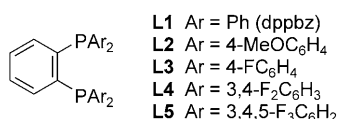


Diastereoselective Carbometalation of Oxa- and Azabicyclic Alkenes under Iron Catalysis**

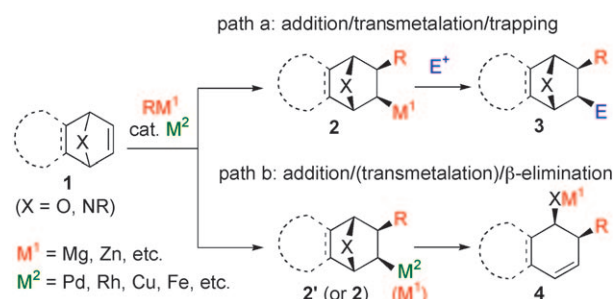
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The transition-metal-catalyzed carbometalation of alkenes is a powerful synthetic tool for the selective formation of carbon–carbon bonds. Through sequential electrophilic trapping of the intermediate organometallic species, regio- and stereoselective construction of contiguous sp^3 carbon centers can be achieved in a single-pot procedure.^[1] Although iron catalysts are attracting increased attention because of their economical and environmental benefits,^[2] their application in stereoselective carbometalation (followed by electrophilic trapping) has been limited to only alkyne^[3] and cyclopropene^[4] substrates.^[5] Herein, we report a highly diastereoselective iron-catalyzed carbometalation of oxa- and azabicyclic alkenes with arylzinc reagents using the newly developed *ortho*-phenylene diphosphine ligands (Scheme 1); these ligands were found to suppress the β -heteroatom elimination pathway and enable sequential electrophilic trapping (Scheme 2, path a versus path b).^[6–8]



Scheme 1. Diphosphine ligands used for the iron-catalyzed carbometalation of oxa- and azabicyclic alkenes.

Heterobicyclic alkenes have been shown to be useful starting materials to synthesize stereochemically complex molecules, as exemplified by palladium, rhodium, and copper-catalyzed asymmetric ring-opening reactions.^[9,10] In the ring-opening reactions, rapid β -heteroatom elimination of the



Scheme 2. Reactions of oxa- and azabicyclic alkenes with organometallic nucleophiles under transition-metal catalysis. E = electrophile.

carbometalation intermediate (**2** or **2'**) affords the corresponding cycloalkenols or cycloalkenylamines (**4**) under reaction conditions in most cases, and the elimination reaction hampered sequential trapping of the organometallic intermediate (**2**) with electrophiles (Scheme 2, path a^[7,8] versus path b^[6,11]). To date, iron catalysis has also been found to promote the ring-opening reaction of the olefinic substrates when used < in combination with Grignard reagents.^[4a,12] Our research group has recently found that chelating diphosphine ligands, such as 1,2-bis(diphenylphosphino)benzene (dppbz, **L1**; Scheme 1),^[13] are particularly effective for the iron-catalyzed cross-coupling of alkyl (pseudo)halides possessing β hydrogen atoms.^[14,15] We envisioned that certain tetrahedral organoiron intermediates proposed in the cross-coupling reactions would also resist β -heteroatom elimination because of the open shell (high spin) nature of the metal center,^[16] and hence, we synthesized new dppbz congeners (**L2–L5**; Scheme 1) for the present carbometalation reaction.

We carried out the reactions of 1,4-dihydro-1,4-epoxynaphthalene (**1a**) with diphenylzinc prepared from anhydrous ZnCl₂ and PhMgBr for ligand screening.^[17] While all the reactions were conducted using 99.99 + % grade anhydrous FeCl₃ (Aldrich) to avoid contamination with trace amount of the other transition metals, lower grade anhydrous FeCl₃ and anhydrous FeCl₂ gave virtually identical results. We confirmed that copper salts, such as Cu₂O and CuCl, did not catalyze the carbocycloaddition reactions by themselves and gave no product.^[18,19]

