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DEVELOPMENT OF SOLVENT-DRIVEN IRON-CATALYZED REACTIONS

Toshiyuki Itoh

Department of Chemistry and Biotechnology, Graduate School of Engineering, Center for Research on Green Sustainable Chemistry, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan

Abstract – The possibility of solvent-driven iron-catalyzed reactions has been investigated using ionic liquids and acetonitrile as key solvents. Three iron-catalyzed reactions, the intramolecular cyclization of cyclopropane dithioacetals, the [2+2]-cycloaddition of (*trans*)-anethole, and the [2+3]-type cycloaddition of styrene derivatives with 1,4-benzoquinone, were first developed using acetonitrile as solvent in the presence of 3~5 mol% of $Fe(ClO_4)_3$•Al_2O_3 or $Fe(BF_4)_2$•$6H_2O$ under air conditions. In particular, we found the rapid cycloaddition of iron-catalyzed [2+3]-type cycloaddition of styrene derivatives with 1,4-benzoquinone when the reaction was carried out in an ionic liquid which contained [PF_6] or [Tf_2N] anion. Homo-coupling reaction of aryl or alkynyl Grignard reagent was next discovered using 1 mol% of $FeCl_3$ as catalyst and the reaction also proceeded very rapidly in an ionic liquid. We also found that 3~5 mol% of $Fe(ClO_4)_2$•Al_2O_3 or $Fe(BF_4)_2$•$6H_2O$-successfully catalyzed Friedel-Crafts type alkylation of indoles or pyrroles with vinyl ketones or α-aryl-β-silylalcohol. In particular, the reaction of chiral α-aryl-β-silylalcohol with indole using $Fe(ClO_4)_3$•nH_2O as catalyst proceeded with retention of the configuration of stereochemistry of the hydroxyl group. Then, we discovered the first example of iron-catalyzed enantioselective C-S bond formation *via* Michael addition of thiols to (*E*)-3-crotonoyloxazolidin-2-one using 10 mol% of $Fe(BF_4)_2$/Pybox. We further demonstrated that $Fe(ClO_4)_3$•Al_2O_3-catalyzed the Nazarov type cyclizations of thiophene, pyrrole, indole, benzofuran, and benzo[*b*]thiophene derivatives using ionic liquids as solvent. Solvents have been recognized as a by-player in chemical reactions in the process of “optimization of reaction conditions”. However, further investigation of the solvent-driven iron-catalyzed reaction will allow discovery of useful reactions for organic syntheses.

1. INTRODUCTION

Iron is one of the most abundant and environmentally friendly metals on the earth and there have been various types of iron metal-catalyzed organic transformations during the past decades.[1] Solvents provide a favorable environment for the intermediates of the chemical reaction and enhances the reactivity of the catalysts. However, solvents have been recognized as a by-player in chemical reactions in the process of "optimization of reaction conditions". We have been investigating the possibility of iron-catalyzed reactions by focusing on the solvent not as a supporting actor of the reaction but as an educator that brings out a masked ability of the iron cation: we have thus developed several of them, *i.e.*, the intramolecular cyclization of cyclopropane dithioacetals,[2] the [2+2]-cycloaddition of (*trans*)-anethole,[3] the [2+3]-type cycloaddition of styrene derivatives with 1,4-benzoquinone,[4] the Michael addition of β-ketoesters to vinyl ketones,[5] the enantioselective Michael addition of thiols to unsaturated carbonyl compounds,[6] Friedel–Crafts type alkylation of indoles or pyrroles with vinyl ketones[7] or α-aryl-β-silylalcohol,[8] homo-coupling reaction of aryl or alkynyl Grignard reagent,[9] and the Nazarov type cyclization of thiophene,[10,11] pyrrole,[12,13] indole,[14] benzofuran,[14] and benzo[*b*]thiophene derivatives.[14] In this chronicle, I report the story of how we developed these iron salt-catalyzed reactions from the beginning to the most recent ones.

2. IRON-CATALYZED REACTIONS BEGAN FROM A SINGLE ELECTRON OXIDATION

Kratochvil and Long reported that the reduction potential of the iron(III)-(II) couple depended on the solvent system which was estimated to be 1.57 volts in acetonitrile (MeCN).[15] I was strongly fascinated by the results because "1.57 volts" was a sufficient level for the single electron oxidation of organic molecules. On the contrary, the oxidation potential of a Fe^{3+} ion shown in textbooks of Inorganic Chemistry was 0.77 volt which was slightly insufficient to oxidize common organic molecules to generate cation radical species. Inspired by the results, I had decided to launch the present project of "development of a solvent driven iron-catalyzed reaction" in 1998. It was by sheer chance for me that I read the article of Kratochvil and Long: an abstract of the paper was in a neighboring column on a page of Chemical Abstracts when I looked for papers concerning the oxidation level of various metal cations as I prepared a lecture in graduate school. We had a strong interest in the iron(III)-catalyzed reactions emanating from a single electron oxidation in MeCN or an ionic liquid (IL) solvent system. ILs have now attracted great interest because of their characteristics of low-volatility, non-flammability, high ion conductivity, and a wide potential window;[16] however, they were not popular in those days. In fact, there were neither commercially available ILs nor any report referring to the oxidation potential of Fe^{3+}/Fe^{2+} when we began the project; the answer was reported by Yamagata and Katayama et al. to be 1.1 V in an ionic liquid, 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)amide ([bmim][Tf_2N]) in 2005

(Figure 1).[17] We also anticipated that the Lewis acidity of Fe^{3+} ion might be increased in ILs: because ILs consisted of non- or less coordinated anions and organic cationic molecules so that iron cation might exist as a "naked cation" in an IL solvent.

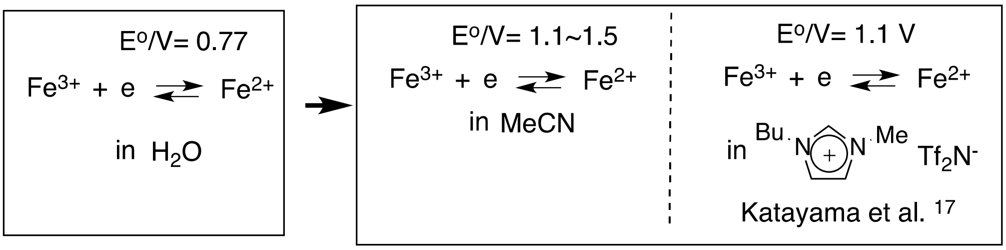


Figure 1. The reduction potential of the iron(III)-(II) couple in different solvent systems

Since there were no commercially available ILs in those days, we prepared ILs for the solvents of iron-catalyzed reactions ourselves and also established a method of recycling them.[18] This experience became a valuable asset for our group because we accumulated much important know-how on to use ILs during the study.

We had started the present project by the investigating a single electron oxidation followed by the ring-opening reaction of cyclopropanes using MeCN as a solvent, because it was well known that the cyclopropane ring opened easily to generate a carbon radical.[19] Several examples of ring-opening reactions of the cyclopropane ring had been reported (Figure 2). Booker-Milburn and co-workers reported that iron(III)-mediated oxidative ring opening of the cyclopropane compound **1** took place and gave the cyclized product **2** through the intermediate **1**$^{\#}$, although the reaction required 3 eq. of iron(III) salts vs. substrate **1** to complete the reaction (Figure 2, left reaction).[20] Takemoto and co-workers reported the similar reaction using a catalytic amount of an oxidant (0.5 eq. of $(p\text{-BrPh})_3NSbCl_6$), and succeeded in obtaining bicyclopentane **4** from *p*-tolylthio-substituted cyclopropane **3** through cation radical **3**$^{\#}$ as illustrated in the right reaction in Figure 2.[21]

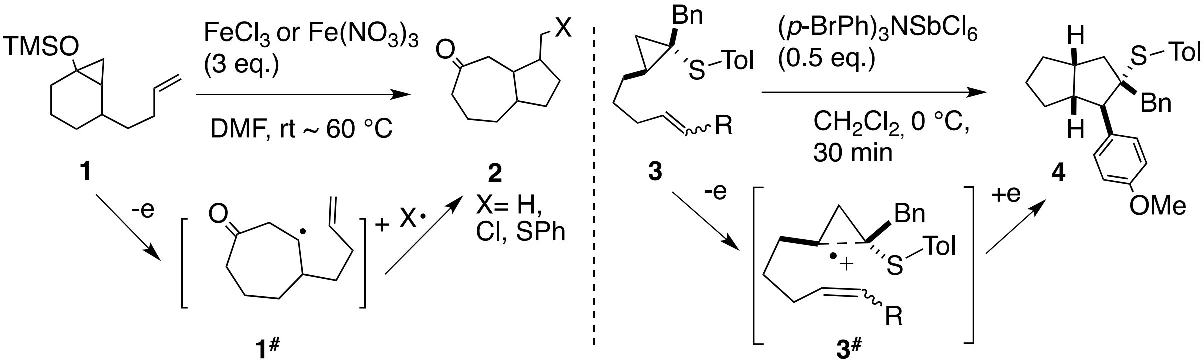


Figure 2. Early examples of cyclization that started from single electron oxidation

Based on the results, we hypothesized that ring-opening of cyclopropanonetrimethylenethioacetal **7**[22] might occur by treatment of iron(III) salt in MeCN as a solvent, because it was reported the reduction potential of dithioacetal was estimated to be 0.88 volt.[23] The desired reaction was indeed realized when **7** was treated with 10 mol% of iron(III) perchlorate ($Fe(ClO_4)_3 \cdot nH_2O$) in MeCN under air, subsequent cyclization with the olefinic part and reduction by an additional 1,3-dithiane giving *cis*-fused oxabicyclo[3.3.0]octane-1,1-trimethylenethioacetals **8** (Figure 3).[2] It was revealed that the key solvent was MeCN and no reaction took place in dichloromethane (CH_2Cl_2), hexane, toluene, THF, or H_2O.[2] The plausible mechanism was suggested by the PM3 calculation illustrated in Figure 3: the single-electron oxidation of the sulfur atom on **7** to afford the cation radical **7-1**$^{\#}$ which easily generated **7-2**$^{\#}$ by the ring opening reaction and subsequent cyclization to afford **7-3**$^{\#}$ that formed the final intermediate **7-4**$^{\#}$, which was finally reduced by 1,3-dithiane to give **8**.

