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Facile Access to Optically Active Ferrocenyl Derivatives with Direct Substitution of the Hydroxy Group Catalyzed by Indium Tribromide

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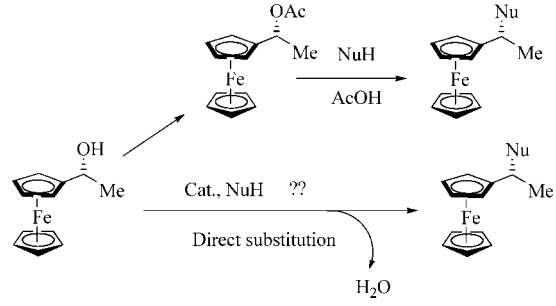
Keywords: Ferrocene / Alcohols / Indium tribromide / Catalysis

Ferrocene derivatives have found many different uses and applications in organometallic chemistry, material chemistry, and catalysis. We have shown that using a catalytic amount (5–10 mol-%) of commercially available indium tribromide, at room temperature, many carbon nucleophiles, such as indoles, allylsilane, enolsilane, silyl ketene acetal, diketone, and trimethylsilylcyanide, smoothly react with different optically active ferrocenyl alcohol derivatives to afford the desired products in high yield, with retention of configuration. Also, many different N-nucleophiles (azide, carbamates) and O-nucleophiles (alcohols) react as well, again with retention of configuration.

Introduction

The discovery of ferrocene and elucidation of its structure could be considered the starting point for modern organometallic chemistry.[1] The ferrocene framework is widely used in asymmetric catalysis[2] because it is able to incorporate a stereogenic plane with stereocenters. Planar stereogenicity and stereocenters often act cooperatively in a variety of stereoselective transformations.[3] The bioorganometallic chemistry of ferrocene has also been developed over recent years as a rapidly growing field.[4] Since the pioneering work of Ugi,[5] it is generally accepted that ferrocenyl derivatives with a leaving group in the α position undergo nucleophilic substitution with complete retention of configuration.[6] This paradigm is extensively used in the preparation of chiral ferrocenyl derivatives.[7] However, in the presence of a relatively poor leaving group, such as an alcohol, racemization occurs in the absence of good nucleophiles.[8] A variety of different nucleophiles, such as phosphanes and amines, can be used with ferrocenyl acetate.[5–7] Although Lewis acids were described as facilitating these reactions, even with carbon nucleophiles, stoichiometric amounts of Brønsted (AcOH) or Lewis acids (BF_3)[9] are normally used (Scheme 1). To expand the chemistry to sensitive nucleophiles and to avoid the acylation step, direct substitution of the hydroxy group in a catalytic process under nearly neutral conditions would be an ideal procedure in ferrocene chemistry. This direct substitution would expand the use of this fascinating molecule in organometallic, bioorganic, and material chemistry and catalysis. Herein we report a straightforward, simple methodology that uses a catalytic amount of indium tribromide and allows the direct addition of a variety of different nucleophiles to optically active hydroxy ferrocenyl derivatives with retention of the stereochemistry.



Scheme 1. Preparation of ferrocenyl derivatives by indirect or direct substitution.

Results and Discussion

Catalytic activation of alcohols is generally rather difficult because of the poor leaving group ability of the hydroxy group. Recently, by using indium[10] or iron[11] salts, Baba and Beller described the efficient replacement of benzylic or allylic alcohols by nucleophiles, various active methylene compounds, indole, and acidic ketones.[12] Baba also used a ferrocenyl carbinol as the starting material in his investigations of the coupling reaction between alcohols and silyl compounds.[13] Although detailed mechanistic investigations have not yet been presented, and there is no clear evidence that a free carbocation is formed in these reactions, we reasoned that the chiral cationic intermediate,

