Utility of a diene–tricarbonyliron complex as mobile chiral auxiliary: iterative use for constructing contiguous chiral centers

Yoshiji Takemoto,*[a] Yasutaka Baba,[b] Naoki Yoshikawa,[b] Chuzo Iwata,[b] Tetsuaki Tanaka*[b] and Toshiro Ibuka[a]

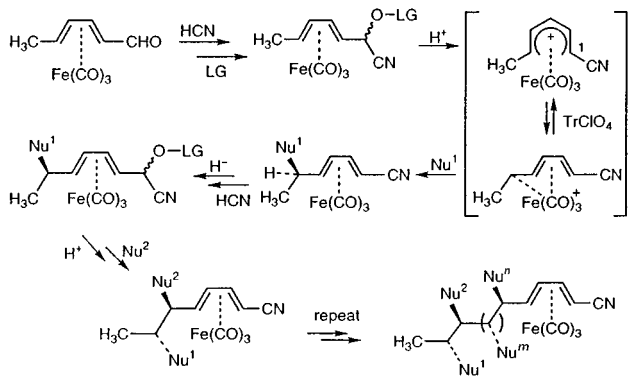
[a] *Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: takemoto@pharm.kyoto-u.ac.jp*

[b] *Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan*

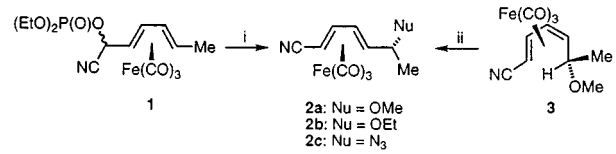
Three stereogenic centers bearing azide, methoxy, and ethylthio groups, have been constructed stereoselectively using the sole chirality of the $Fe(CO)_3$ group with concurrent 1,2-migration of the $Fe(CO)_3$ group and the obtained product was converted to an *anti*-aminoalcohol derivative to determine the absolute stereochemistry.

Nucleophilic attack on coordinated polyenes is an important reaction in π-organometallic chemistry.[1] If reactions of this type occur with predictable regio- and stereo-selectivity, they can be of synthetic utility. For example, the reactivity of acyclic (pentadienyl)iron(1+) cations has been the subject of recent intense investigations.[2] However, compared with cyclic iron(1+) cation complexes,[3] regio- and stereo-selective nucleophilic addition to the acyclic (pentadienyl)iron(1+) cations seems to be difficult due to their configurational flexibility. Thus far, several efficient methods, which skip the isolation of the acyclic (pentadienyl)iron(1+) cations (*in situ* generation), have been developed and applied to natural product synthesis.[4] Previously, we described the regio- and stereo-selective 1,5-nucleophilic substitution of the cyanophosphate $Fe(CO)_3$ complexes with several heteroatomic nucleophiles, giving the 1,2-migrated products of the $Fe(CO)_3$ group with (*E*,*Z*)-configuration.[5] Here, we wish to describe the regio- and stereoselective synthesis of (*E*,*E*)-1,5-substituted adducts and their novel application to construction of contiguous stereogenic centers in acyclic alkenes (Scheme 1).

During our studies on the 1,5-nucleophilic substitution of the cyanophosphate **1**† with methanol, we found that the 1,5-substitution of **1** into the (*E*,*E*)-adducts was catalyzed by trityl perchlorate ($TrClO_4$) in the presence of various nucleophiles. Indeed, treatment of **1** with 10 equiv. of heteroatomic nucleophiles such as methanol, ethanol, and $TMSN_3$ in the presence of 1.1 equiv. of $TrClO_4$ in THF at room temperature gave the desired products **2a**–**c**‡ in moderate yields in all cases (Scheme 2). Furthermore, $TrClO_4$ also promoted the isomerization of the (*E*,*Z*)-adduct **3**‡ to the (*E*,*E*)-adduct **2a**‡ in 81% yield.



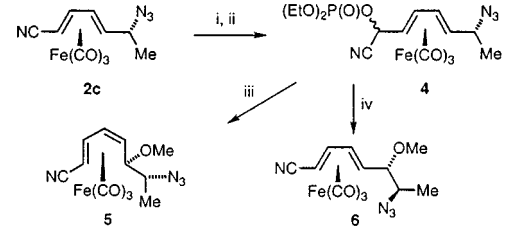
Scheme 1 Utility of an iron–tricarbonyl complex as a mobile chiral ligand



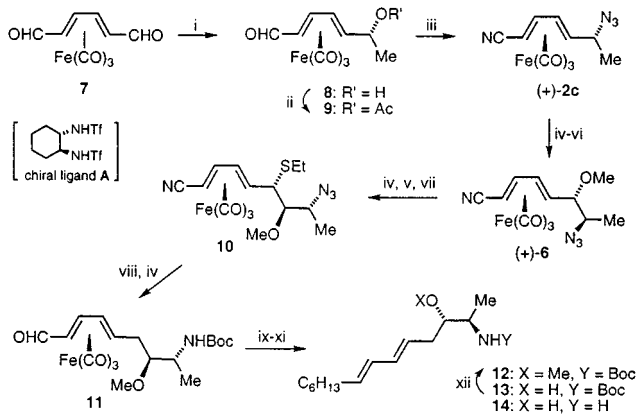
Scheme 2 *Reagents and conditions*: i, NuH (10 equiv.), $TrClO_4$ (1.1 equiv.), THF, r.t., 49% (Nu = MeOH) for **2a**; 41% (Nu = EtOH) for **2b**; 56% (Nu = $TMSN_3$) for **2c**; ii, MeOH (10 equiv.), $TrClO_4$ (1.1 equiv.), THF, r.t., 81%