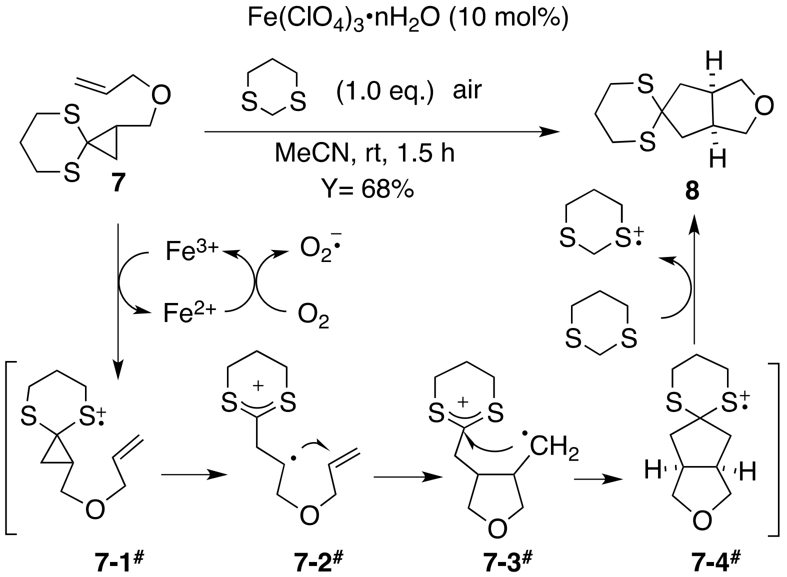


Figure 3. Iron(III) salt-catalyzed radical cyclization of cyclopropanone dithioacetal in MeCN

We next found [2+2] cyclodimerization of (*trans*)-anethole (**9**) and synthesized cyclobutane **10** in 92% yield with perfect *anti*-selectivity in the presence of 3 mol% of iron(III) salts (Figure 4):[3] iron(III) perchlorate ($Fe(ClO_4)_3 \cdot Al_2O_3$) catalyzed the reaction and *anti*-adduct **10** was produced as the sole product due to the presence of equilibrium of the final intermediate *syn*-**10**$^{\#}$ and *anti*-**10**$^{\#}$.

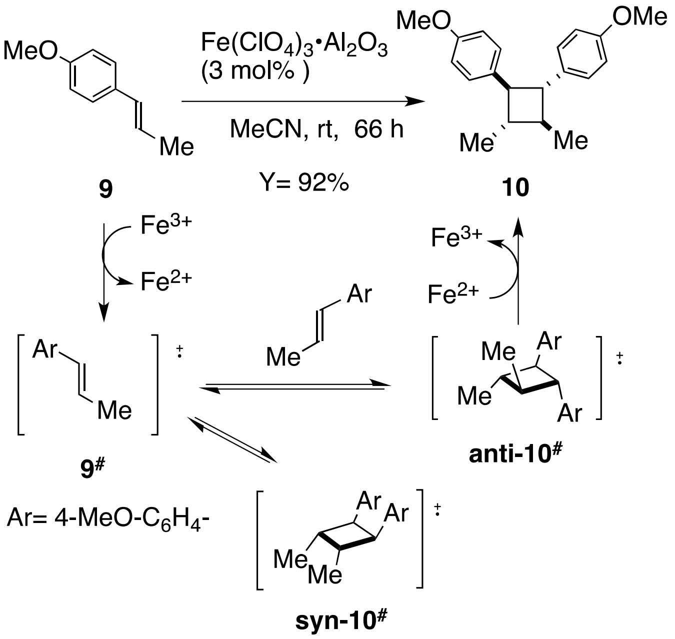


Figure 4. Iron(III)-catalyzed cyclodimerization of (*trans*)-anethole

Based on these results, we next tested reaction of *(trans*)-anethole with but-3-en-2-one (**11**). Although the desired [2+2]-cycloaddition product **12** was indeed obtained, we failed to improve the chemical yield (Figure 5). Hence, we switched the reactant to 1,4-benzoquinone **13** from **11**, and found that the product was not the expected [2+2]-cycloadduct **14** but 2,3-dihydrobenzofuran derivative **15** with excellent yield (92%) in the presence of just 3 mol% of $Fe(ClO_4)_3•Al_2O_3$ in MeCN as solvent.[4a] On the other hand, Engler and co-workers reported the preparation of the same compound using 1.2 eq. of Ti(IV) salt ($TiCl_4$: $Ti(OiPr)_4$ = 1.8:1) in 68% yield.[24]

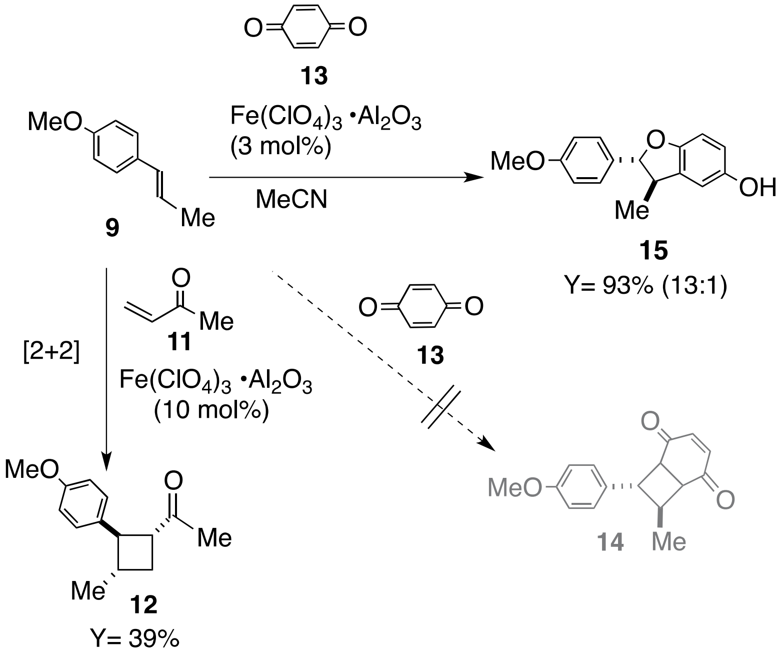
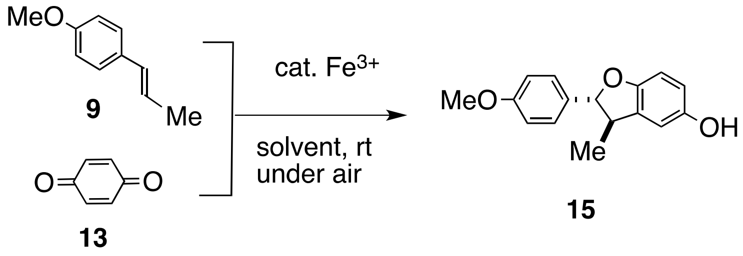


Figure 5. Reaction of (*trans*)-anethole with electron defficient olefinic compounds in the presence of iron(III) salt

We obtained very important results for further investigation in this study: the reaction rate drastically accelerated when the reaction was carried out in ILs as solvents (Scheme 1 and Table 1). To our surprise, the reaction was completed in less than 10 min in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), while it took 2 hours in MeCN with the same concentration (entries 1 and 2 in Table 1).