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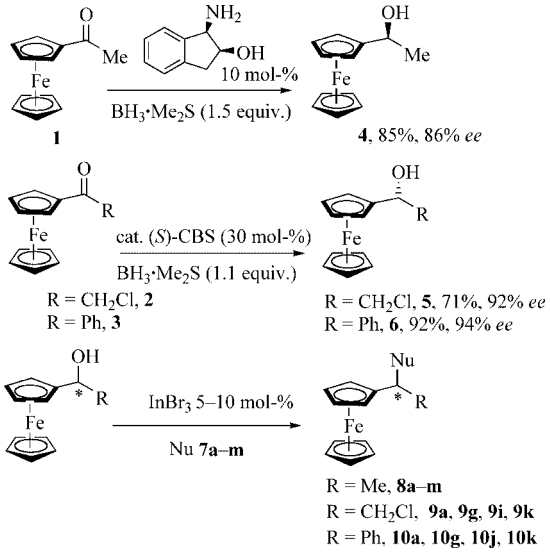
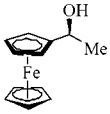
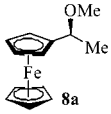
formed by treatment of α-ferrocenyl carbinol with a catalytic amount of indium salt, could be used in substitution reactions with a variety of different nucleophiles (Scheme 2). Encouragingly, in the preliminary experiment, we observed the desired reaction when ferrocenyl alcohol **4**, obtained in 86% *ee* by the aminoindanol/BH_3 reduction[14] of ketone **1**, was treated with MeOH (**7a**, 2 equiv.)[15] in the presence of different indium salts and reaction solvents (Table 1). Dichloromethane was the optimal solvent, whereas THF (40%) and other noncoordinating solvents provided inferior yields. $InBr_3$ gave better results relative to those of the other indium salts that were tested. In all the reactions, we observed retention of the stereochemical information. We used the selected reaction conditions with a variety of different nucleophiles, **7a**–**m**, with optically active ferrocenyl alcohols **4**, **5**, and **6** as substrates,[16] and some of the results obtained are reported in Table 2. The water



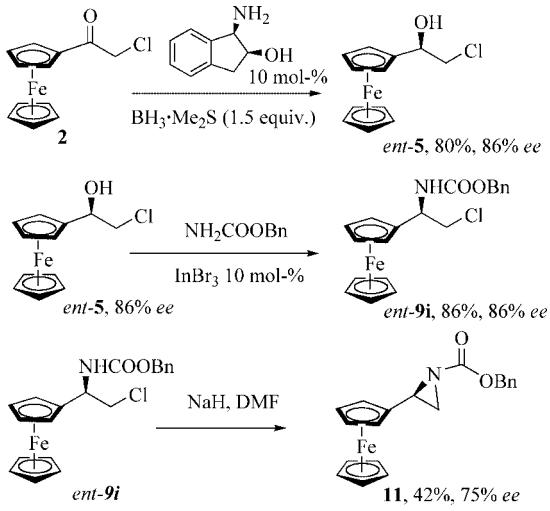
Scheme 2. Direct substitution of ferrocenyl alcohols catalyzed by $InBr_3$.

Table 1. Direct addition of MeOH to ferrocenyl alcohol **4** catalyzed by indium salts.

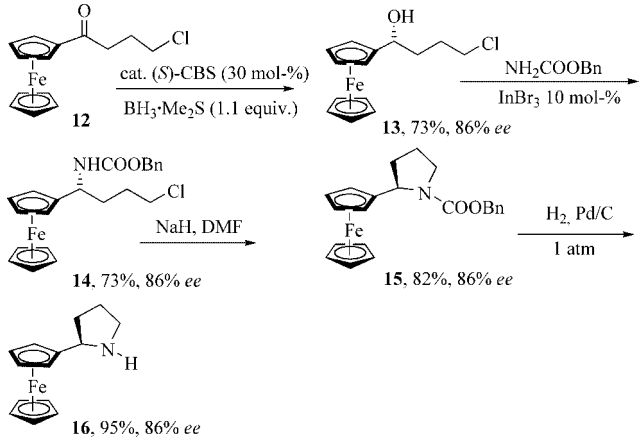
Entry[a]	Alcohol	Solvent	Yield [%][b]	Product	*ee* [%][c]
1	 **4**, 86% *ee*	CH_2Cl_2	98	 **8a**	86
2	**4**	CH_3CN	72	**8a**	86
3	**4**	THF	40	**8a**	86
4	**4**	Et_2O	51	**8a**	86
5	**4**	toluene	81	**8a**	86
6[d]	**4**	CH_2Cl_2	86	**8a**	86
7[e]	**4**	CH_2Cl_2	84	**8a**	86

