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Iron-Catalyzed Cross-Coupling Reactions between a Bicyclic Alkenyl Triflate and Grignard Reagents

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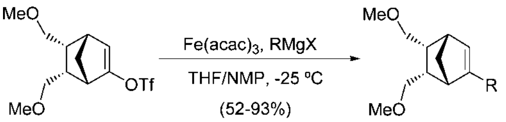
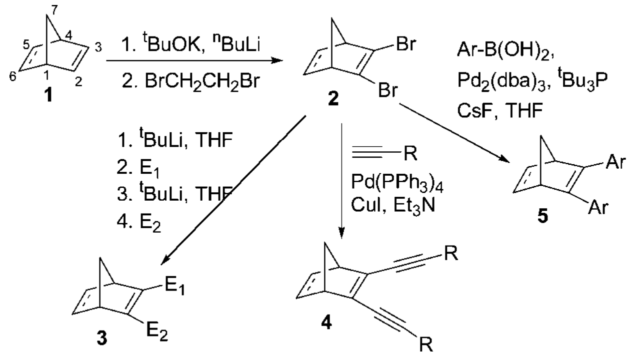


Fe-catalyzed cross-coupling reactions between a bicyclic alkenyl triflate and Grignard reagents were investigated. Under the optimized reaction conditions, various 2-substituted bicyclic alkenes were synthesized in moderate to excellent yields (52−93%). This method provided an efficient route for the synthesis of 2-substituted bicyclic alkenes with 2° alkyl groups which cannot be synthesized using previous methods such as Pd-catalyzed coupling reactions and lithium−halide exchange reactions.

Bicyclo[2.2.1]hept-2-ene and bicyclo[2.2.1]hepta-2,5-diene (**1**), commonly known as norbornene and norbornadiene, respectively, are strained bicyclic structures. Substituted norbornenes and norbornadienes are important compounds. They have been used as key intermediates for the synthesis of natural products, such as prostaglandin endoperoxides PGH_2 and PGG_2,[1] *cis*-Trikentrin B,[2] and β-santalol.[3] Chiral 2,5-disubstituted norbornadienes have recently been used as chiral ligands in asymmetric catalysis.[4] Photochemical valence isomerization between norbornadiene and quadricyclane is of interest as a solar energy conversion and storage system.[5] Extensive investigation of substituted norbornadienes/quadricyclanes for solar energy storage has demonstrated the efficiency and switching potential of these reversible systems.[6] This photochemical isomerization reaction has recently been investigated as an optical waveguide utilizing photoinduced refractive index changes,[7] as a photochromaic system potentially applicable to data storage,[8] or as light-driven, carrier-mediated, active transport across a membrane against a concentration gradient.[9]

Traditionally, substituted norbornenes and norbornadienes can be synthesized by Diels−Alder reactions between cyclopentadiene and an alkene or an alkyne. Since unactivated alkenes and alkynes are poor dienophiles in Diels−Alder cycloadditions,[10] the variety of 2,3-disubstituted bicyclic alkenes that could be synthesized using the Diels−Alder method is rather limited (usually contain at least one electronic withdrawing group such as an ester, an amide, a cyano group, etc.). We have recently reported the synthesis of a variety of 2,3-disubstituted bicyclic alkenes by three different methods. Double lithium−halide exchange of 2,3-dibromo bicyclic alkenes **2** produced a variety of substituted bicyclic alkenes **3** with E_1, E_2 = 1° alkyl groups, silyl groups, Cl, Br, I, R_3Sn, COOR, $R_1R_2C(OH)$ (Scheme 1).[11]

SCHEME 1. Previous Synthesis of Substituted Bicyclic Alkenes



Palladium-catalyzed Sonogashira couplings of 2,3-dibromo bicyclic alkenes **2** with terminal alkynes yielded bicyclic alkene-2,3-diynes **4**,[12] and palladium-catalyzed Suzuki couplings of 2,3-dibromo bicyclic alkenes **2** with aryl boronic acids afforded 2,3-diaryl bicyclic alkenes **5**.[13] These studies significantly broadened