Scheme 1

Table 1. Iron-catalyzed [2+3]-cyclization of (*trans*)-anethole with benzoquinone

Entry	Solvent	Cat. (3 mol%)	Yield of **15** (*trans*/*cis*)
1	MeCN (rt 2 h)	$Fe(ClO_4)_3•Al_2O_3$	93% (13:1)
2	[bmim][PF_6] (rt 10 min)	$Fe(ClO_4)_3•Al_2O_3$	90% (15:1)
3	[bmim][PF_6] (rt 10 min)	$FeCl_3$	91% (11:1)
4	[bmim][PF_6] (rt 4 h)	$FeCl_2$	94% (12:1)
5	[bmim][PF_6] (rt 24 h)	$FeSO_4•7H_2O$	no reaction
6	[bmim][PF_6] (rt 10 min)	$Fe(BF_4)_2•6H_2O$	98% (11:1)
7	MeCN (rt 24 h)	$Fe(BF_4)_2•6H_2O$	no reaction
8	[bmim][BF_4] (rt 3 h)	$Fe(BF_4)_2•6H_2O$	68% (43:1)
9	[bmim][Tf_2N] (rt 10 min)	$Fe(BF_4)_2•6H_2O$	98% (15:1)
10	[bmim][OTf] (rt 24 h)	$Fe(BF_4)_2•6H_2O$	no reaction
11	[bmim][*n*-$C_5H_{11}SO_4$] (rt 12 h)	$Fe(BF_4)_2•6H_2O$	no reaction
12	[N_{221ME}][BF_4](rt 2 h)	$Fe(BF_4)_2•6H_2O$	63% (25:1)
13	[N_{221ME}][Tf_2N] (rt 10 min)	$Fe(BF_4)_2•6H_2O$	93% (15:1)

It was found that even iron(II) dichloride ($FeCl_2$) worked as a good catalyst in the IL (entry 4), though a long period was required to complete the reaction. On the contrary, no product was obtained for iron(II) sulfate ($FeSO_4$) (entry 5). We finally found that iron(II) tetrafluoroborate ($Fe(BF_4)_2•6H_2O$) worked the best in [bmim][PF_6] as a solvent (entry 6). Since the reaction proceeded smoothly under dry air conditions and it was well known that ferrous ion was easily oxidized by air to generate ferric ion, the real catalyst was speculated to be Fe^{3+} cation which caused the initial oxidation of (*trans*)-anethole (**9**). However, since

$Fe(BF_4)_2$•$6H_2O$ provided no product in MeCN (entry 7), the reactivity of this salt was strongly dependent on the solvent system. We further found that the reaction was also influenced by the counter-anion of the ILs employed as solvent. Very rapid reaction was also recorded for [bmim][Tf_2N] (entry 9), while the reaction rate was dropped for [bmim][BF_4] (entry 8), and no reaction occurred when [bmim][OTf] or [bmim][n-$C_5H_{11}SO_4$] was used as solvent (entries 10 and 11). Rapid reaction was again observed in *N*,*N*-diethyl-*N*-methyl-*N*-(2-methoxy)ethylammonium bis(trifluoromethylsulfonyl)amide ([N_{221ME}][Tf_2N]) (entry 13), and the reaction rate declined for [N_{221MEM}][BF_4] (entry 12). It was thus found that the reaction rate depended on the anions of the ILs in the following order, $PF_6 \simeq Tf_2N >> BF_4$. These results indicated that the counter-anions of both the iron cation and the ILs might play the key role in realizing this [2+3]-cycloaddition.

Engler et al. proposed that 2,3-dihydrobenzofuran **15** was generated by [2+2]-cyclization of anethole **9** with benzoquinone **13** and subsequent rearrangement of the resulting cation intermediate.[24] The reaction was stopped by addition of 1 eq. of TEMPO, then the positive solvatochromism was observed when the reaction was conducted in [N_{221ME}][Tf_2N]; these results indicated that a radical cation or anion intermediate existed in the reaction course.[4c] ILs are highly polar liquids, hence the environment provided by the IL might be appropriate for generation of a radical cation intermediate but not stabilize it because [PF_6] or [Tf_2N] anion is a less coordinative anion. Therefore, marked acceleration was accomplished. Fuchigami and co-workers reported that a charge-separated intermediate was destabilized by an IL and accelerated the corresponding reaction.[25] Another mechanism might also be possible: the “naked Fe^{3+} cation” may coordinate with 1,4-benzoquinone **13** and accelerate electron transfer reaction to (*trans*)-anethole (**9**). Although we were the first to find the activation of the iron salts mediated reaction by ILs, we did not pursue this further. Lee, Song and co-workers reported many examples of activation of several Lewis acids using ILs three years later after our publication; the activity of a Lewis acid depended on the counter anions of the solvent ILs following the order $PF_6 > Tf_2N >> BF_4$.[26,27,28] This was almost the same as that we obtained in the reaction of iron-catalyzed [2+3]-cyclization of (*trans*)-anethole with benzoquinone in ILs.

Styrene derivative **16** reacted with benzoquinone **13** in the presence of $Fe(ClO_4)_3$•Al_2O_3 in MeCN gave the adduct **17** in 84% yield. Then, the acetyl group of **17** was removed by methanolysis to afford **18** which was converted to optically active acetate **19** with >99% ee via lipase-catalyzed transesterification as shown in Figure 6.[4b] The aim to catalyze the reaction of acetate **16**, $Fe(ClO_4)_3$•Al_2O_3/ MeCN resulted better results as a catalyst than that of $Fe(BF_4)_2$•$6H_2O$/[bmim][PF_6].

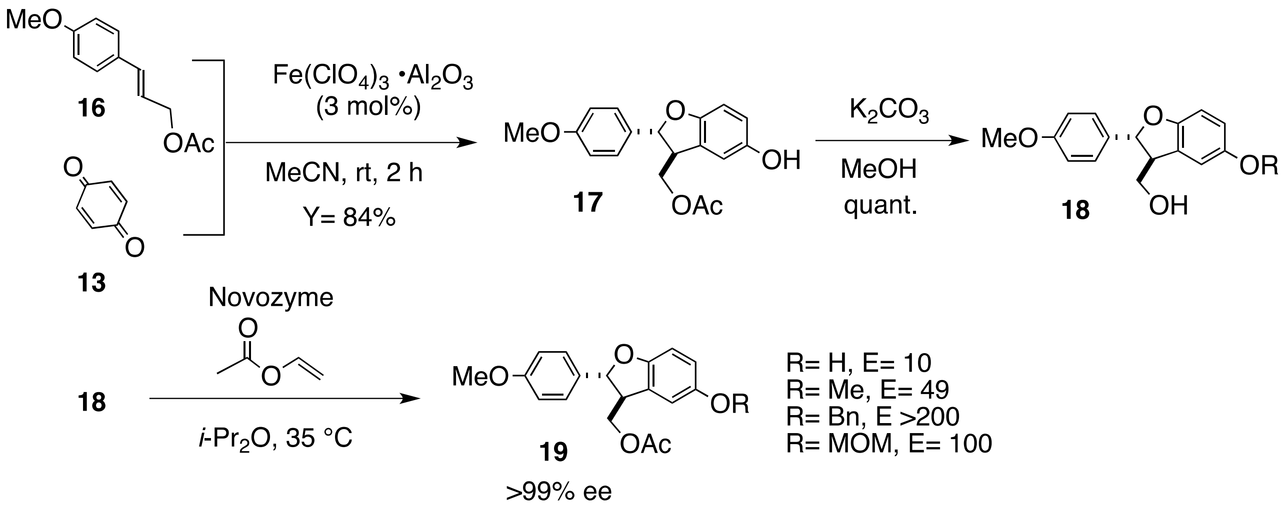


Figure 6. Preparation of chiral 2,3-dihydrobenzofuran derivatives by a combination of iron(III)-catalyzed cycloaddition reaction and subsequent lipase-catalyzed transesterification. "E value"[29] indcates the enantioselectivity of this enzymatic reaction: E= ln(1-c)(1+ ee19)/ln(1-c)(1-ee19)], here c means conv. which was calculated by the following formula: c= ee18/(ee19 + ee18). For details see ref. 29

This work revealed an interesting property of ILs in activating of electron transfer type reactions. Since electron transfer is the essential starting point of many chemical reactions, we next focused on the possibility of ILs-driven iron-catalyzed reactions.