In the absence of a ligand, the ring-opening product, 2-phenyl-1,2-dihydronaphthalen-1-ol (**4a**), was isolated as the sole product (Table 1, entry 1). The ligands widely used for iron-catalyzed cross-coupling reactions such as *N,N,N',N'*-tetramethylethylenediamine (tmeda)^[15,20] and *N*-methylpyrrolidine (nmp)^[21] also led to the formation of **4a** (Table 1, entries 2 and 3); these results are consistent with prior reports.^[12] On the other hand, chelating diphosphine ligands

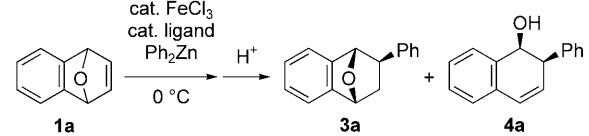
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[**] We thank the Ministry of Education, Culture, Sports, Science, and
 Technology of Japan for financial support. M.N. gratefully
 acknowledges a Grant-in-Aid for Scientific Research on Priority
 Areas “Synergistic Effects for Creation of Functional Molecules”
 (18064006) and a Grant-in-Aid for Young Scientists (S; 2075003).

Supporting information for this article is available on the WWW
 under <http://dx.doi.org/10.1002/ange.201006180>.

Table 1: Effect of ligands or additives on the product selectivity and reactivity.^[a]



Entry	Ligand	t [h]	Yield [%] ^[b]		
			3a	4a	1a
1	none	15	0	87	12
2	tmeda (1.5 equiv)	2	0	99	0
3	nmp (1.5 equiv)	15	6	90	1
4	dppe	5	87	8	3
5	dppp	5	70	22	6
6	dppb	5	3	95	0
7	L1 (dppbz)	5	88	12	0
8	L2	4	83	17	0
9	L3	2	95	5	0
10	L4	5	89	11	0
11 ^[c]	L5	6	< 1	27	71
12	(R)-binap	5	2	59 ^[d]	33

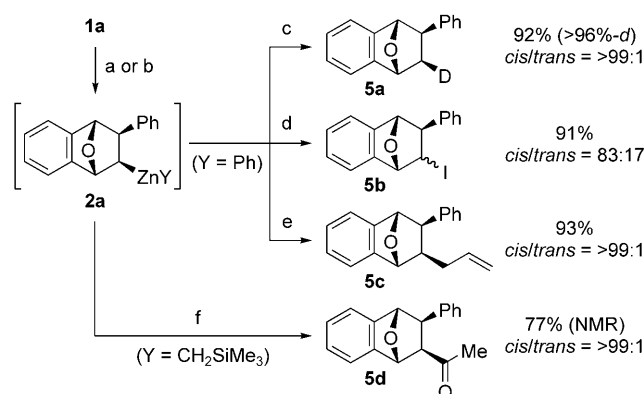
[a] The reactions of **1a** with diphenylzinc (1.5 equiv) were carried out in THF/toluene (1:1) at 0 °C for 2–15 h in the presence of FeCl₃ (1 mol %) and ligand (2 mol %). [b] Yield based on ¹H NMR spectroscopy. [c] The reaction was performed at 25 °C. [d] No chiral induction was observed.

significantly affect the product distributions: in the presence of 1,2-bis(diphenylphosphino)ethane (dppe; Table 1, entry 4), 1,3-bis(diphenylphosphino)propane (dppp; Table 1, entry 5), dppbz (**L1**; Table 1, entry 7), and related diphosphine ligands (**L2–L4**; Table 1, entries 8–10), the *exo*-arylated compound 1,2,3,4-tetrahydro-2-phenyl-1,4-epoxynaphthalene (**3a**) was isolated as the main product. Given that dppb exhibited no positive effect on the yield of **3a** (Table 1, entry 6), the bite angle of diphosphine ligands is essential to attenuate the reactivity of the iron catalyst. Regarding the dppbz congeners, electron-donating ligand **L2** decreased the yield of **3a** (Table 1, entry 8), whereas electron-deficient phosphine **L3** significantly improved the yield. Thus, the reaction of **1a** with diphenylzinc proceeded at 0 °C in the presence of FeCl₃ and **L3** and afforded **3a** in 95 % yield (Table 1, entry 9). The ligand with difluorophenyl groups **L4** was slightly less effective and the one with trifluorophenyl groups **L5** slowed down the reaction and inversed the carbometalation/ring-opening selectivity (Table 1, entries 10 and 11). Furthermore, (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(*R*)-binap], which was effective in the enantioselective carbocyclization of cyclopropenone acetals,^[4a] promoted the ring-opening reaction to obtain **4a**, but unfortunately, in a racemic form (Table 1, entry 12).