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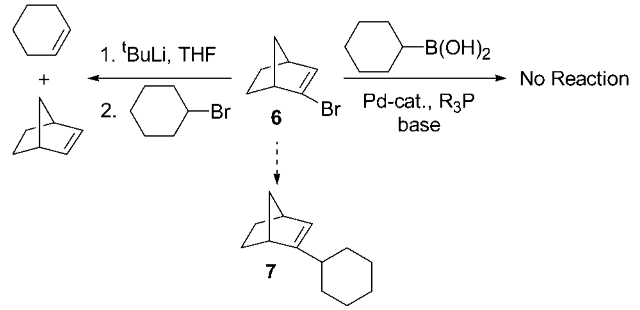
the variety of substituted bicyclic alkenes that cannot be prepared by the Diels−Alder methodology.

These methods allow the formation of a carbon−carbon bond between a bicyclic alkene and a sp-hybridized carbon (Scheme 1, **4**), a sp^2-hybridized carbon (**5**), and a sp^3-hybridized carbon of a 1° alkyl group (**3**). However, one limitation to these syntheses is that substitutents with 2° alkyl groups (e.g., ^{i}Pr or cycloalkyl) cannot be prepared using these methods. In fact, lithium−halide exchange of 2-bromonorbornene **6** followed by trapping with bromocyclohexane did not afford 2-cyclohexylnorbornene **7**; only cyclohexene and norbornene were formed (Scheme 2). Attempts to synthesize 2-cyclohexylnorbornene **7** using palladium-catalyzed Suzuki couplings of 2-bromonorbornene **6** with cyclohexylboronic acid using various conditions were also unsuccessful. To the best of our knowledge, there is no general method for the synthesis of 2-substituted bicyclic alkenes with a 2° alkyl group. In this paper, we report our studies on Fe-catalyzed cross-coupling reactions between bicyclic alkenyl triflates and Grignard reagents for the synthesis of 2-substituted bicyclic alkenes with 2° alkyl groups.

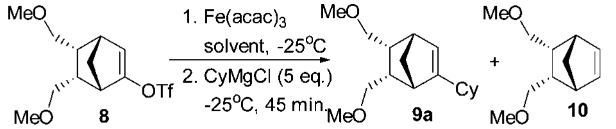
SCHEME 2. Attempted Synthesis of 7



In 1945, Kharasch and co-workers reported the first Fe-catalyzed alkenylation of Grignard reagents.[14a,b] Kochi and co-workers improved the procedures and studied the mechanism of the reaction in 1971, but the yields of the reactions were low and not convenient for preparative applications.[14c,d] More recently in 1998, Cahiez reported that the use of NMP or DMPU as a cosolvent which greatly improved the yields of Fe-catalyzed alkenylations of Grignard reagents, and alkenyl chlorides, bromides, and iodides as well as alkenyl phosphates can be used successfully.[15b] In 2004, Fürstner extended Cahiez's conditions to include alkenyl triflates as successful substrates in Fe-catalyzed alkenylations of Grignard reagents. This methodology has been successfully applied to synthesize biologically active natural products such as Muscopyridine,[16] Latrunculin,[17] immunosuppressive agent FTY720,[18] Ciguatoxin,[19] (−)-α-Cubebene, (−)-Cubebol, Sesquicarene, and related terpenes.[20]

To begin our investigation, bicyclic alkenyl triflate **8** was synthesized (see Supporting Information) and the study on the Fe-catalyzed coupling reaction was carried out (Table 1). In the presence of 5 equiv of cyclohexylmagnesium chloride (CyMgCl) and 20 mol % of Fe(acac)$_3$ in Et$_2$O at −25 °C, the desired coupling product **9a** was formed in 26% isolated yield accompanied with 1% of the reduced product **10** and 22% of the unreacted starting triflate **8** (Table 1, entry 1). To optimize the yield of the reaction, an investigation on the effect of solvent, different Fe catalysts, number of equivalent of Grignard reagent, and reaction temperature was carried out (Tables 1−3).