We next examined the possibility of iterative manipulation of this 1,5-nucleophilic substitution with the obtained azide **2c** (Scheme 3). The requisite cyanophosphate **4** was prepared from **2c** as follows. The reduction of **2c** with diisobutylaluminium hydride (DIBAL-H) was followed by the reaction with diethylphosphoryl cyanide[6] to afford the desired cyanophosphate **4**.† The crude cyanophosphate **4** was subjected to a catalytic amount of $BF_3{\cdot}OEt_2$ in methanol at 0 °C to give rise to the (*E*,*Z*)-1,2-migrated product **5**‡ as a single isomer in 53% yield in two steps (method A).[5] On the other hand, the subjection of **4** to 1.1 equiv. of $TrClO_4$ and 10 equiv. of methanol in THF at room temp. afforded the (*E*,*E*)-1,2-migrated product **6**‡ as a single isomer in 52% yield in two steps (method B). These results indicate that the second nucleophile was introduced regio- and stereo-selectively with the 1,2-migration of the $Fe(CO)_3$ group without influence of the azide group.

In order to determine the absolute stereochemistry of **6** and also to extend this method to the asymmetric synthesis of a natural product such as 2,3-*anti*-aminoalcohol[7] **14** (Scheme 4), we next applied this iterative manipulation to the chiral compound (+)-**2c**. Although we have already reported the efficient asymmetric synthesis of the chiral $Fe(CO)_3$ complexes by the catalytic asymmetric alkylation of *meso*-hexadienal $Fe(CO)_3$ complex **7**, the reaction with dimethylzinc resulted in low yield and poor enantioselectivity.[8] So, we first investigated other reaction conditions to obtain (+)-**2c** enantioselectively. After many experiments, we found that Kobayashi's procedure[9]



Scheme 3 *Reagents and conditions*: i, DIBAL-H, CH_2Cl_2, −78 °C, 78%; ii, $(EtO)_2P(O)CN$, LiCN, THF, r.t.; iii, $BF_3{\cdot}Et_2O$, MeOH, 0 °C, 53%; iv, $TrClO_4$, MeOH, THF, r.t., 52%



Scheme 4 *Reagents and conditions*: i, Me_2Zn, $Ti(OPr^i)_4$, chiral ligand (A), −20 → 0 °C, toluene, 71%; ii, Ac_2O, pyridine, CH_2Cl_2, r.t., 80%; iii, $TMSN_3$, $Sc(OTf)_3$, CH_2Cl_2, r.t., 90%; iv, DIBAL-H, CH_2Cl_2, −78 °C, 88% for **2c**, 77% for **6a**, 78% for **10**; v, $(EtO)_2P(O)CN$, LiCN, THF, r.t.; vi, $TrClO_4$, MeOH (10 equiv.), THF, r.t., 52%; vii, $TrClO_4$, EtSH (10 equiv.), THF, r.t., 61%; viii, H_2 (5 atm), 10% Pd/C, $(BOC)_2O$, MeOH, r.t., 81%, ix, $C_5H_{11}PPh_3Br$, Bu^nLi, toluene, −78–0 °C, 73%; x, H_2 (3 atm), 10% Pd/C, MeOH, r.t., 81% xi, Me_3NO, benzene, 60 °C, 85%; xii, MeI, Ag_2O, MeCN, reflux, 53%

was suitable for the purpose. The reaction of **7** with 1.8 equiv. of dimethylzinc and 1.8 equiv. of titanium(IV) isopropoxide in the presence of the chiral ligand (**A**) in toluene at 0 °C gave rise to monomethylated complex **8** in 71% yield with 96% ee. After acetylation of **8**, an azide group was introduced stereoselectively by the treatment of **9** with $TMSN_3$ and $Sc(OTf)_3$ in CH_2Cl_2 to afford (+)-**2c**.§ Here we undertook the same manipulation developed above (method B) with (+)-**2c** to obtain the *anti*-adduct (+)-**6**‡ in a comparable yield without any racemization. The further introduction of an ethylthio group into (+)-**6** by a similar procedure using $TrClO_4$ and ethanethiol (method B) also proceeded successfully to give the desired (*E*,*E*)-adduct **10**‡ as a single isomer in 61% yield. The hydrogenation in the presence of di-*tert*-butyl dicarbonate and sequential reduction with DIBAL-H of **10** gave the carbamate **11**, which was converted to **12** by a three-step sequence [Wittig reaction, hydrogenation over 10% Pd/C, and decomplexation]. This compound **12** was identical to the synthetic sample which was prepared from the known (2*R*,3*S*)-aminoalcohol derivative **13**[10] by the methylation (MeI, Ag_2O, MeCN, reflux; 53%) in respect of ^1H NMR, IR, mass, and $[\alpha]_D$. Based on these results, it is revealed that all substituents in **6** and **10** would be introduced from the opposite side of the $Fe(CO)_3$ group to give all *anti*-adducts in this iterative manipulation using method B. In conclusion, we have achieved the highly stereoselective synthesis of **12**, a key compound for the asymmetric synthesis of the natural product **14**, by using the (diene)$Fe(CO)_3$ group as a sole and mobile chiral auxiliary. This is the first example in the π-organometallic chemistry that the π-coordinated metal-group controls the contiguous stereogenic centers in acyclic compounds with concurrent 1,2-migration.

Notes and References

† Owing to the instability of **1** and **4** towards column chromatography, these compounds were used as a diastereomixture (2 : 3) without purification.

‡ The relative and absolute stereochemistry of **2a**–**c**, **3**, **5**, **6** and **10** were elucidated from the reported examples[2] and conversion of **10** and the reported product **13** to **12**.

§ Under these reaction conditions, the aldehyde group was converted to a nitrile group.

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