978 *J. Am. Chem. Soc.* **2000,** *122,* 978−979

Iron-Catalyzed Olefin Carbometalation

Masaharu Nakamura, Atsushi Hirai, and Eiichi Nakamura*

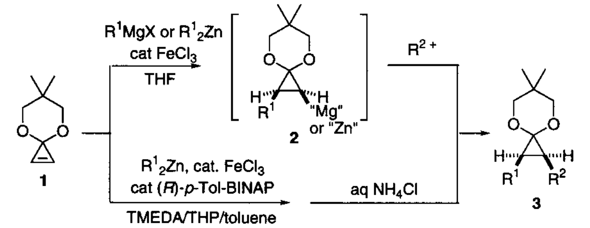
Department of Chemistry, The University of Tokyo
Hongo, Bunkyo-ku, 113-0033, Japan

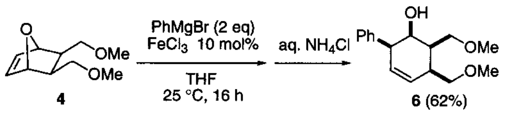
Received August 26, 1998

Among various transition metals, iron is nontoxic, cheap, and hence of great potential synthetic use. We report herein the first use of iron complexes as catalysts for olefin carbometalation and for an asymmetric organometallic reaction. The reaction adds to the repertoire of iron-catalyzed organometallic reactions, of which only a few examples have thus far been reported;[1] no effective chiral ligand system for alkyliron species has been previously developed. We have been studying the carbometalation of olefins for their stereochemistry[2,3] and for the possibility of using them in new reactions, such as an olefinic analogues of the aldol reaction.[4] Here we describe the iron catalysis in the olefin carbometalation as exemplified by the addition of Grignard and organozinc reagents to cyclopropenone acetal **1** (Scheme 1) and bicyclic olefins **4** and **5** (eqs 1 and 2). A new ternary catalytic system, consisting of iron, chiral diphosphine, and diamine, has been developed for catalytic enantioselective carbometalation with dialkylzinc reagents. The present reaction allows the use of functionalized alkyl, vinyl, and aryl organometallics, thus broadening the scope of nucleophiles to be used for olefin carbometalation reactions.[5,6]

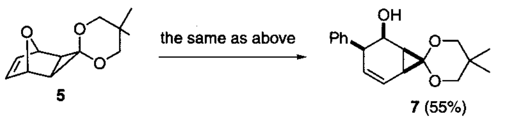
The reaction of a Grignard reagent was investigated first. Uncatalyzed reaction in THF did not take place at low temperatures and gave a complex mixture at higher temperatures (up to 65 °C). Among various transition metal complexes examined, some metal complexes of Groups 6, 8, and 9 were found to catalyze the reaction to a varying extent,[7] and FeCl$_3$ (3−5 mol %) was the most effective. Poor catalytic activity was found for nickel catalysts.[5] Addition of a THF solution of FeCl$_3$ to a mixture of **1** and a Grignard reagent (1.2−1.5 equiv) kept between −78 and −45 °C immediately afforded a dark brown solution and after 0.5−5 h gave the desired 2-substituted cyclopropanone acetal **3** upon aqueous quenching. The reactions of phenyl, vinyl, and alkyl Grignard reagents under these conditions afforded the substituted cyclopropanone acetal **3** in good to excellent yields (entries 1−4 in Table 1). Notably, the reaction of the Grignard reagent possessing β-hydrogen atoms took place in good yield. For instance, 2-phenylethylmagnesium bromide (entry 4) afforded the desired carbometalation product in high yield. Styrene and 1,4-diphenylbutane (β-elimination and oxidative coupling products in the initial transformation of Fe(III) to Fe(I))[8] were formed in a few percent yields, and there was no trace of unsubstituted cyclopropanone acetal **3** (R^1, R^2 = H), which could have formed if metal hydride species had been generated in situ.[9]

Scheme 1





(1)



(2)

