, **17** (Scheme 3); this predominantly yields the ring-closed product **18** as well as the simple coupled product **19**.

In summary we have shown that iron catalysts with phosphine, phosphite, arsine, and carbene ligands are all active catalysts for the coupling of aryl Grignard reagents with primary and secondary alkyl halide substrates bearing β-hydrogens. Many of the catalysts examined show excellent activity. Representative examples of the catalysts give similar results in coupling experiments designed to highlight the intermediacy of radical species, implying similar manifolds in all cases. We are currently investigating the mechanism in greater depth and also probing whether common catalyst species are formed with differing ligands—for instance nanoparticulate iron species—and the results from this study will be published in due course.

Experimental Section

All catalytic reactions were performed on a Radleys Carousel reactor. This consists of 12 ca. 45 mL tubes which are fitted with screw-on Teflon caps that are equipped with valves for the introduction of inert gas and septa for the introduction of reagents. The 12 reaction tubes sit in two stacked aluminum blocks; the lower one fits on a heater-stirrer and can be maintained at a constant temperature with a thermostat, while the upper block has water

(20) Scott Smith, R.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502.
(21) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.
(22) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.
(23) For the use of (bromomethyl)cyclopropane as a probe of radical pathways in coupling reactions see: Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514, and references therein.

circulating which cools the top of the tubes, allowing reactions to be performed at reflux temperature.

General Method for the Coupling of 4-Tolylmagnesium Bromide with Bromocyclohexane (Tables 1, 2, and 4). The appropriate amount of phosphine, phosphite, arsine, or carbene ligand precursor in CH_2Cl_2 (2 mL) was added to anhydrous $FeCl_3$ (0.05 mmol) in a Radleys Carousel reaction tube, and then after standing (2 min) the solvent was removed in vacuo. In the reaction with complex **18**, the precatalyst was introduced as a CH_2Cl_2 (2 mL) solution and the solvent removed in vacuo. Et_2O (3 mL) was added, and the solution was stirred (∼2 min). CyBr (1.0 mmol) was added, and the solution stirred for 5 min and then heated to reflux temperature (external temperature 45 °C; reaction temperature ∼36−38 °C), and 4-MeC_6H_4MgBr (1.0 M solution in Et_2O, 2.0 mL) was added in one portion. The reaction was then heated for 30 min, quenched with H_2O (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), and dried ($MgSO_4$). Mesitylene (internal standard, 0.1439 M in CH_2Cl_2, 1.00 mL) was added, and the conversion to products **2**−**6** was determined by GC analysis.

General Method for the Coupling of Aryl Grignard Reagents with Alkyl Halides (Tables 3 and 5). The reactions were performed as above with appropriate alkyl halide (2.0 mmol), ArMgBr (4.0 mmol), and catalyst (5 mol % Fe). Reactions were quenched (H_2O, 5 mL), extracted with CH_2Cl_2 (3 × 5 mL), and dried ($MgSO_4$). Mesitylene (internal standard, 0.667 M CH_2Cl_2, 1.00 mL) was added; an aliquot (2 mL) was removed from which the solvent was removed at room temperature under reduced pressure. The residue was dissolved in $CDCl_3$ (∼0.7 mL), and the conversion to coupled product was determined by ^{1}H NMR spectroscopy. For selected examples of each reaction, the organic phases were recombined, the solvent removed in vacuo and the coupled product isolated by column chromatography (silica).

1-Cyclohexyl-4-methylbenzene, 6 (Table 3, Entry 3). Cyclohexane eluent. Colorless oil, 0.178 g (51%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (m, 5H, CH_2 of Cy), 1.81 (m, 5H, CH_2 of Cy), 2.30 (s, 3H, Me); 2.45 (m, 1H, CH of Cy); 7.08 (s, br, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.1, 26.4, 27.2, 34.8, 44.4, 126.9, 129.1, 135.3, 145.3. HRMS (EI). Calcd for $C_{13}H_{18}$ [M^+]: 174.140 851. Found: 174.140 762.

1-Cyclohexyl-4-methoxybenzene, 7 (Table 3, Entry 4). Toluene eluent. Colorless oil, 0.282 g (74%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (m, 5H, CH_2 of Cy), 1.81 (m, 5H, CH_2 of Cy), 2.44 (m, 1H, CH of Cy), 3.79 (s, 3H, OMe), 6.84 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.13 (d, 2H, $^3J_{HH}$ = 8.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 26.3, 34.8, 43.8, 55.3, 55.4, 113.7, 127.7, 140.5, 157.7. HRMS (EI). Calcd for $C_{13}H_{18}O$ [M^+]: 190.135 765. Found: 190.135 215.

