Fe-Electrocatalytic Deoxygenative Giese Reaction

Longhui Yu, § Shangzhao Li, § Hiroshige Ogawa, § Hugh Nakamura*

Department of Chemistry, The Hong Kong University of Science and Technology, Hong Kong, China

Supporting Information Placeholder

ABSTRACT: A redox-neutral Fe-electrocatalytic deoxygenative Giese reaction is reported. Hydroxyl groups are among the most abundant functional groups. The advancement of efficient conversion reactions holds significant importance in medicinal and process chemistry. In this report, we present a redox-neutral Giese reaction via anodic oxidation to generate phosphonium ions and cathodic reduction to yield low-valent Fe catalysts. This reaction constitutes a ground-breaking account of a redox-neutral reaction utilizing Fe-catalyst and electrochemistry. It will facilitate the exploration of diverse novel reactions employing this redox cycle in the future.

INTRODUCTION

The development of efficient transformations of abundant functional groups has been a central topic in synthetic organic chemistry. For example, among the numerous C–C bond formations, transition metal-catalyzed cross-coupling reactions are generally the most reliable and indispensable.[1] On the one hand, these cross-coupling reactions generally require the use of halogenated substrates and a two-step process involving a halogenation step and C–C bond formation. Hydroxyl group is one of the most abundant functional groups, and several efficient conversion reactions have recently been reported (Figure 1A).[2] In 2018 and 2022, Suga, Ukaji *et al*. reported direct conversion reactions of alcohols using Ti-reagents.[3] This reaction is applicable to primary to tertiary alcohols and proved to be useful because it can be used for aliphatic alcohols. In 2020, Wang, Shu *et al*. reported the first C–O bond cleavage of tertiary alcohols using Cp^*TiCl_3 as a catalyst.[4] In the meantime, the development of sustainable chemical reactions with less waste using photoredox chemistry[5] and electrochemistry[6,7] has gained momentum recently. In 2021, Li *et al*. reported nickel-catalyzed dehydroxylative cross-coupling using electrochemistry.[8] This reaction is an excellent way to directly form $C(sp^2)$–$C(sp^3)$ bonds from primary and secondary alcohols. From 2021 to 2023, MacMillan *et al*. reported a direct alcohol conversion reaction using NHC, photoredox catalyst, Ni- or Fe-catalyst.[9] This reaction is applicable from primary to tertiary alcohols. Iron is abundant, inexpensive, non-toxic, and has been used for a long time. Even in recent years, some Fe-catalyzed organic chemical reactions have been reported.[10] However, the catalytic use of iron in organic chemistry is less common than that of other transition metals such as Pd-, Ni-, and Co-catalyst. In this context, we report the direct C-C bond formation reaction using a redox-neutral Fe-electrocatalytic deoxygenative Giese reaction.

RESULTS AND DISCUSSION

First, an Fe-catalyzed redox-neutral Giese-type reaction was investigated using 4-phenyl-2-butanol (**1**) and 4-tert-butylstyrene (**2**) as the substrate (Figure 1C). The most challenging aspect of this reaction is that the halogenation of the alcohol at the anode electrode and the reduction of the Fe catalyst at the cathode electrode must proceed at appropriate reaction rates and potentials. More than several hundred conditions for the optimization of this redox-neutral Giese-type reaction with respect to metal catalysts, ligands, base, phosphine, Br source, electrolyte, electrode, and current values have been studied extensively. For the screening of the alcohol halogenation reaction at anode electrodes, the conditions of the Ni-catalyzed paired electrolysis approach pioneered by Li *et al*. were used as initial attempt to investigate the optimal condition for the present reaction.[8] Detailed investigations revealed that the best results were obtained using $FeCl_2$ (15 mol%), IPr ligand (L**1**) (15 mol%), PPh_3 (4 eq.), TBAB (4 eq.), DIPEA (4 eq.), $n$$Bu_4NBF_4$ (0.5 eq.) in DMA. In terms of electrochemical conditions, a current of 6 mA (0.2 mmol scale, constant current) was effective at room temperature in an undivided cell, and the redox-neutral Giese reaction of secondary alcohol **1** and styrene derivative **2** was found to proceed with 60% isolation yield using carbon plates as anode electrodes and Ni forms as cathode electrodes.