The intermediate **2** can be trapped with carbon electrophiles (entries 8−11). The reaction with *trans*-cinnamyl bromide under iron catalysis took place exclusively in an S$_N$2 manner with conservation of the olefin geometry.[10] The stereochemistry of the trapping was exclusively (>97%) cis, as determined by NOE experiment as well as by comparison with authentic samples.[2]

Organozinc reagents also took part in the iron-catalyzed reaction under similar conditions. The reaction with diethylzinc and dipentylzinc at −25 °C proceeded under the iron catalysis conditions to give **3** with $R^1 = C_2H_5$, R^2 = H and **3** with $R^1 = C_5H_{11}$, R^2 = H in 73% and 91% yields, respectively (entries 5 and 6). The advantage of organozinc reagent rests on the tolerance of the electrophilic center in the nucleophile,[11] and zinc homoenolate[12] of isopropyl propionate smoothly reacted with **1** through a transition metal homoenolate species[13] (entry 7).

The iron catalysis also operates in alkylative ring-opening reactions of oxabicyclo olefins[14] **4** and **5**, as shown in eqs 1 and 2. The addition of PhMgBr to **4**, thus, took place at ambient temperature in the presence of 10 mol % of FeCl$_3$ to give cyclohexenol **6** selectively in 62% yield. The Diels−Alder product of furan and CPA (**5**) also takes part in the reaction to give the bicyclic hexenol **7** in 55% yield.

---

(1) Davies, S. G. *Organotransition Metal Chemistry—Application to Organic Synthesis*; Pergamon Press: Oxford, 1982. Pearson, A. J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 939.

(2) (a) Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297−1298. (b) Nakamura, E.; Kubota, K.; Isaka, M. *J. Org. Chem.* **1992**, *57*, 5809−5819. (c) Kubota, K.; Nakamura, M.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5867−5368. (d) Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179−1180.

(3) Hoveyda, A. H.; Heron, N. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 431.

(4) (a) Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792−793. (b) Nakamura, E.; Kubota, K.; Sakata. G. *J. Am. Chem. Soc.* **1997**, *119*, 5457−5458. (c) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491−2493. (d) Nakamura, E.; Kubota, K. *Tetrahedron Lett.* **1997**, *38*, 7099−7102. (e) Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157−2159.

(5) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535−544. Kondakov, D. Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1996**, *118*, 1577−1578. Kondakov, D. Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1995**, *117*, 10771−10772. Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F, *J. Am. Chem. Soc.* **1995**, *117*, 8853−8854.

(6) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649−7650. Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 366−368.

(7) In the presence of 3 mol % of a transition metal complex, the addition of C$_6$H$_5$MgBr to **1** took place at −45 °C for 2 h in 30% (FeCl$_3$), 20% (Fe(acac)$_3$), 16% (CoCl$_2$), 16% (CrCl$_2$), 8% (CoCl(PPh$_3$)$_3$), 7% (CoCl$_2$(PPh$_3$)$_2$, and 4% yields (CrCl$_3$). FeCl$_2$, RuCl$_3$, Ru(acac)$_3$, RhCl(PPh$_3$)$_3$, and Cr(acac)$_3$ afforded **3** in less than 2% yield under the same conditions.

(8) Cf.: Tamura M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487−1489. Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599−606. Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502−509.

(9) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978; p 246.

(10) Yanagisawa, A.; Nomura, N.; Yamamoto H. *Synlett* **1991**, 513−514. Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *40*, 5155−5156.

(11) Nakamura, E. *Synlett* **1991**, 539. Nakamura, M.; Nakamura, E. *J. Synth. Org. Chem., Jpn.* **1998**, *56*, 632−644.

(12) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056−8066.

(13) Cf.: Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296−3298. Fujimura, T.; Aoki, S.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2810−2821.

(14) Lautens, M.; Ma, S. *J. Org. Chem.* **1996**, *61*, 7246−7247.