1-Cyclohexyl-2-Methylbenzene, 8 (Table 3, Entry 5). Cyclohexane eluent. Colorless oil, 0.17 g (49%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (m, 3H, CH_2 of Cy), 1.53 (m, 2H, CH_2 of Cy), 2.15 (m, 5H CH_2 of Cy), 2.33 (s, 3H, Me), 2.70 (m, 1H, CH of Cy), 7.14 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.3, 26.3, 33.6, 37.5, 53.5, 125.3, 125.4, 126.0, 130.1, 135.0, 145.8. HRMS (EI). Calcd for $C_{13}H_{18}$ [M^+]: 174.140 851. Found: 174.140 662. Product contaminated with bicyclohexyl.

1-Methyl-4-(4-methylcyclohexyl)benzene, 10 (Table 3, Entry 7). Cyclohexane eluent. Colorless oil, 0.27 g (72%). HRMS (EI). Calcd for $C_{14}H_{20}$ [M^+]: 188.156 501. Found: 188.156 196.

(a) Trans Isomer. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (d, 3H, $^3J_{HH}$ = 6.4 Hz, Me), 1.51 (m, 9H, CH_2 of Cy), 2.32 (s, 3H, Me), 2.42 (m, 1H, Cy), 7.11 (s, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.0, 22.8, 32.5, 34.5, 35.8, 44.0, 126.7, 129.0, 135.3, 145.0.

(b) Cis Isomer. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (d, 3H, $^3J_{HH}$ = 7.2 Hz, Me), 1.70 (m, 9H, CH_2 of Cy), 2.32 (s, 3H, Me), 2.51 (m, 1H, Cy), 7.11 (s, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.3, 21.0, 27.6, 28.8, 32.0, 43.9, 126.7, 129.0, 135.3, 145.0.

1-Methyl-4-(pentan-3-yl)benzene, 11 (Table 3, Entry 8). Cyclohexane eluent. Colorless oil. 0.14 g (43%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, 6H, CH_2CH_3), 1.68 (m, 4H, CH_2), 2.33 (m, 4H including a singlet at 2.38), 7.08 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ar), 7.14 (d, 8.3 Hz, 2H, Ar). HRMS (EI). Calcd for $C_{12}H_{18}$ [M^+]: 162.140 851. Found: 162.140 668.

Product contains 2,4-di-*tert*-butylphenol, tris(2,4-di-*tert*-butylphenyl)phosphite, and 3-bromopentane.

1-(2-Cyclohexylethyl)-4-methylbenzene, 12 (Table 3, Entry 9). Cyclohexane eluent. Colorless oil, 0.27 g (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (m, 2H, CH_2 of Cy), 1.30 (m, 4H, CH_2 of Cy), 1.58 (m, 2H, CH_2 of Cy), 1.81 (m, 5H, CH_2 & CH of Cy), 2.40 (s, 3H, Me), 2.67 (t, 2H, $^3J_{HH}$ = 8.3 Hz CH_2CH_2Ar), 7.16 (s, br, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 26.5, 26.9, 32.9, 33.5, 37.4, 39.7, 128.4, 129.1, 135.0, 140.3. HRMS (EI). Calcd for $C_{15}H_{22}$ [M^+]: 202.172 151. Found: 202.171 664. Contains 2,4-di-*tert*-butylphenol.

1-Methyl-4-octylbenzene, 13 (Table 3, Entry 10). Cyclohexane eluent. Colorless oil. (51%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.03 (t, 3H, $^3J_{HH}$ = 6.9 Hz, CH_3), 1.44 (m, 10H, CH_2 of alkyl chain), 1.74 (m, 2H, CH_2 of alkyl chain), 2.45 (s, 3H, Me), 2.70 (t, 2H, $^3J_{HH}$ = 7.9 Hz), 7.41 (s, br, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.3, 22.9, 27.1, 29.5, 29.6, 29.8, 31.9, 32.1, 35.8, 128.4, 129.1, 135.0, 140.0. HRMS (EI). Calcd for $C_{15}H_{24}$: 204.187 801. Found: 204.186 998.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the coupled products. This material is available free of charge via the Internet at http://pubs.acs.org.

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