TABLE 1. Effect of Solvent



		yield (%)[c]		
entry[a]	solvent[b]	coupling product **9a**	reduced product **10**	recovered **8**
1	Et$_2$O	26	1	22
2	THF	81	6	0
3	DME	9	3	61
4	NMP	82	6	0
5	DMPU	88	1	0
6	DMF	50	5	8
7	TEA	5	4	70
8	TMEDA	0	0	74
9	THF/NMP (1:3)	88	6	0
10	THF/NMP (1:1)	79	5	0
11	THF/NMP (3:1)	78	12	0
12	THF/DMPU (1:3)	75	7	0
13	THF/DMPU (1:1)	66	8	0
14	THF/DMPU (3:1)	69	13	0

[a] 20 mol% of Fe(acac)$_3$ was used in all cases. [b] DME = 1,2-dimethoxyethane; NMP = 1-methyl-2-pyrrolidinone; DMF = *N*,*N*-dimethylformamide; TEA = triethylamine; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DMPU = *N*,*N*′-dimethylpropyleneurea. [c] Isolated yield after column chromatography.

Solvent plays an important role in Fe-catalyzed coupling reactions.[15] On the basis of various solvent systems used in the literature in Fe-catalyzed coupling reactions,[15] a wide range of ether, amide, and amine-based solvents were screened. The use of THF, NMP, DMPU, as well as THF/NMP (1:3) gave the desired coupling product **9a** in >80% isolated yields (entries 2, 4, 5, and 9), and in all cases, a small amount of the undesired reduced product **10** was also isolated. Fortunately, these products (**9a** and **10**) could be separated by column chromatography. The highest yield of the desired coupling product **9a** was obtained when THF/NMP (1:3) or DMPU was used as solvent (entries 5 and 9).

To determine the effect of different Fe catalysts on the coupling reaction, several Fe catalysts which were found to be

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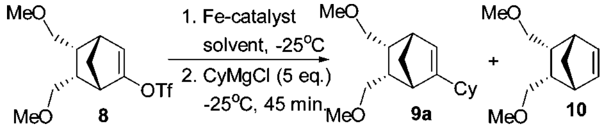
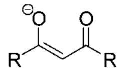
TABLE 2. Effect of Different Fe Catalysts

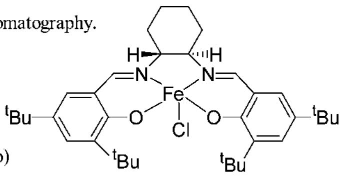


entry	Fe catalyst (20 mol %)	solvent	yield (%) coupling product **9a**	yield (%) reduced product **10**
1	Fe(acac)$_3$	THF/NMP (1:3)	88	6
2		DMPU	88	1
3	FeCl$_3$	THF/NMP (1:3)	79	8
4		DMPU	85	4
5	Fe(dpm)$_3$	THF/NMP (1:3)	67	6
6		DMPU	55	8
7	Fe(dbm)$_3$	THF/NMP (1:3)	72	6
8		DMPU	68	7
9	Fe cat. **11**	THF/NMP (1:3)	63	4
10		DMPU	60	7

[a] Isolated yield after column chromatography.



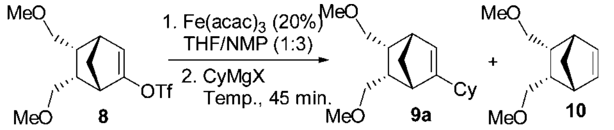
R = Me (acac, acetoacetonato)
R = ^{t}Bu (dpm, dipivaloylmethio)
R = Ph (dbm, dibenzoylmethio)



Fe-cat. **11**

active in the literature in Fe-catalyzed coupling reactions were screened, and the results are shown in Table 2. The catalysts Fe(dpm)$_3$, Fe(dbm)$_3$, and Fe cat. **11** were prepared by literature procedures.[15e,21] All Fe catalysts tested afforded the desired coupling product **9a** in moderate to good yields. The commercially available, air-stable Fe(acac)$_3$ catalyst seems to be the best choice with high yields and easy handling.