[a] In all reactions 10 mol-% of $InBr_3$ and 2 equiv. of MeOH were used. The reactions were quenched after 1 h. [b] Yields of isolated product. [c] Enantiomeric excesses were determined by HPLC (see Supporting Information). [d] 10 mol-% of $InCl_3$ was used. [e] 10 mol-% of $In(OTf)_3$ was used.

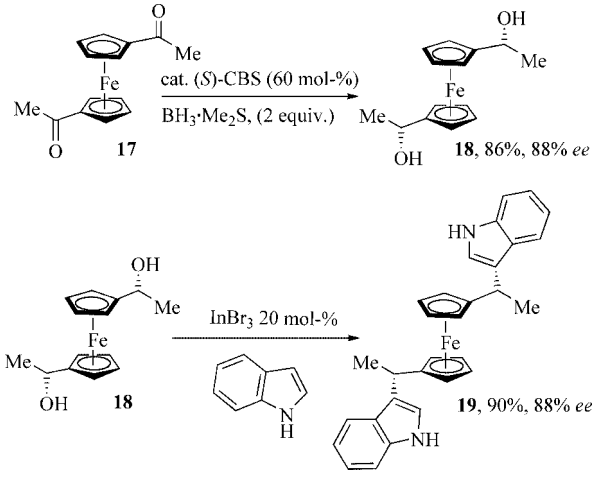
resistance of indium salts and their Lewis acidity in the presence of different coordinating nucleophiles are important factors in these reactions. The reaction of ferrocenyl alcohol **4** with nucleophiles **7a**–**m** easily provided the corresponding products (Table 1, Entry 1; Table 2, Entries 1–16).



Scheme 3. Synthesis of a ferrocenyl aziridine.



Scheme 4. The preparation of pyrrolydinyl ferrocene.



Scheme 5. Addition of indole to bishydroxy ferrocenyl ethanol.

The strategy was applied to indole and substituted indoles to give the 3-alkylated products in high yield, complete selectivity, and with complete retention of the stereochemical information.[10a] We observed no regioisomers derived from N- or 2-alkylation.[17] Different silyl nucleophiles (allylsilane, silyl enol ethers, silylazide, and silylcyanide) were examined and afforded the corresponding products, once again with no loss of stereochemical information. An active methylene compound (Table 2, Entry 5) and carbamates[12m] (Table 2, Entries 11 and 12) provided the corresponding products in high yields. To gain preliminary information about the scope of the reaction, we briefly examined ferrocenyl derivatives **5** and **6** (Table 2, Entries 17–24) with some selected nucleophiles. As is possible to see from the reported examples, ferrocenyl aryl alcohols give the corresponding derivatives in high yield. However, in the reactions of **6** with the nucleophiles employed, racemization is observed, and it is more pronounced with methoxy derivative **10a**, which was obtained in only 60% *ee*.[18] To illustrate some potential applications of our methodology, we used our chemistry to obtain unknown aziridine **11** (Scheme 3), although the isolated yield and enantiomeric excess were only moderate due to the instability of **11** during the purification step. To the best of our knowledge, this is the first preparation of a ferrocenyl aziridine of this type that could be employed to prepare a large variety of useful intermedi-

Table 2. $InBr_3$-catalyzed direct reaction of **4**, **5**, and **6** with nucleophiles **7a**–**m**.