Direct control experiments revealed that no desired product **3** was obtained in the absence of electric current or Fe catalyst (entries 1-2). In addition, the yield was significantly reduced to 10% when a sacrificial Zn electrode was used as the anode electrode instead of a carbon plate (entry 3). According to this result, it can be concluded that the oxidation reaction at the anode electrode is necessary for this reaction. When 9 mA was used as the constant current or only10 mol% catalyst was used in this reaction, the yield decreased (entries 4-5). Fe catalysts were also investigated. When $Fe(acac)_2$ was applied instead, the reaction proceeded, but only 34% yield was obtained (entry 6). In general, $Fe(acac)_2$ has two acac ligands coordinated to Fe, making it very unfavorable for other ligands to coordinate. When $FeCl_3$ was used, the yield decreased to 37% (entry 7) probably due to $FeCl_3$ is more hygroscopic than $FeCl_2$, making it difficult to handle, and thus the small amount of water in the reaction system may be the cause of the low yield. Another controlled experiment was performed on the ligand effect of this reaction, only 20% yiled of the desired product **3** was obtained in the ligand-free condition (entry 8).

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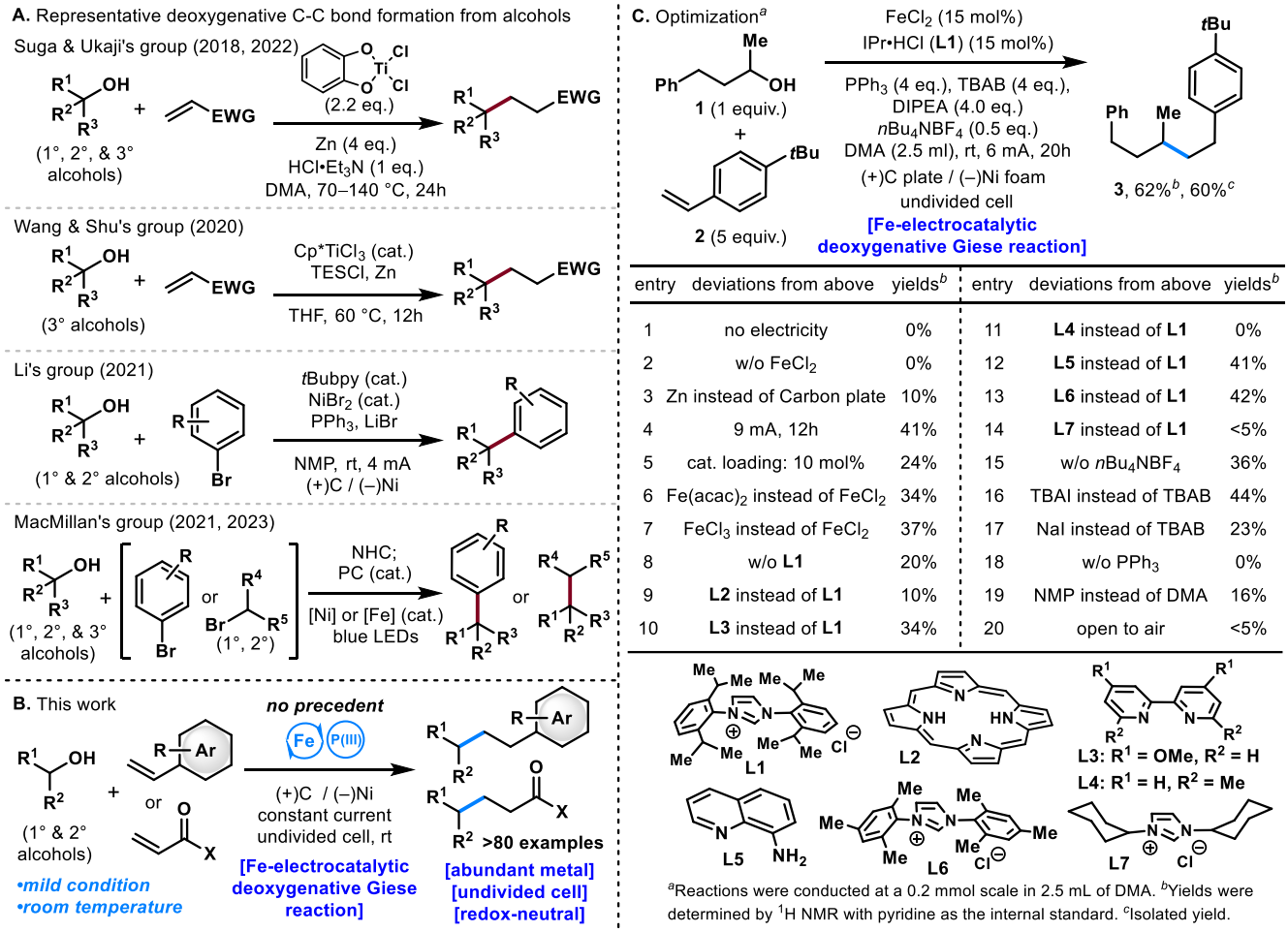