TABLE 3. Effects of Reaction Temperature, Different Grignard Halides, and Equivalency of Grignard Reagent



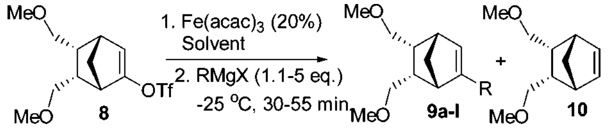
entry	X	equiv of CyMgX	temp (°C)	yield (%)[a] **9a**	yield (%)[a] **10**
1	Cl	5	−40[b]	78	6
2	Cl	5	−25	88	6
3	Cl	5	0	80	5
4	Cl	5	25	71	5
5	Cl	5	50	55	4
6	Br	5	−25	80	8
7	I	5	−25	58	15
8	Cl	10	−25	61	11
9	Cl	2.1	−25	86	4
10	Cl	1.1	−25	93	1

[a] Isolated yield after column chromatography. [b] THF/NMP (1:1) was used to avoid freezing of the solvent at −40 °C.

The effects of reaction temperature (entries 1−5), different Grignard halides (entries 2, 6, and 7), and equivalent of Grignard reagent (entries 2, 8−10) are shown in Table 3. Reaction temperatures above 0 °C led to decomposition of the starting triflate, and lower yields of the desired coupling product **9a** were observed. Although the reaction seems to work at as low as −40 °C (little reaction was observed for temperature lower than −40 °C), −25 °C gave the best results among all the temperatures tested (entries 1−5). The use of CyMgBr gave a slightly lower yield of the desired coupling product **9a** than CyMgCl, and CyMgI afforded the desired coupling product **9a** in much lower yield, and a significant increase in the formation of the reduced product **10** was observed (entries 2, 6, and 7). The effect of the number of equivalents of Grignard reagent is shown in entries 2 and 8−10. The use of a larger excess (10 equiv) of the Grignard reagent led to a decrease in yield of the desired coupling product **9a** and an increase in the formation of the reduced product **10** (entry 8). Using 5 or 2.1 equiv of the Grignard reagent (entries 2 and 9) gave similar yields, and the highest yield was obtained using 1.1 equiv of the Grignard reagent (entry 10).

To explore the scope of the Fe-catalyzed cross-coupling reactions of bicyclic alkenyl triflate **8**, various Grignard reagents (RMgX) were employed, and the results are shown in Table 4.

TABLE 4. Fe-Catalyzed Cross-Coupling of Triflate 8 and RMgX



entry	R	X	equiv of RMgX	solvent	product **9**	yield (%)[a] **9**	yield (%)[a] **10**
1	cyclohexyl	Cl	1.1	THF/NMP (1:3)	**9a**	93	1
2	cycloheptyl	Br	1.6	DMPU	**9b**	52	2
3	cyclopentyl	Cl	1.6	DMPU	**9c**	71	7
4	cyclobutyl	Cl	1.6	DMPU	**9d**	62	13
5	cyclopropyl	Br	1.6	DMPU	**9e**	67	3
6	^{i}Pr	Cl	1.6	DMPU	**9f**	87	3
7	^{s}Bu	Cl	1.6	DMPU	**9g**	87	0
8	Me	Br	5	THF/NMP (1:3)	**9h**	80	0
9	Bn	Cl	2.1	THF/NMP (50:1)	**9i**	72	0
10	Ph	Cl	1.6	THF/NMP (1:3)	**9j**	85	0
11	*m*-MeO-C$_6$H$_4$	Br	1.6	THF/NMP (1:3)	**9k**	74	0
12	*m*-CF$_3$-C$_6$H$_4$	Br	1.6	THF/NMP (1:3)	**9l**	73	0

[a] Isolated yield after column chromatography.