10.1021/ja983066r CCC: $19.00

Table 1. Iron-Catalyzed Carbometalation of Cyclopropenone Acetal, Forming **3** (Scheme 1, Top)[a]

entry	organometallics, R^1-metal	**3**	
		$R^{2\,b}$	yield (%)[c]
1	C_6H_5MgBr	H	96
2	$CH_2{=}CHMgBr$	H	75
3	CH_3MgBr	H	66
4	$C_6H_5CH_2CH_2MgCl$	H	85
5	$(C_2H_5)_2Zn$[d]	H	73
6	$(C_5H_{11})_2Zn$[d]	H	91
7	$({}^iPrOCOCH_2CH_2)_2Zn$	H	76
8	C_6H_5MgBr	$CH_2{=}CHCH_2$	85[e]
9	C_6H_5MgBr	(E)-$C_6H_5CH{=}CHCH_2$	75[e]
10	C_6H_5MgBr	CH_3	90[e]
11	C_6H_5MgBr	$CH(C_6H_5)OH$	56[f]

[a] The reactions were carried out in THF or THF/toluene at −78 to −25 °C for 0.5−5 h in the presence of 3−5 mol % of $FeCl_3$. [b] Saturated aqueous NH_4Cl was used as electrophile (entries 1−7). Allyl bromide, (*E*)-cinnamyl chloride, methyl iodide, and benzaldehyde (2−3 equiv) were used as electrophile for entries 8−11, respectively. [c] Yield based on pure isolated material. [d] Purchased as 1.0 M toluene solution from Tri Chemical Laboratory Inc. [e] Diastereomeric ratio was determined as >97:3 by ^{1}H NMR. [f] A 1:1 diastereomer mixture for the benzylic chiral center.

Despite numerous reports on the metal/ligand systems in transition metal catalysis, nothing has been known about the effect of chiral ligand on the alkyliron species. Exploration of enantioselective reaction led to a new ternary catalytic system, iron/chiral chelate diphosphine/diamine[15] for the reaction of zinc reagent (bottom of Scheme 1). As shown in Table 2, addition of dialkylzinc to CPA proceeded with 89−92% ee in the presence of (*R*)-*p*-Tol-BINAP[16] (7.5 mol %), $FeCl_3$ (5 mol %), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 2.5 equiv for organozinc reagent) in toluene/tetrahydropyran (THP) solution (entries 1−3).[17] Enantioselectivity was significantly reduced by the use of THF instead of THP as cosolvent (entry 2 vs 4). Despite only small structural difference, BINAP ligand showed significantly lower enantioselectivity (entries 4 and 6).

Table 2. Enantioselective Carbozincation Reaction (Scheme 1, Bottom)[a]

entry	R_2Zn	ligand[b]	cosolvent	yield (%)[c]	ee (%)[d]
1	Pr_2Zn	**A**	THP	62[e]	92(*R*)
2[f]	Et_2Zn	**A**	THP	64[g]	90(*R*)
3	Et_2Zn	**A**	THP	88[e]	89(*R*)
4	Et_2Zn	**A**	THF	73	85(*R*)
5	Pr_2Zn	**B**	THF	82[g]	71(*R*)
6	Et_2Zn	**B**	THF	78[g]	79(*R*)
7[h]	Et_2Zn	**B**	THF	69	0(−)
8	Et_2Zn	**C**	THF	55	2(*R*)
9	Et_2Zn	**D**	THF	73	13(*S*)
10	Et_2Zn	**E**	THF	4	35(*R*)

[a] The reaction were carried out in a manner described in footnote 16. [b] **A**, [(*R*)-*p*-Tol-BINAP]: (*R*)-2,2′-bis[bis(4-methylphenyl)phosphino]-1,1′-binaphthyl. **B**, [(*R*)-BINAP]: (*R*)-2,2′-bis(diphenylphosphino)-1,1′binaphthyl. **C**, [(*R*)−(*S*)-BPPFA]: (*R*)-*N*,*N*-dimethyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine. **D**, [(*S*,*S*)-BPPM]: (2*S*,4*S*)-*tert*-butyl 4-(diphenylphosphino)-2-(diphenylphosphinomethyl)-1-pyrrolidinecarboxylate. **E**, [(*R*)−(*S*)-PPFA]: (*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine. TMEDA (2.0−3.0 equiv for dialkylzinc) was also added unless otherwise noted. [c] GLC yield otherwise noted. [d] Absolute configuration, which was determined by correlation to a known compound[2d] for the propyl product or by inference for the ethyl product, is shown in the parentheses. [e] NMR yield. [f] Large scale experiment. [g] Isolated yield. [h] TMEDA was absent.