entry	deviations from above	yields[b]	entry	deviations from above	yields[b]
1	no electricity	0%	11	**L4** instead of **L1**	0%
2	w/o $FeCl_2$	0%	12	**L5** instead of **L1**	41%
3	Zn instead of Carbon plate	10%	13	**L6** instead of **L1**	42%
4	9 mA, 12h	41%	14	**L7** instead of **L1**	<5%
5	cat. loading: 10 mol%	24%	15	w/o nBu_4NBF_4	36%
6	$Fe(acac)_2$ instead of $FeCl_2$	34%	16	TBAI instead of TBAB	44%
7	$FeCl_3$ instead of $FeCl_2$	37%	17	NaI instead of TBAB	23%
8	w/o **L1**	20%	18	w/o PPh_3	0%
9	**L2** instead of **L1**	10%	19	NMP instead of DMA	16%
10	**L3** instead of **L1**	34%	20	open to air	<5%

[a]Reactions were conducted at a 0.2 mmol scale in 2.5 mL of DMA. [b]Yields were determined by ^1H NMR with pyridine as the internal standard. [c]Isolated yield.

Figure 1. (A) Representative deoxygenative C-C bond formation from alcohols; (B) This work; (C) Optimization.

A range of ligands (L**2**-L**7**) were screened sequently, and it proved to be ineffective for this reaction in terms of yield (entries 9-14). It is worth mentioning that the use of nBu_4NBF_4 (0.5 eq.) as electrolyte in this reaction led to higher yield (entry 15). Next, the halogen sources were investigated, which play the dual role of not only halogen source but also electrolyte. It was found that the yield decreased using TBAI or NaI (entries 16-17). This is probably due to the high reactivity of the alkyl iodide generated in the reaction system, which may cause side reactions such as reduction and elimination. Furthermore, this reaction did not proceed at all when PPh_3 was not used (entry 18). To confirm the solvent effect, NMP used very frequently in electrochemical reactions, was tested in this reaction, but the yield dropped to 16% (entry 19). And when the reaction was performed under air, the yield was less than 5% (entry 20).

With the optimal condition in hand, a range of substrates were investigated sequentially. First, we screened different Michael acceptors using 4-phenyl-2-butanol (**1**) as the alcohol and found that a variety of substrates were applicable as styrene derivatives (Table 1A). Substrates with alkyl groups such as *t*Bu and Me groups on the aromatic ring easily provided the desired compounds (**3**, **4**). When styrene was used, the reaction proceeded in 72% isolated yield to give the desired compound **5**. Gram scale experiment (**5**) revealed that this reaction proceeded in 75% isolated yield. The investigation of the range of substrates of Michael acceptors continued. The electrochemical deoxygenative Giese reaction proceeded when styrene derivatives with electron withdrawing groups such as fluorine and chlorine, good yields of the desired products were obtained with styrene derivatives containing fluorine substituents (**6**, **7**). And a slightly decrease in yield was observed for styrene derivatives with chlorine substituents (**8**-**10**). However, when the reaction was attempted for styrene derivatives substituted with bromine and iodine, the dehalogenation was observed and the desired product was not obtained. Besides, the reaction proceeded for styrene derivatives with different ester groups as electron-withdrawing groups (**11**-**12**). The reaction was also applicable to other styrene derivatives such as 1-vinyl naphthalene, 2-vinyl naphthalene, and 4-vinyl biphenyl (**13**-**15**). When the disubstituted olefins 1,1-diphenylethylene and α-methylstyrene were applied in the reaction (**16**-**17**), the desired product were obtained. As we all know, the functional group transformation of heterocyclic compounds is critical in medicinal chemistry. Therefore, we attempted this reaction for heterocyclic compounds. As a result, the electrochemical deoxygenative Giese reaction proceeded for pyridine, thiazole, thiophene, and