The highest yield of 93% of the coupling product 2-cyclohexyl bicyclic alkene **9a** was obtained using 1.1 equiv of CyMgCl in THF/NMP (1:3) (Table 4, entry 1). In the case of other cycloalkyl Grignard reagents, the use of DMPU as solvent gave better results in the coupling reactions than using THF/NMP as solvents, and the corresponding 2-cycloalkyl bicyclic alkenes **9b**−**9e** were formed in moderate yields (52−71%, entries 2−5). With cyclobutyl and cyclopentyl magnesium chlorides (entries 3 and 4), significant amounts of the reduced product **10** were produced. This Fe-catalyzed coupling reaction of bicyclic triflate **8** not only works well with cycloalkyl Grignard reagents, it also works well with acyclic 2 and 1° alkyl groups (entries 6−9), giving 2-alkyl-substituted bicyclic alkenes **9f**−**9i** in good yields (72−87%). The use of aromatic Grignard reagents in the Fe-catalyzed coupling reaction of bicyclic triflate **8** also afforded the corresponding 2-aryl-substituted bicyclic alkenes **9j**−**9l** in good yields (73−85%, entries 10−12).

A proposed mechanism for the Fe-catalyzed cross-coupling reaction[22] between bicyclic alkenyl triflate **8** and cyclohexylmagnesium chloride, which accounts for the formation of coupling product **9a** and the reduced product **10**, is shown in

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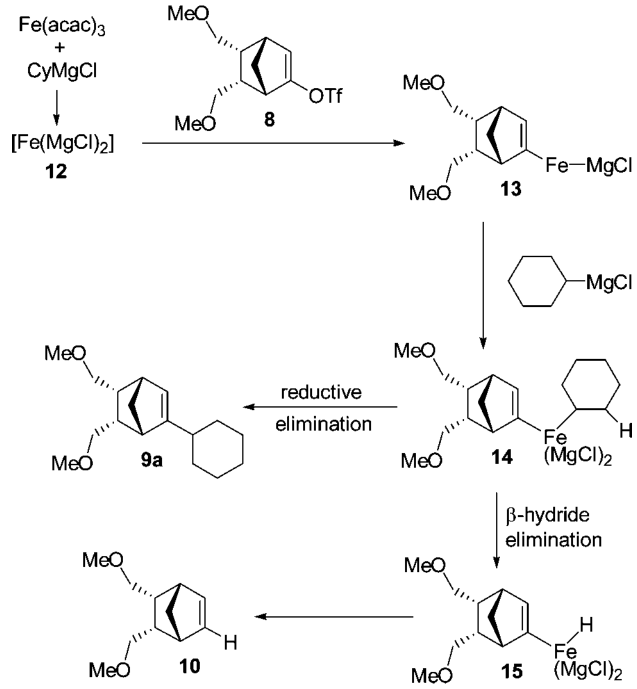
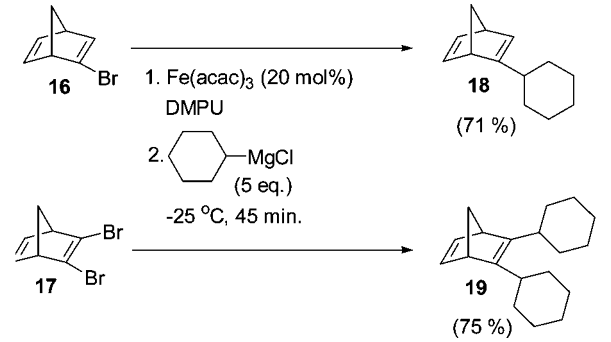
SCHEME 3. Proposed Mechanism



Scheme 3. Reduction of the Fe(acac)$_3$ precatalyst with the Grignard reagent produced the active catalyst, the Fe-IGR (**12**). Oxidative insertion of the Fe-IGR to the bicyclic alkene triflate **8** gave intermediate **13**. Addition of the Grignard reagent afforded **14**. Reductive elimination of **14** would provide the coupling product **9a** and regenerate the Fe-IGR active catalyst **12**. With alkyl groups containing a β-hydrogen, β-hydride elimination is possible and Fe-hydride **15** would be formed. Reductive elimination of **15** would give the reduced product **10**.