Recently iron-catalyzed cross coupling reactions have gained strong interest among synthetic chemists.[30] Among such examples, we turned our attention to the $FeCl_3$-mediated homocoupling reaction of aryl Grignard reaction reported by Hayashi[31] and Cahiez et al.[32] The authors proposed that the reaction included electron transfer steps and the key step might be a reduction step of iron (III) cation by aryl Grignard reagent or a transmetallation step on the iron.[31a] However, ILs have been considered inappropriate for strong base-mediated reactions. Clyburn and co-workers reported the first example of Grignard reaction in an IL.[33] Since then, several groups, including ours, reported successful examples of the designs ILs for strong base-mediated reactions such as the Grignard reaction.[34-36] We succeeded in designing an IL by introduction of alkyl ether moiety on the side arm of phosphonium salt: methoxyethyl(tri-*n*-butyl)phosphonium bis(trifluoromethanesulfonyl)imide ($[P_{444ME}][NTf_2]$) was thus developed.[36] We applied this IL as solvent of the homo-coupling reaction of aryl Grignard reagent in the presence of 1 mol% of $FeCl_3$ using 1,2-dichloroethane or 1,2-diiodoethane as an oxidant (Figure 7).[9]

We found that the desired coupling reaction of **20** proceeded very rapidly; **21** was obtained in less than 5 min at 0 °C in excellent yields (86 ~ 100%) except for bulky 2,4,6-tirimethylphenylMgBr.[9] The reaction using 2-thienylMgBr **22** was very successful and the desired bithiophene **23** was obtained in 91% yield after just 10 min reaction at 25 °C. The IL solvent system was also useful for the homo coupling reaction of alkynyl Grignard reagent.[9] In this case, use of 1,2-diiodoethene was essential to afford the coupling product, and we obtained the desired **25** in 80% yield.[9]

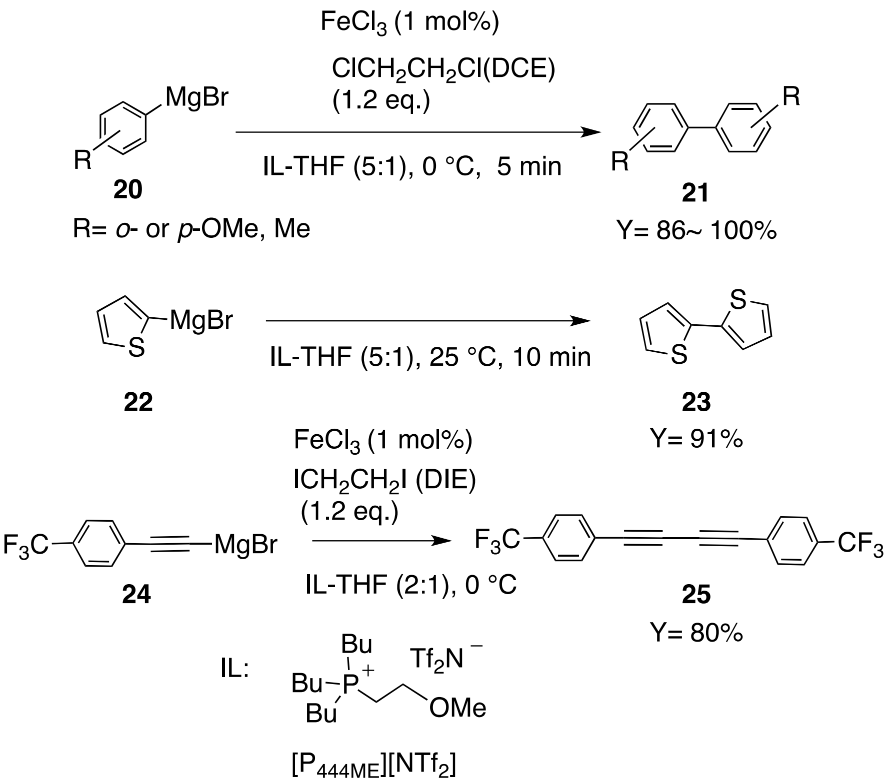


Figure 7. Iron(III)-catalyzed homo-coupling reaction of aryl or alkynyl Grignard reagents

3. IRON-CATALYZED FRIEDEL–CRAFTS TYPE ALKYLATION IN AN IL SOLVENT SYSTEM

We next investigated iron-catalyzed Friedel–Crafts type alkylation in ILs, focusing in particular, on the use of indole[7a,7c] and pyrrole[7b] derivatives as donor molecules, because the products of the reactions contain important structural motifs found in natural products and are essential intermediates in the preparation of pharmaceuticals and other chemicals.

The Lewis acid-mediated Friedel–Crafts type alkylation of indole with unsaturated carbonyl compounds has gained growing interest.[37] However, due to the basicity of indole, protection of the nitrogen atom in the indole ring was essential to realize such alkylation.[37] In the previous chapter, we found that $Fe(ClO_4)_3 \cdot Al_2O_3$ and $Fe(BF_4)_2 \cdot 6H_2O$ worked as excellent catalysts of cycloaddition reaction. We anticipated that these iron salts might work as an effective catalyst for Friedel–Crafts type alkylation of the N-protecting group–free indole. We found that the reaction indeed proceeded smoothly in MeCN or ILs as solvent, while no reaction took place when the reaction was conducted in CH_2Cl_2, $CHCl_3$, Et_2O, THF, toluene, or benzene in the presence of 3 mol% of $Fe(BF_4)_2 \cdot 6H_2O$ under air conditions at rt.[7] We thus obtained **27a** in 92% yield when indole **26** (R= H) was reacted with 5-phenylpent-1-en-3-one (Figure 8).[7a]

The reaction of indole with cyclopentenone afforded **27b** in 86% yield.[7a] Unfortunately, the reaction in the presence of chiral ligands, such as the (*R*,*R*)-Jacobsen[38] or (*S*,*S*)-bis-(oxazolinyl)pyridine (pybox) ligand,[39] gave the product with a racemic state under our reaction conditions,[7a] although Xia and Huang et al. recently reported chiral Brϕnsted acid directed $FeCl_3$-catalyzed enantioselective alkylation of indole.[40]

Control of regioselectivity of electrophilic substitution reaction of indole is an important task to be solved. We expected that regioselective electrophilic alkylation might be obtained using weak Lewis acid $Fe(BF_4)_2•6H_2O$ or $Fe(ClO_4)_3•Al_2O_3$ as a catalyst. As expected, the reaction showed perfect regioselectivity: alkylation took place at 3-position of the indole **26** to give 3-alkylated product **27**: we thus succeeded in obtaining the indole derivatives **27a** and **27b** were obtained in 92% and 86%, respectively (Figure 8, upper).[7c] We further established that the second alkylation took place at 2-position of **27**. After optimization of the reaction conditions, interestingly, solvent free conditions gave the best results: 7-methylindole **26c** was reacted with hept-1-en-3-one in the presence of 3 mol% of $Fe(ClO_4)_3•nH_2O$ to form 3-alkylated compound **27c**, after completion the reaction, addition of non-1-en-3-one with additional 5 mol% of $Fe(ClO_4)_3•nH_2O$ afforded the desired 2,3-double alkylated indole **28** (Figure 8, down).[7c] In the case, it was supposed that substrate indole and vinyl ketone worked as good solvents for the iron-catalyzed reactions.

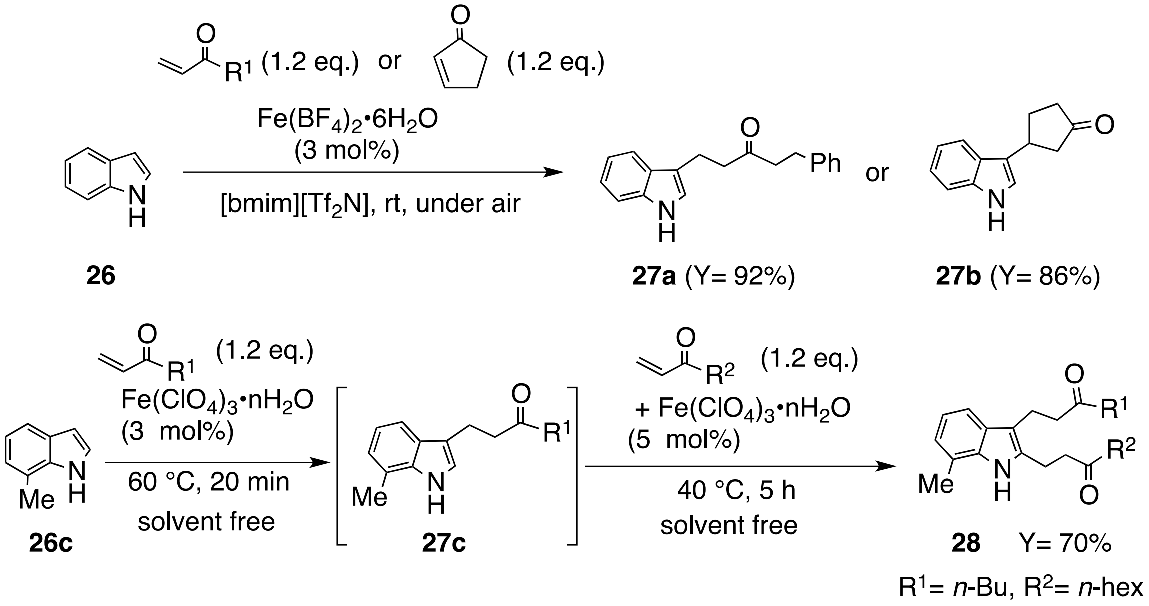


Figure 8. Iron salt-catalyzed alkylation of indole derivatives

The pyrrole group is found in many natural products as an important structural motif. However, since pyrrole is very sensitive to strong Lewis or Brϕnsted acid, no electrophilic alkylation method had been reported when we launched the project. Although we tested the reaction of pyrrole with 1-buten-3-one in the presence of 3 mol% of $FeCl_3$, neither alkylated product nor starting compound and only polymerized compounds were formed.[7b] We found that 2,5-dialkylated pyrrole and 2,3,5-trialkylated pyrrole was obtained in 37% and 12% yield, respectively, when the reaction was carried out in the presence of 3 mol% of $Fe(BF_4)_2•6H_2O$ in MeCN.[7b] After optimization of the reaction conditions of 2-acetylpyrrole **29**, we established double alkylation of 2-acetylpyrrole with vinyl ketones using 3 mol% of $Fe(ClO_4)_3•Al_2O_3$ and succeeded in preparing tri-substituted pyrrole derivative **30a**, **30b**, and **30c** in an 80%, 52%, and 78% yield, respectively (Figure 9).[7b] Solvent free conditions again gave the best results, though the reaction itself proceeded very smoothly in an IL, [bmim][Tf_2N], because extraction of the products from the IL layer was unsuccessful using conventional organic solvents such as Et_2O, cyclohexane, ethyl acetate or CH_2Cl_2.