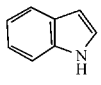
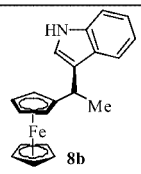
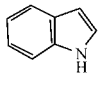
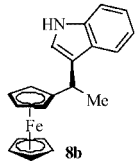
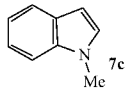
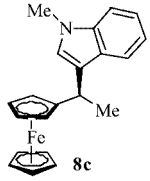
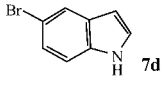
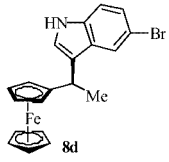
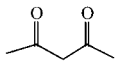
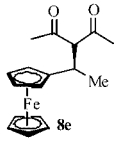
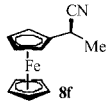
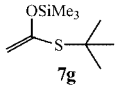
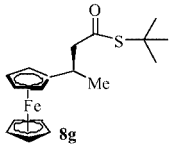
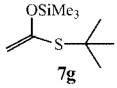
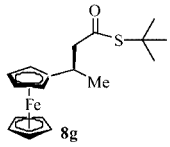
Entry[a]	Alcohol	Nucleophile	Yield [%][b]	Product	*ee* [%][c]
1	**4**	 **7b**	83	 **8b**	86
2[d]	**4**	 **7b**	78	 **8b**	86
3	**4**	 **7c**	83	 **8c**	86
4	**4**	 **7d**	87	 **8d**	86
5	**4**	 **7e**	82	 **8e**	86
6	**4**	Me_3SiCN **7f**	86	 **8f**	86
7	**4**	 **7g**	84	 **8g**	85
8[e]	**4**	 **7g**	80	 **8g**	85

Table 2. *(continued)*

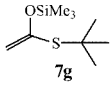
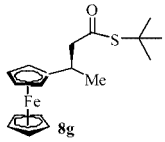
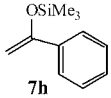
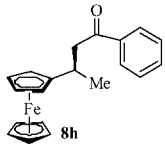
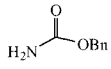
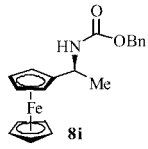
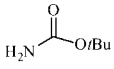
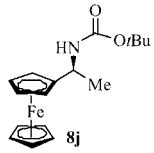
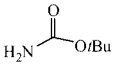
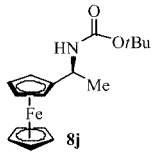
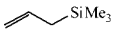
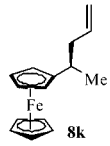
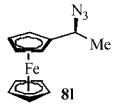
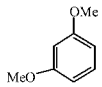
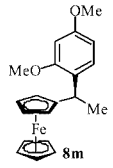
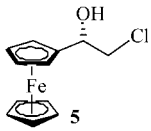
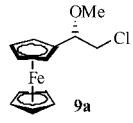
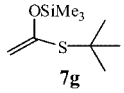
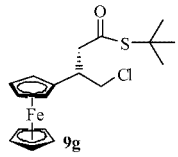
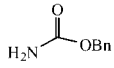
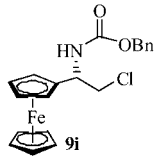
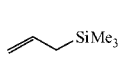
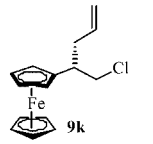
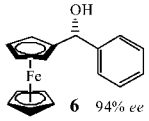
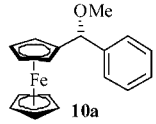
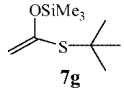
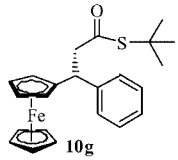
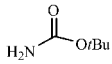
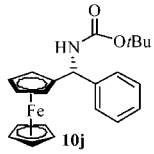
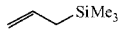
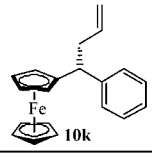
Entry[a]	Alcohol	Nucleophile	Yield [%][b]	Product	*ee* [%][c]
9[f]	**4**	 **7g**	70	 **8g**	85
10	**4**	 **7h**	40	 **8h**	84
11	**4**	 **7i**	85	 **8i**	85
12	**4**	 **7j**	88	 **8j**	84
13[d]	**4**	 **7j**	84	 **8j**	83
14	**4**	 **7k**	80	 **8k**	86
15	**4**	Me_3SiN_3 **7l**	84	 **8l**	85
16[g]	**4**	 **7m**	84	 **8m**	80
17	 **5** 92% *ee*	MeOH **7a**	76	 **9a**	92
18	**5**	 **7g**	82	 **9g**	93
19	**5**	 **7i**	79	 **9i**	93