The scope of the present iron-catalyzed carbometalation is summarized in Table 2. Treatment of **1** with 1.5 equivalents of diarylzinc reagents were typically performed at 0 °C in the presence of FeCl₃ (1 mol %) and **L3** (2 mol %). A range of oxabicyclic alkenes bearing fluoro groups (**1b**; Table 2, entry 2) and methoxy groups (**1c** and **1d**; Table 2, entries 3 and 4) reacted smoothly and gave the arylated products **3b–3d** in excellent yield. Electron-rich (Table 2, entries 5–7) and electron-deficient (Table 2, entries 8–10) arylzinc reagents as well as a heteroarylzinc reagents (Table 2, entry 11), can

participate in the carbometalation reaction. Notably, highly reactive functional groups, such as methoxycarbonyl (Table 2, entry 9) and cyano groups (Table 2, entry 10),^[22] were compatible under the present reaction conditions. When less reactive oxabicyclic alkenes such as **1l** (Table 2, entry 12) and **1m** (Table 2, entry 13) were employed, a higher catalyst loading and longer reaction time were required to achieve smooth conversion. Azabicyclic alkenes **1n** and **1o** also take part in the reaction, thereby affording the arylated products **3n** and **3o** in 94 % and 96 % yield, respectively (Table 2, entries 14 and 15). The reaction of nonsymmetrical substrate **1p** took place such that the aryl group is introduced to the olefinic terminus distal from the methyl group to give a mixture of regioisomers **3p** and **3p'**. The regioselectivity of carbometalation is estimated at approximately 4:1 (**3p/3p'**), thus suggesting that the steric interaction between the methyl group and the introduced phenyl group is dominant (Table 2, entry 16).^[23]

The carbometalation intermediate **2a** was sufficiently stable at 0 °C and it could be trapped with various electrophiles. The treatment of **2a** with CD₃COOD gave the corresponding deuterated product **5a** in 92 % yield with greater than 96 % deuterium incorporation and more than 99 % *cis* selectivity (Scheme 3). The *cis* configuration was



Scheme 3. Electrophilic trapping of carbocation product **2a**.^[18] Reaction conditions: a) the same procedure as described in Table 1 (Y = Ph); b) the same procedure as (a) but using PhZnCH₂SiMe₃ instead of PhZn (Y = CH₂SiMe₃); c) CD₃COOD; d) I₂; e) allyl bromide, cat. CuBr·SMMe₂; f) MeCOCl, CuBr, CuBr·SMMe₂.

confirmed by the fact that both bridgehead protons of **5a** were observed as a pair of singlets in the ¹H NMR spectrum. This observation is consistent with the fact that no ¹H–¹H coupling was generally observed between bridgehead protons and vicinal *endo* protons in similar heterobicyclic compounds.^[10b,d,e] Other electrophiles such as iodine, allyl bromide, and acetyl chloride worked well and gave the corresponding products **5b–5d** in 91 %, 93 %, and 77 % yield, respectively, with good *cis* selectivity. Notably, the use of ArZnCH₂SiMe₃ for the generation of **2a** (Y = CH₂SiMe₃) was essential to trap **2a** with acetyl chloride to obtain **5d** in high yield.