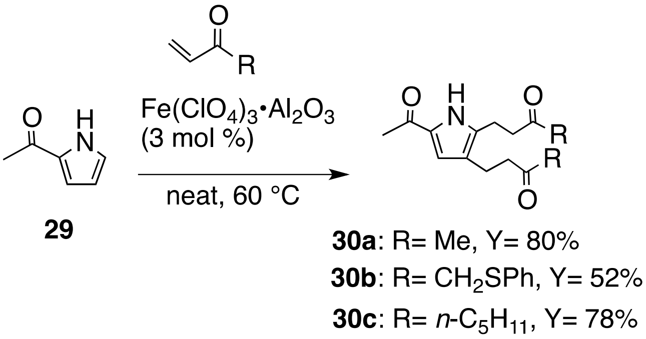


Figure 9. Iron-catalyzed alkylation of 2-acetytlpyrrole with vinyl ketones

We next turned our interest to the Friedel–Crafts alkylation using α-aryl alcohols as alkylating agents,[41] because several leading works had been reported.[42] We found that the cationic iron salt $Fe(BF_4)_2•6H_2O$ was a very effective catalyst for the Friedel–Crafts alkylation of indole derivatives **31** with β-silyl-alcohols **32**. The combination of indole derivatives with 2-furyl and 2-thienyl derivatives using $Fe(BF_4)_2•6H_2O$ was the best system and the corresponding products **33a** to **33d** were obtained in high yield; on the other hand, $Fe(ClO_4)_3•nH_2O$ gave better results for the reaction of phenyl derivative of β-silylalcohol, and **33h** was obtained in good yield (Figure 10).[8] However, no reaction took place for the reaction of 5-cyano- or nitro-*1H*-indole. In addition, reaction of indole with 1-(pyridin-2-yl)-2-(trimethylsilyl)ethanol also gave no desired product (Figure 10).

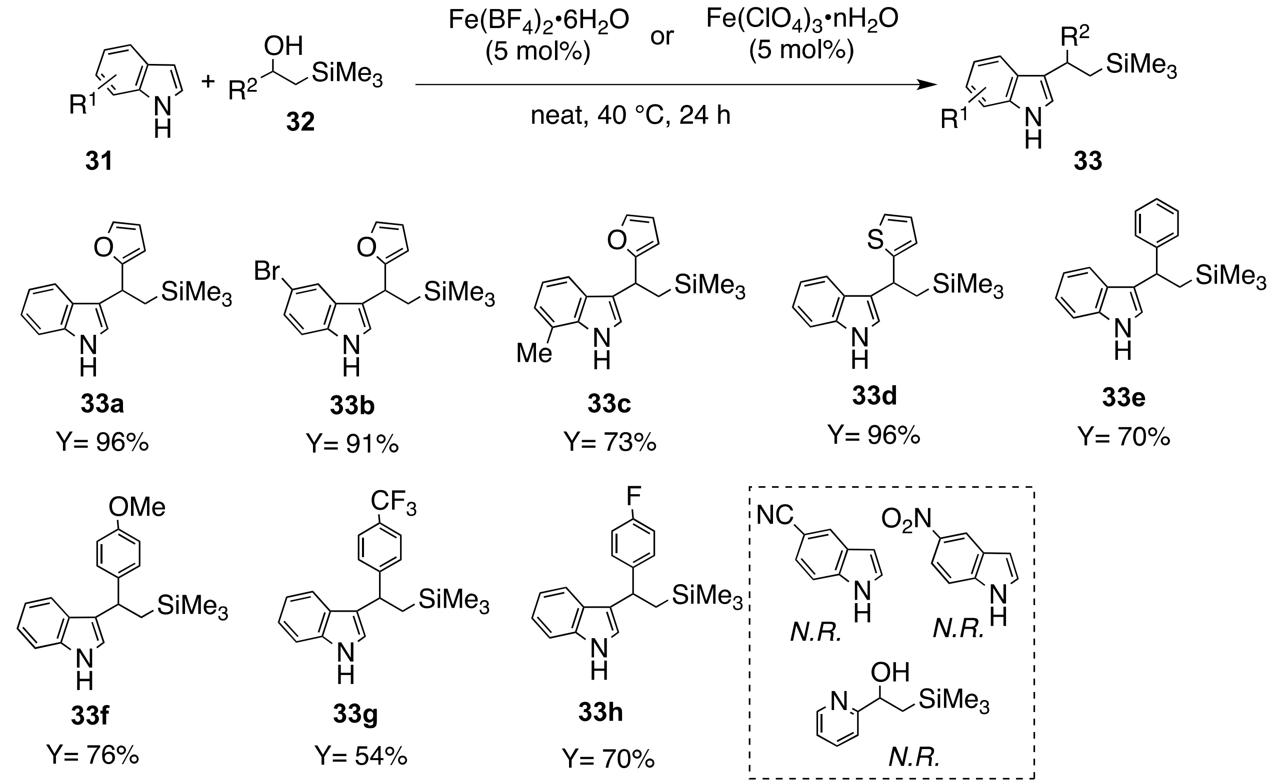


Figure 10. Iron salt-catalyzed Friedel–Crafts type alkylation of indole derivatives with β-silylalcohols

During the course of this study, we discovered that the Friedel–Crafts alkylation of chiral α-arylalcohols with a trimethylsilyl group was found to proceed with retention of the configuration of the hydroxy group as a leaving group (Figure 11).[8] Although the memory of chirality is useful in carbanion chemistry,[43] such reaction in carbocation chemistry is rare and there is no general means of achieving it.[44] Ugi and co-workers first reported the retentive electrophilic substitution of the α-substituted alkylferrocenes.[45] Another example is the electrochemical generation of the *N*-acyliminium ion and the in situ trap with a nucleophile reported by Matsumura and Onomura et al.[46] To our surprise, chiral alkylation product (+)-(*R*)-**33e** (91% ee) was obtained when we subjected chiral β-silylalcohol (+)-(*S*)-**32e** (92% ee) to the reaction of indole **31a** (Figure 11).[8] The result indicated that the Friedel–Crafts alkylation of chiral β-silylalcohols proceeded with retention of the configuration. After optimization of the catalyst, we found that the same level of the memory chirality reaction was observed with other Lewis acids such as $AlCl_3$, $FeCl_3$, and $Sc(OTf)_3$, but it was confirmed that our iron catalyst was most effective to realize the reaction. The stereoselective reactions of carbocations have gained strong interest among synthetic chemists.[47] Bach and co-workers reported *syn*-selective Friedel–Crafts alkylation at the benzylic position of 2,3,3-trimethyl-1-phenylbutan-1-ol using 1.2 molar equivalent of strong Lewis or Brϕnsted acid through benzylic carbocation intermediate,[48] and they also reported successful diastereoselective reactions *via* carbocation intermediates.[48] But this reaction, however, is the diastereoselective reaction but the memory chirality reaction: we are now assuming that the origin of the reaction stems from the carbocation intermediate which is conformationally stable.[8]