Table 2. *(continued)*

Entry[a]	Alcohol	Nucleophile	Yield [%][b]	Product	*ee* [%][c]
20	**5**	 **7k**	63	 **9k**	92
21	 **6** 94% *ee*	MeOH **7a**	92	 **10a**	60
22	**6**	 **7g**	67	 **10g**	89
23	**6**	 **7j**	95	 **10j**	94
24	**6**	 **7k**	98	 **10k**	80

[a] In all reactions 10 mol-% of $InBr_3$ and 2 equiv. of the nucleophile were used. All reactions were quenched by water after completion, checked by TLC (2–10 h). [b] Yields of isolated purified product. [c] Enantiomeric excesses were determined by HPLC (see Supporting Information). [d] A catalytic amount of 5 mol-% of $InBr_3$ was used. The reaction was quenched after 24 h. [e] A catalytic amount of 10 mol-% of $In(OTf)_3$ was used. [f] A catalytic amount of 10 mol-% of $InCl_3$ was used. [g] The ferrocenyl alcohol was slowly added to the mixture of 1,3-dimethoxybenzene and $InBr_3$ in CH_2Cl_2 (see Supporting information).

ates before purification. Our methodology could be applied in general to access new and useful chiral ligands (Scheme 4). Ketone **12** was reduced with the CBS (Corey–Bakshi–Shibata)[14] method to **13**. Addition of benzylcarbamate **7i** took place in high yield and with high stereoselection. Product **14**, isolated in high yield, was transformed into protected ferrocenyl pyrrolidine **15**. The pyrrolidine was easily deprotected with Pd/C and H_2 to afford enantioenriched ferrocenyl pyrrolidine **16**, which was recently reported by Guiry[19] using a different synthetic route. Our chemistry also worked using ferrocenyl diols (Scheme 5). Diacetyl ferrocene **17** was reduced according to Knochel[20] to corresponding bishydroxy derivative **18**. The successive indium-catalyzed reactions with indole provided corresponding bisindole **19** in high yield and with retention of stereochemistry. The attachment of nucleophiles catalyzed by indium proceeds with retention of configuration in the case of benzylcarbamate and methanol, as demonstrated by the chemical correlations (see Supporting Information), and it is assumed to proceed with retention of configuration for all other nucleophiles.

Conclusion

We reported a convenient and general indium-catalyzed direct substitution of the hydroxy group in ferrocenyl alcohols by nucleophiles such as allyl, enol, cyano, azido silane, indoles, an active methylene compound, and carbamates. This reaction is operationally simple as it occurs simply by mixing the substrates and the nucleophiles with $InBr_3$ in CH_2Cl_2 at room temperature or "0 °C" to give practical access to a variety of enantioenriched useful ferrocenyl intermediates. Investigation of direct substitution of enantioenriched ferrocenyl alcohol with other Lewis or Brønsted acids is in progress and will be reported in due time.

Supporting Information (see footnote on the first page of this article): Complete data (^1H and ^{13}C NMR spectral data, HPLC analysis) for compounds **8a**–**m**, **9a**, **9g**, **9i**, **9k**, **10a**, **10g**, **10i**, **10k**, **13**, **14**, **15**, **16**, and **19**.

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