In summary, we have developed an iron-catalyzed, highly diastereoselective carbometalation of various oxa- and aza-

Table 2: Iron-catalyzed arylzincation of oxa- and azabicyclic alkenes.^[a]

Entry	Bicyclic alkene	Ar	t [h]	Product	Yield [%] ^[b]
1	1a (R ¹ = R ² = H)	Ph	2	3a	94 (92 ^[c])
2	1b (R ¹ = H; R ² = F)	Ph	1	3b	96
3	1c (R ¹ = H; R ² = MeO)	Ph	2	3c	94
4	1d (R ¹ = MeO; R ² = H)	Ph	5	3d	90
5	1a	4-MeC ₆ H ₄	2	3e	95
6	1a	2-MeC ₆ H ₄	8	3f	86
7	1a	4-MeOC ₆ H ₄	2	3g	95
8	1a	4-FC ₆ H ₄	2	3h	94
9 ^[d]	1a	4-MeO ₂ CC ₆ H ₄	4	3i	66
10 ^[d]	1a	4-NCC ₆ H ₄	6	3j	63
11	1a	2-thienyl	24	3k	81
12 ^[e]	1l	Ph	24	3l	65 ^[f] (48)
13 ^[g]	1m	Ph	24	3m	75
14 ^[h]	1n	Ph	2	3n	94
15 ^[h]	1o	Ph	2	3o	96
16 ^[i]	1p	Ph	9	3p 3p'	62 ^[j]

[a] The reactions of **1** (0.5 mmol) with diarylzinc reagents (1.5 equiv) were carried out in THF/toluene (1:1) at 0°C for 1–24 h in the presence of FeCl₃ (1 mol%) and **L3** (2 mol%), unless otherwise noted. [b] Yield of isolated product. [c] 5.0 mmol scale. [d] The reaction was carried out with FeCl₃ (10 mol%) and **L3** (20 mol%). [e] The reaction of **1l** (0.3 mmol) was carried out at 40°C for 24 h with FeCl₃ (3 mol%) and **L3** (6 mol%). [f] Yield based on ¹H NMR spectroscopy. The yield in parenthesis is the yield of the products isolated after desilylation (see the Supporting Information). [g] The reaction was carried out at 40°C with FeCl₃ (3 mol%) and **L3** (6 mol%). [h] The reaction was carried out at 25°C. [i] The reaction was carried out at 10°C with FeCl₃ (10 mol%) and **L3** (20 mol%). [j] **3p/3p'** = 4:1. Boc = *tert*-butoxycarbonyl, TBDPS = *tert*-butyldiphenylsilyl.

bicyclic alkenes with arylzinc reagents. The carbocation products **2** were quenched with acid or trapped with electrophiles, thereby giving the corresponding products **3** or **5**, respectively, in excellent yield. Among a series of novel dpbz derivatives, electron-deficient **L3** was found particularly effective to facilitate the carbometalation and suppress the β-heteroatom elimination. Further study on the reaction mechanism and the development of enantioselective variants are currently under way.

Experimental Section

A typical procedure: In a dry reaction vessel, a mixture of **L3** (0.10 mmol), ZnCl₂ (a 1.0 M THF solution, 7.5 mL, 7.5 mmol) and phenylmagnesium bromide (a 1.17 M THF solution, 12.8 mL, 15.0 mmol) in toluene (THF/toluene = 1:1) was stirred at room temperature for 0.5 h. The resulting suspension was cooled to 0°C before FeCl₃ (a 0.10 M THF solution, 0.50 mL, 0.050 mmol) and oxabicyclic alkene **1a** (0.72 g, 5.0 mmol) were added and the reaction was stirred at 0°C for 2 h. The reaction mixture was quenched with an ice-cooled, degassed solution of 5% AcOH/MeOH and then extracted with *n*-hexane and 30% Et₂O/*n*-hexane, passed through a pad of Florisil, and concentrated in vacuo. Compound **3a** (1.02 g, 92% yield) was obtained as a colorless solid after column chromatography on silica gel (*n*-hexane/EtOAc = 20:1, R_f = 0.36).

Received: October 2, 2010

Published online: December 10, 2010

Keywords: bicyclic alkenes · carbometalation · diastereoselectivity · diphenylphosphine ligands · iron

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