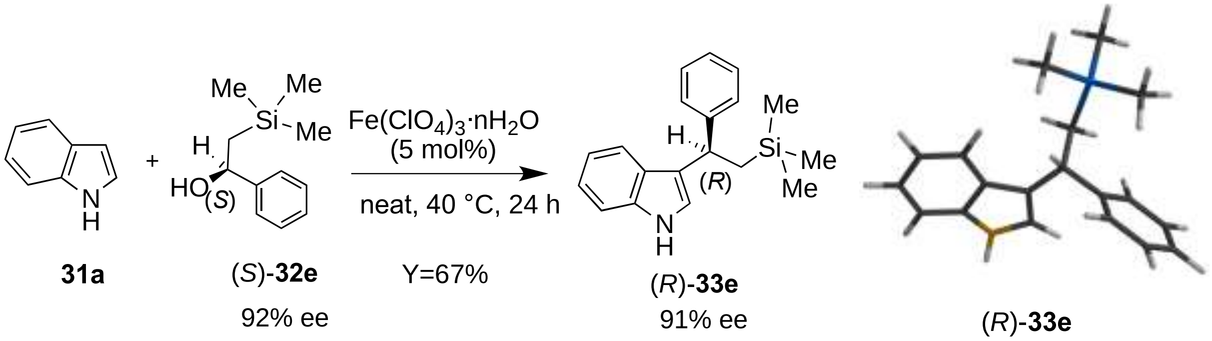
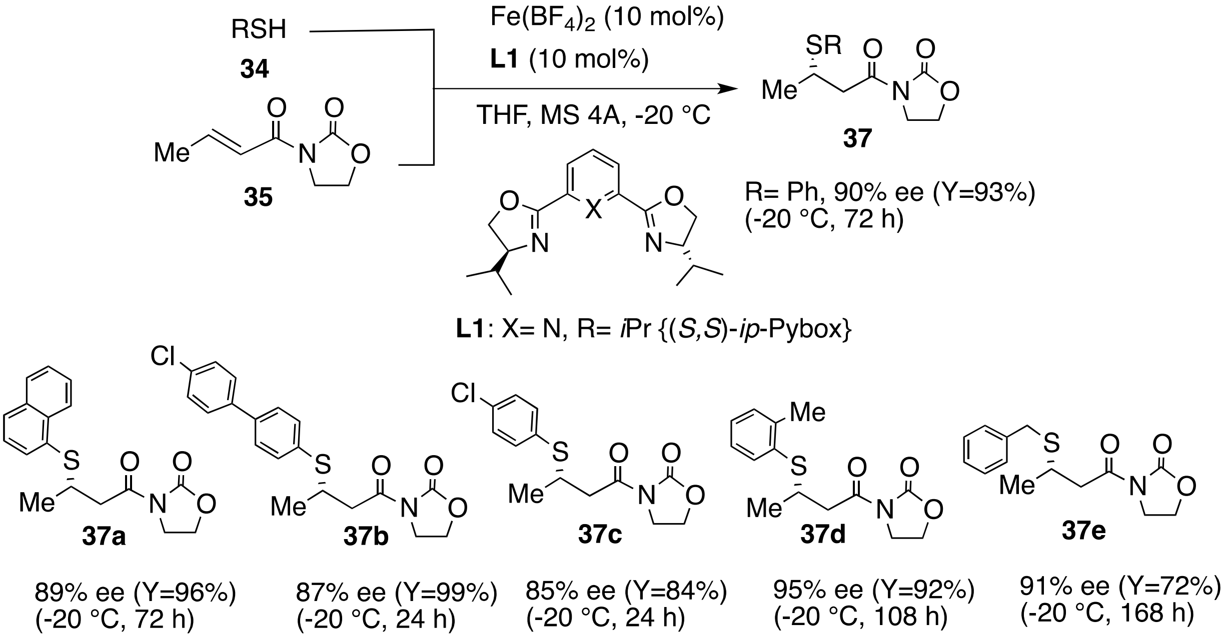


Figure 11. Friedel–Crafts type alkylation of indole with chiral β-silylalcohol

4. IRON-CATALYZED CONJUGATED REACTION

Conjugate addition is one of the most important bond forming reactions in synthetic organic chemistry. The asymmetric conjugate addition of thiols to α,β–unsaturated substrates is also a very useful reaction because it produces optically active compounds such as pharmaceuticals.[49] The first example was reported by Kanemasa et al. in 1999: Ni/DBFOX catalyzed the highly enantioselective reactions.[50] However, there have been only limited examples of the transition metal catalyzed enantioselective addition of thiols to (*E*)-3-crotonoyloxazolidin-2-one. We found the chiral cobalt or iron catalyzed asymmetric conjugate addition of aromatic thiols (**34**) to (*E*)-3-crotonoyloxazolidin-2-one (**35**) (Figure 12).[6] Several types of thiols were reacted with (*E*)-3-crotonoyloxazolidin-2-one to provide the desired chiral adducts with high optical purities (Figure 12).[6] Aiming at obtaining high enantioselectivity, the reaction was conducted at a lower temperature (–20 ˚C) in the presence of molecular sieves 4Å and we thus succeeded in obtaining the addition products, **37a** ~ **37e** with high optical purity. The highest enantioselectivity (95% ee) was recorded for the reaction of the sterically hindered 2-methylbenzenethiol (**37d**), though it required a longer time to complete the reaction (Figure 12).[6b]



34

35

37

R= Ph, 90% ee (Y=93%)
(-20 °C, 72 h)

L1: X= N, R= *i*Pr {(*S,S*)-*ip*-Pybox}

37a 89% ee (Y=96%) (-20 °C, 72 h)

37b 87% ee (Y=99%) (-20 °C, 24 h)

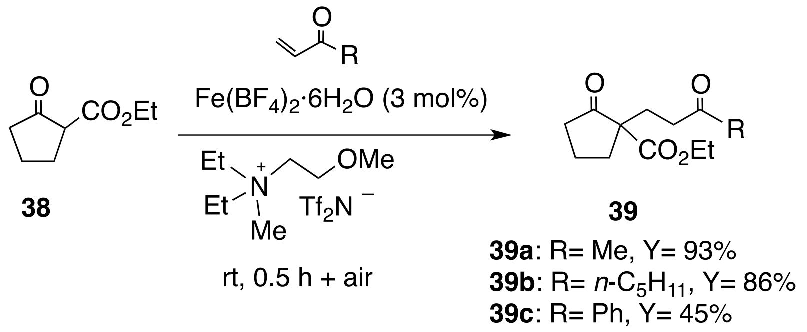
37c 85% ee (Y=84%) (-20 °C, 24 h)

37d 95% ee (Y=92%) (-20 °C, 108 h)

37e 91% ee (Y=72%) (-20 °C, 168 h)

Figure 12. Enantioselective C-S bond formation by iron/Pybox catalyzed Michael addition of thiols to (*E*)-3-crotonoyloxazolidin-2-one

The 1,4-addition of appropriate donor molecules such as active methylene compounds with α,β-unsaturated carbonyl compounds is well recognized as an important C-C bond forming reaction in organic synthesis.[51] Transition-metal catalysis of the 1,4-additions have recently been developed as a valuable alternative to the classic base catalyzed reaction.[51] We found that the 1,4-addition reaction of β-ketoester **38** with vinyl ketones was accomplished by $Fe(BF_4)_2•6H_2O$ as catalyst to afford desired product **39a** ~ **39c** in modest (45%) to excellent (93%) yield, and the catalyst was used repeatedly more than 10 times in an ionic liquid solvent system (Figure 13).[5]



38

39

39a: R= Me, Y= 93%
39b: R= *n*-C_5H_{11}, Y= 86%
39c: R= Ph, Y= 45%

Figure 13. Iron-catalyzed 1,4-addition reaction of β-ketoester with vinyl ketone

To gain the insight of the reaction mechanism in the present reaction, we tested the additive effect of 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical (TEMPO). Interestingly, the inhibitory action of

TEMPO was significantly dependent on the reaction medium. The reaction was completely inhibited by TEMPO with an equal amount of the catalyst (3 mol%) in MeCN. On the other hand, 1.0 eq. of TEMPO was needed to inhibit the reaction in the ionic liquid solvent. These results may indicate that the catalytic mode of $Fe(BF_4)_2$ depends on the solvent system. Although we attempted to isolate TEMPO-iron complex, we isolated neither TEMPO-substrate complex nor TEMPO-Fe salt complex from the reaction mixture.[5]

5. IRON-CATALYZED NAZAROV CYCLIZATION

Nazarov cyclization is promoted by Lewis or Brϕnsted acids and is known as an important method for the preparation of five-membered carbocycles.[52] Iron(III) chloride ($FeCl_3$) is well recognized as the most typical strong Lewis acid and Denmark and Jones reported the first example of the $FeCl_3$-catalyzed Nazarov cyclization;[53] Kang and co-workers extended the catalytic reaction.[54] Initially, we gave our attention to the use of $FeCl_3$ for the Nazarov cyclization of the 3-substituted thiophene derivative **40**, because thiophenes are respected as important components of many biologically active compounds and some optical materials. We established that the combination of $FeCl_3$ (10 mol%) with toluene as a solvent was the best system to afford the desired product when the reaction was carried out at 60 °C (Figure 14).[10] The reaction of substrate which has an electron donating group, such as the phenyl, *p*-tolyl, or *p*-methoxyphenyl group proceeded smoothly and gave the cyclized products **41a**, **41b**, and **41c** in 90%, 82% and 83%, respectively. On the other hand, the reaction rates of substrates that have an electron withdrawing group or aliphatic group, such as *p*-cyanophenyl or cyclohexyl group, were significantly lower and **41d** and **41e** were obtained in 52% and 47% yield, respectively (Figure 14).[10]