SCHEME 4. Synthesis of 18 and 19



2-Cyclohexylnorbornene **18** and 2,3-dicyclohexylnorbornadiene **19** could also be synthesized in good yields using the Fe-catalyzed cross-coupling reactions of 2-bromonorbornadiene **16** or 2,3-dibromonorbornadiene **17** with cyclohexylmagnesium chloride (Scheme 4). Note that these 2° alkyl-substituted norbornadienes were not accessible by palladium-catalyzed Suzuki coupling reactions or by lithium–halide exchange reactions followed by trapping with bromo- or iodocyclohexane.

In conclusion, we have investigated the Fe-catalyzed cross-coupling reactions between bicyclic alkenyl triflate **8** and Grignard reagents. Under the optimized reaction conditions, Fe(acac)$_3$ (20 mol %), 1.1–5 equiv of RMgBr or RMgCl, in DMPU or THF/NMP (1:3) at −25 °C, various 2-substituted bicyclic alkenes were synthesized in moderate to excellent yields (52–93%). This method provided an efficient route for the synthesis of 2-substituted bicyclic alkenes with 2° alkyl groups, which cannot be synthesized using the previous methods of Pd-catalyzed coupling reactions or lithium–halide exchange reactions.

Experimental Section

General Procedure for the Fe-Catalyzed Cross-Coupling of Bicyclic Alkenyl Triflate 8 and RMgX. To an oven-dried vial containing triflate **8** (1.0 equiv) dissolved in a solvent (~0.15 M) was added Fe(acac)$_3$ (20 mol %) under nitrogen, and reaction mixture was cooled to −25 °C. The Grignard reagent (1.1–5 equiv) was added dropwise, and the reaction mixture was stirred at −25 °C for 30–55 min. The reaction was quenched with HCl (1 M) at −25 °C and extracted with diethyl ether. The organic layers were washed with saturated sodium bicarbonate solultion, dried on magnesium sulfate, and concentrated using rotary evaporation. The crude product was purified by column chromatography (EtOAc–hexane mixtures) to give the product.

***endo*-5,6-Bis(methoxymethyl)-2-cyclohexylbicyclo[2.2.1] hept-2-ene (9a, Table 4, entry 1).** Following the above general procedure, using triflate **8** (26.2 mg, 0.0793 mmol), THF (0.11 mL)/NMP (0.33 mL) as solvent, Fe(acac)$_3$ (5.9 mg, 0.017 mmol), and cyclohexylmagnesium chloride (1.1 equiv, 1.4 M in diethyl ether, 0.06 mL, 0.084 mmol). The reaction was stirred at −25 °C for 45 min. The crude product was purified using column chromatography (EtOAc:hexanes = 1:9, $R_f = 0.41$) to obtain **9a** as a light yellow oil (19.5 mg, 0.0738 mmol, 93%): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.58 (m, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 3.22–3.12 (m, 2H), 3.05–2.99 (m, 1H), 2.91–2.83 (m, 2H), 2.81–2.77 (m, 1H), 2.49–2.38 (m, 2H), 2.05–1.96 (m, 1H), 1.84–1.61 (m, 5H), 1.47–1.41 (m, 1H), 1.34–1.10 (m, 5H), 0.99–0.86 (m, 1H); ^{13}C NMR (APT, CDCl$_3$, 75 MHz) δ 156.2, 123.3, 73.1, 72.7, 58.7, 58.4, 49.4, 47.2, 45.2, 41.7, 41.2, 39.5, 32.9, 30.5, 26.6, 26.5, 26.3; IR (neat, NaCl, cm^{-1}) 2975 (w), 2923 (m), 2851 (m), 2806 (w), 1613 (w), 1482 (w), 1449 (m), 1388 (w), 1338 (w), 1295 (w), 1258 (w), 1192 (w), 1168 (w), 1104 (m), 969 (w), 943 (w), 826 (w); HRMS (CI) calcd for $C_{17}H_{28}O_2$ (M$^+$) 264.2089, found 264.2093.

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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