Although TMEDA (>2.0 equiv for Et_2Zn) slowed the reaction, its presence was essential for the enantioselective carbometalation. Thus, in the absence of TMEDA, the $FeCl_3$-catalyzed reaction of Et_2Zn with **1** in the presence of (*R*)-BINAP (7.5 mol %)[15] gave a racemic mixture (Table 2, entry 7).

Various chiral phosphine ligands were examined for the enantioselective carbozincation and found to be much less effective than *p*-Tol-BINAP and BINAP.[18] The reaction also took place smoothly with bidentate phosphines other than BINAP, but with much lower selectivities (e.g., **C**, (*R*)−(*S*)-BPPFA, entry 8**,** and **D**, (*S*,*S*)-BPPM, entry 9). In addition, the reaction rate depended on the phosphine structure; thus, the reaction was faster with a bidentate phosphine than with a monodentate one (e.g., **E**, (*R*)−(*S*)-PPFA, with which the reaction was extremely sluggish (4% yield, entry 10)).

In summary, we found that iron catalysts are effective for promotion of olefin carbometalation. The new (soft) phosphine/(hard) diamine ligand system for the iron/zinc bimetallic reagent provides a prospect for further development of enantioselective synthetic transformations using iron as catalyst.

Acknowledgment. We thank Prof. K. Mashima at the University of Osaka for helpful discussions. A.H. thanks the Japan Society for Promotion of Science for a scholarship. This work is supported by Monbusho, Grant-in-Aid for Scientific Research on Priority Area (No. 403-11166220, “Molecular Physical Chemistry”).

Supporting Information Available: Experimental and characterization details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA983066R

---

[15] A tridentate amine, *N*,*N*,*N*′,*N*”,*N*”-pentamethyldiethylenetriamine, exerted the same effects. Interestingly enough, monodentate amines (triethyl-*N*,*N*-methylpyrroridine and *N*-methylmorphorine) produced a racemic product.

[16] Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketori, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629−635. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932−7934.

[17] To a mixture of (*R*)-*p*-Tol-BINAP (0.102 g, 0.15 mmol) and 1.0-M toluene solution of Et_2Zn (4.0 mL, 4.0 mmol) was added dropwise a 0.1−M THP solution of $FeCl_3$ (1.0 mL, 0.1 mmol) and TMEDA (1.51 mL, 10.0 mmol) at 25 °C. After being stirred for 10 min at 25 °C, the reaction mixture was diluted with toluene (8.2 mL). A solution of CPA (**1**, 0.28 mL, 2.0 mmol) in toluene (5 mL) was added over 2 h. The reaction mixture was stirred for 6 days at 0 °C and at 10 °C for 1 day and then quenched with saturated NH_4Cl. Purification with silica gel chromatography and bulb-to-bulb distillation (130−140 °C/15−20 mmHg) afforded pure 2-ethylcyclopropanone acetal **3** (R^1 = Et, R^2 = H) (0.219 g, 64% yield). Chiral GLC analysis showed that the (*R*)-product was obtained as a major enantiomer with 90% ee. In a smaller scale (0.4 mmol) experiment, the carbozincation product was obtained in 88% yield with 89% ee (Table 2, entry 3).

[18] Chiral ligands such as (−)-sparteine, PyBOX, bis-oxazoline (BOX), DIOP, and CHIRAPHOS were ineffective either to promote the reaction or to effect enantioselective reaction.