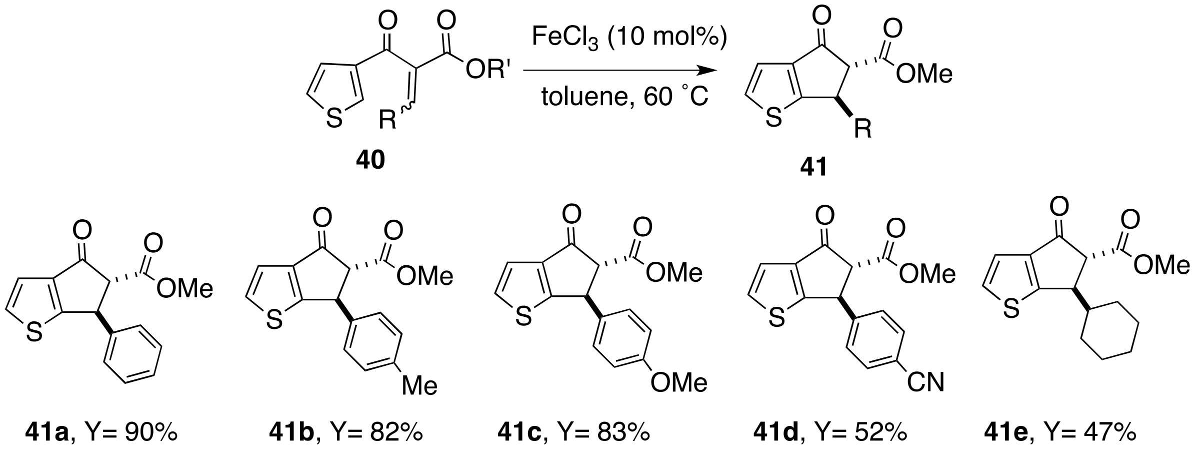
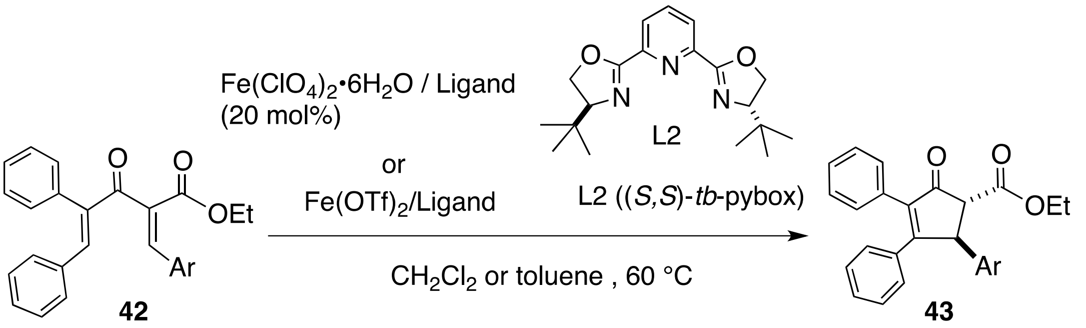


Figure 14. $FeCl_3$-catalyzed Nazarov cyclization of thiophene derivatives

We next found that the cyclized product **43a** was obtained when substrate **42** (Ar= Ph) was heated at 60 °C in the presence of 20 mol% of $Fe(OTf)_2$ with (*S,S*)-*tb*-pybox (L2) in a mixed solvent of

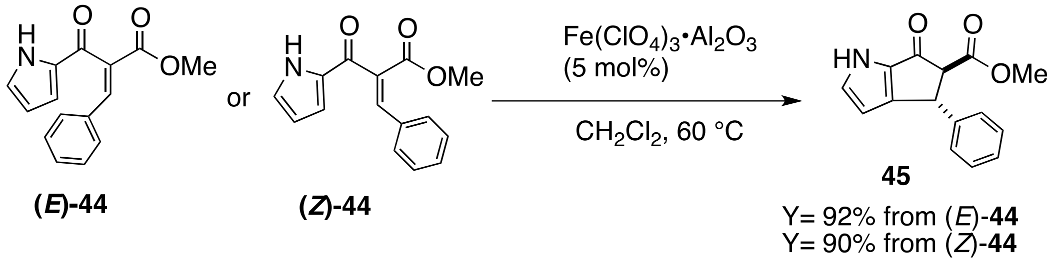
CH_2Cl_2-hexane (2:1) with 83% ee.[11] The enantioselectivity was increased when **42b** (Ar= 4-CF_3-C_6H_4) was subjected to the reaction using $Fe(OTf)_2$/L to give **43b** in 53% yield with 89% ee (Figure 15). The best enantioselectivity was recorded for **42c** (Ar= 2-naphthyl) and **43c** was obtained in 40% yield with 93% ee (Figure 15).[11] This example was the first iron-catalyzed asymmetric Nazarov cyclization.



43a: Ar= Ph, Y= 69% (83% ee)/ CH_2Cl_2-hexane (2:1)
43b: Ar= 4-CF_3-C_6H_4, Y= 53% (89% ee)/ toluene
43c: Ar= 2-naphthyl, Y= 40% (93% ee)/ toluene

Figure 15. Iron-Catalyzed asymmetric Nazarov cyclization

The pyrrole moiety is common in many biologically-active or functional molecules. Therefore, we next focused on the iron salts-catalyzed Nazarov cyclization of pyrrole derivatives. We anticipated that the key point to realize the desired Nazarov cyclization might be use of a weaker Lewis acid as mentioned earlier. It was also assumed that the intermediate of Nazarov cyclization might be favorable in a highly polar IL solvent. Therefore, we tested the reaction using various combination of iron salts with solvents using pyrrole derivative **44** as a model substrate. The results were dependent on the combinations of iron salt with solvent but independent of the stereochemistry of the starting substrate: the desired cyclized product **45** was obtained in excellent yield from (*E*)-**44** and (*Z*)-**44** in 92% yield and 90% yield, respectively, when the reaction was conducted in the presence of 5 mol% of $Fe(ClO_4)_3$•Al_2O_3 in CH_2Cl_2 at 60 °C (Figure 16).[12]



Y= 92% from (*E*)-**44**
Y= 90% from (*Z*)-**44**

Figure 16. Iron salt-catalyzed Nazarov cyclization of pyrrole derivatives

An X-ray crystallographic analysis of the cyclized product **45** revealed the *trans* relationship between the α-carbomethoxy group and the β-phenyl group.[12] The solvent choice was very important in the reaction and CH_2Cl_2 or the ionic liquids, 1-butyl-3-methylimidazolium bis(trifuluoromethyl)sulfonylamide ([bmim]$[NTf_2]$), tributyl(2-methoxyethyl)phosphonium bis(trifuluoromethyl)sulfonylamide ($[P_{444ME}][NTf_2]$), or *N,N*-diethyl-*N*-(2-methoxyethyl)-*N*-methylammonium bis(trifuluoromethyl)sulfonylamide ($[N_{221ME}][NTf_2]$) provided excellent results.[12] Since avoiding the use of a haloalkane solvent is now a strong requirement from an environmental aspect, this feature is a very important element in our reaction.

As mentioned earlier, iron-catalyzed 1,4-addition reaction of β-ketoester with vinyl ketone was possible. In fact, we found that the compound **45** further reacted with but-3-en-2-one to afford the corresponding Michael product **46a** with an excellent *trans* selectivity in 86~90% yield (Figure 17).[12,13] Hence, we next attempted tandem type Nazarov cylization and 1,4-addition; the yield of desired **46a** was only 32% due to formation of further alkylated compounds on the pyrrole moiety. Desired **46a** (R^1= Me) and **46b** (R^1= H) was obtained in 86% and 87% yield, respectively, when the reaction was conducted as a step-by-step method (Figure 17).

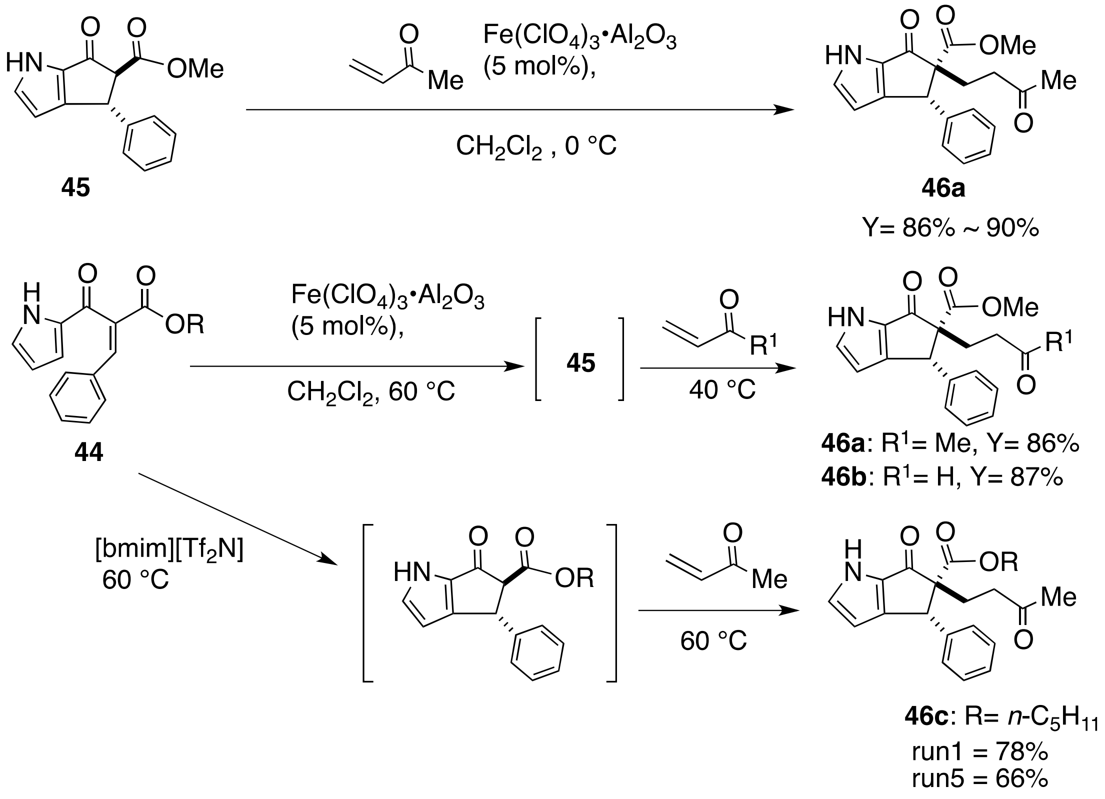
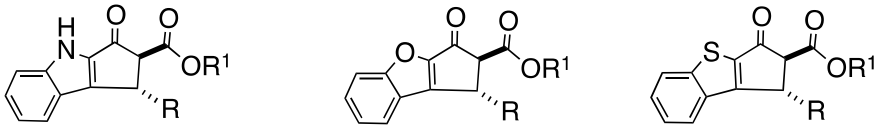


Figure 17. Iron salt-catalyzed Michael cyclization of pyrrole derivatives; sequential type one pot Nazarov cyclization/Michael reaction of pyrrole derivatives in an ionic liquid, [bmim]$[NTf_2]$

We then investigated the possibility of recycling the iron catalyst for the Nazarov cyclization/Michael reaction using an ionic liquid, [bmim][Tf$_2$N] as solvent. We initially encountered an unexpected difficulty; isolation of the product **46a** (R= Me) from the reaction mixture was unsuccessful because **46a** was very soluble in [bmim][NTf$_2$]. We finally resolved this by modification of the substrate and using the *n*-pentyl ester or benzyl ester instead of the methyl ester. Extraction of the *n*-pentyl ester **46c** from the IL solvent was successful and we demonstrated repetition of the reaction using [bmim][NTf$_2$] solution as follows: the reaction course was monitored by silica gel thin layer chromatography analysis and but-3-en-2-one was added when the spot of **44** had been consumed and the spot of **45** appeared, the reaction mixture was then stirred at 60 °C until the spot of **45** disappeared completely. The desired product **46c** was isolated as the sole stereo isomer in 78% yield by a mixed solvent (hexane and Et$_2$O= 2:1). The Nazarov/Michael product **46c** was obtained in 66% yield after repetition of the reaction five times without any addition of the catalyst (Figure 17).[13]

The Nazarov cyclization of indole, benzofuran, and benzo[*b*]thiophene was also accomplished in the presence of catalytic amounts of the iron salts, though we had to choose an appropriate iron salt and solvent for the substrates. For the indole, the corresponding cyclization product **47** was obtained using Fe(ClO$_4$)$_3$•Al$_2$O$_3$ in [bmim][Tf$_2$N] in 85% yield. On the other hand, 10 mol% of FeCl$_3$ was essential to obtain **48** or **49** as catalyst (Figure 18).[14] Since the iron catalyst remained in the IL layer, recycling the catalyst was, of course, possible for the Nazarov cyclization of indole derivatives. We thus succeeded in obtaining **47** in 79% yield after five repetitions of the reaction without any addition of the catalyst to the [bmim][NTf$_2$] solvent system.[14]



47

Fe(ClO$_3$)$_3$•Al$_2$O$_3$ (5 mol%)
[bmim][Tf$_2$N], 60 °C,
Y= 65 ~ 85%

48

FeCl$_3$ (10 mol%)
ClCH$_2$CH$_2$Cl, 60 °C,
Y= 52 ~ 64%

49

R^1= Et,FeCl$_3$ (10 mol%),
CH$_2$Cl$_2$, 40 °C, Y= 63%

Figure 18. Iron salt-catalyzed Nazarov cyclization of indol, benzofuran, or benzothiophene derivatives

6. CONCLUSION

The most interesting feature of iron is that it can act as various catalyst types for chemical reactions, the changing of counter anion and solvents. As described in this chronicle, we succeeded in developing many types of iron-catalyzed reactions (Figure 19). As mentioned in the introduction, the project took from when I recognized a paper by Kratochvil and Long[15] of a reading room in the library of Okayama University. Since then we have been attempting to expand the scope of iron-catalyzed reaction using ionic liquids or acetonitrile as key solvents as summarized in Figure 19. Further investigation will allow us to develop further iron-catalyzed reactions by focusing on the solvent not as a supporting actor of the reaction but as an educator that brings out a masked ability of the iron cation.

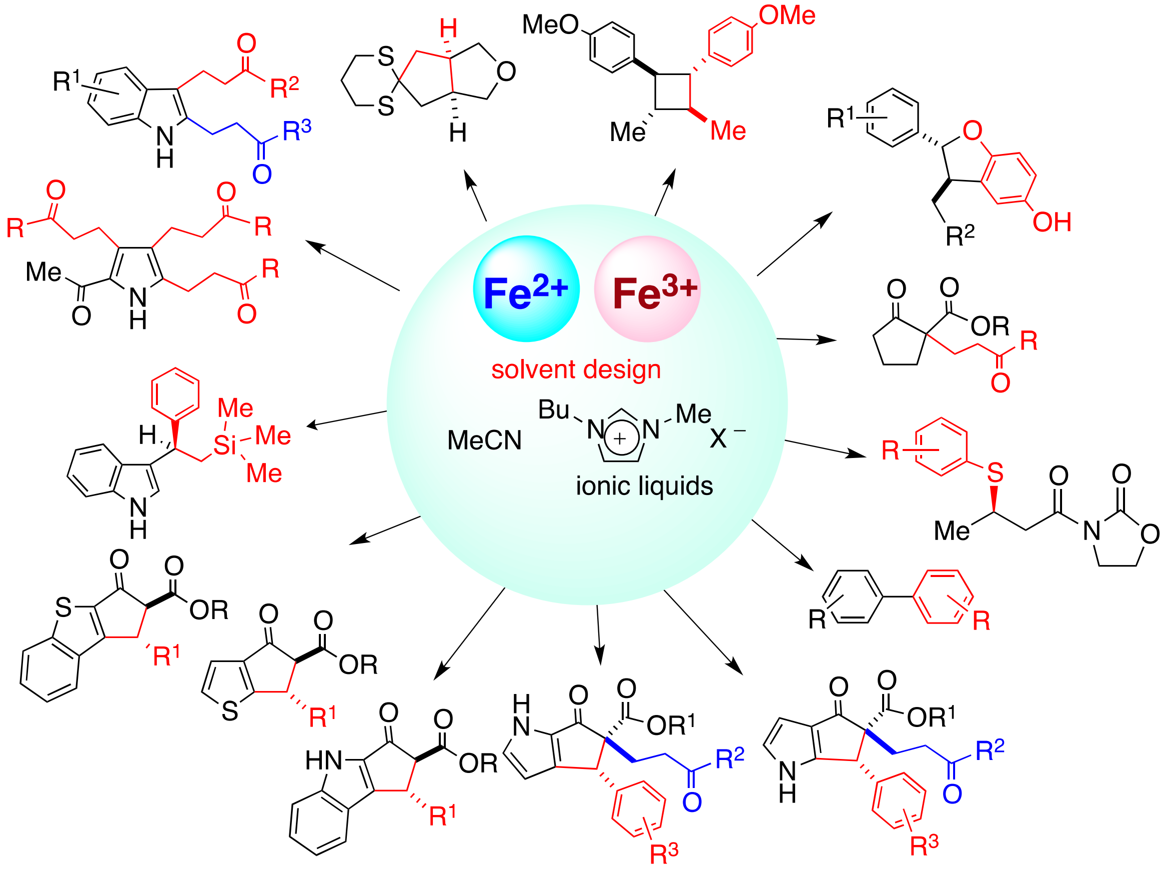


Figure 19. List of compounds developed by the iron-catalyzed reactions in the present study

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Toshiyuki Itoh was born in Matsusaka, Mie, Japan, in 1954. He graduated Tokyo University of Education in 1976. After working as a chemistry teacher in high schools in Mie prefecture, he decided to go back to the University and received his Ph.D. degree in 1986 from the University of Tokyo under the supervision of Professor Teruaki Mukaiyama. He was appointed Assistant Professor of Okayama University in 1987, then promoted to Associate Professor in 1990. He worked with Professor Anthony G. M. Barrett as a visiting scholar at Colorado State University in 1990-1991 and moved to Tottori University in 2002, where he was promoted to full Professor in 2004 and is now director of the Center for Research on Green Sustainable Chemistry. He is recipient of the Society of Synthetic Organic Chemistry Japan Award (2010), and The 8th Green and Sustainable Chemistry Award (2009). He served as President of the Society of Fluorine Chemistry, Japan (2013~2015), and has been the representative of the managing committee of the Ionic Liquids Research Association, Japan since 2014.