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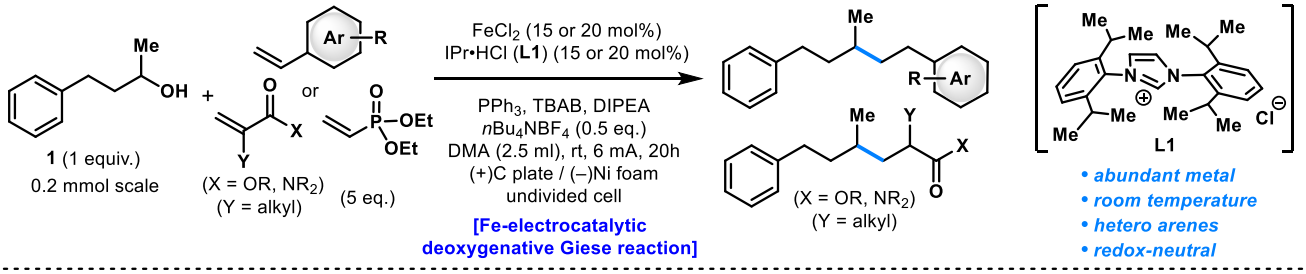
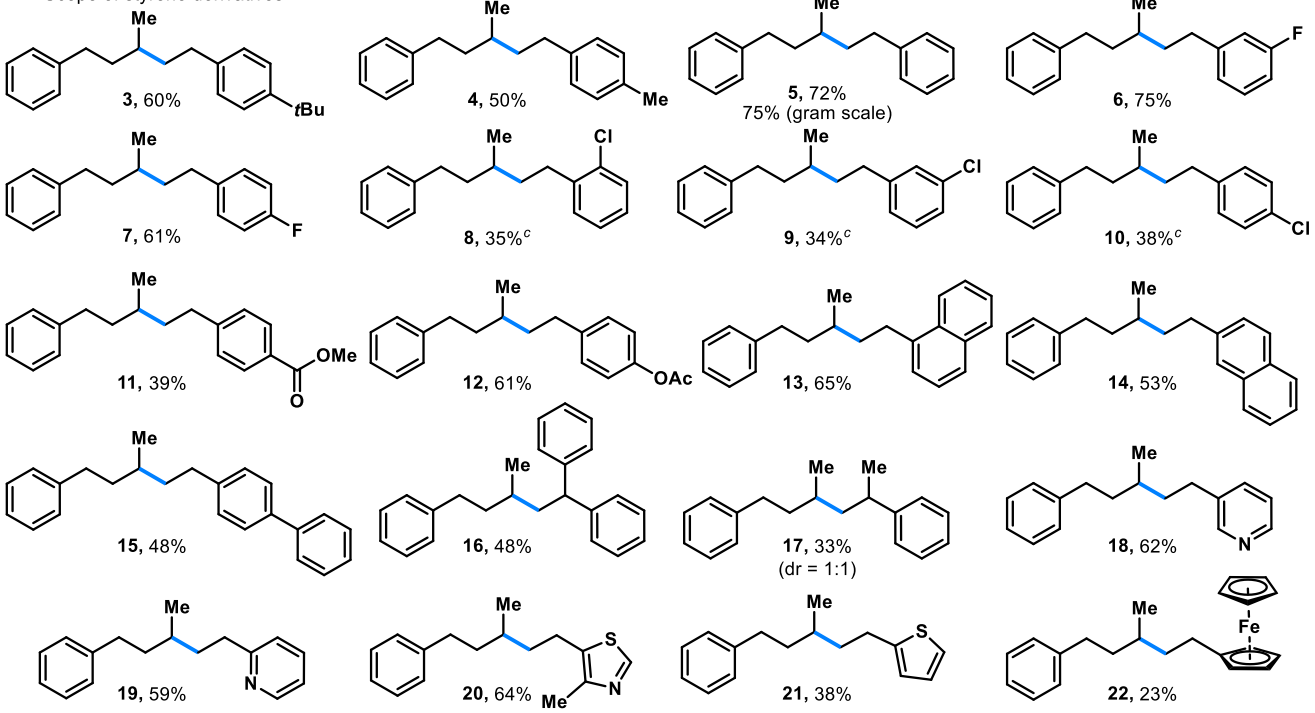
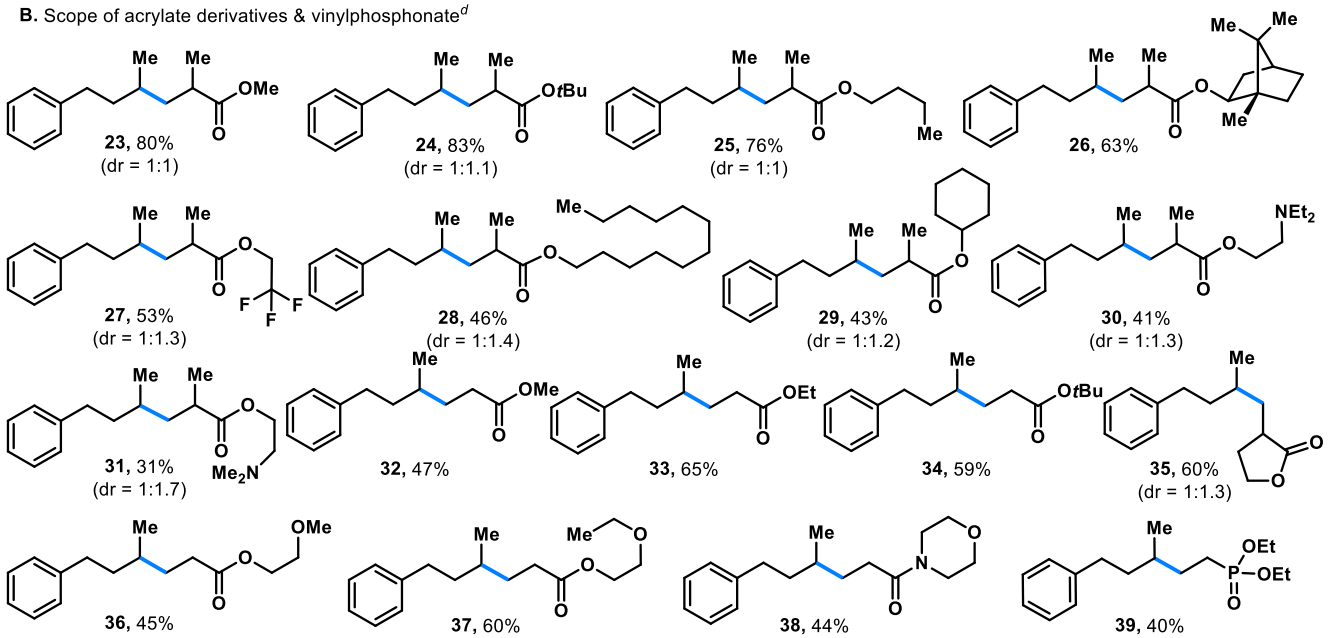
Table 1. Substrate scope of Fe-catalyzed electrochemical deoxygenative Giese reaction[a]



A. Scope of styrene derivatives[b]



B. Scope of acrylate derivatives & vinylphosphonate[d]



[a]Isolated yield. [b]$FeCl_2$ (15 mol%), IPr·HCl (15 mol%), PPh_3 (4 eq.), TBAB (4 eq.), and DIPEA (4 eq.) was used. [c]TBAI (4 eq.) was used instead of TBAB. [d]$FeCl_2$ (20 mol%), IPr·HCl (20 mol%)), PPh_3 (6 eq.), TBAB (4 eq.), and DIPEA (2 eq.) was used.

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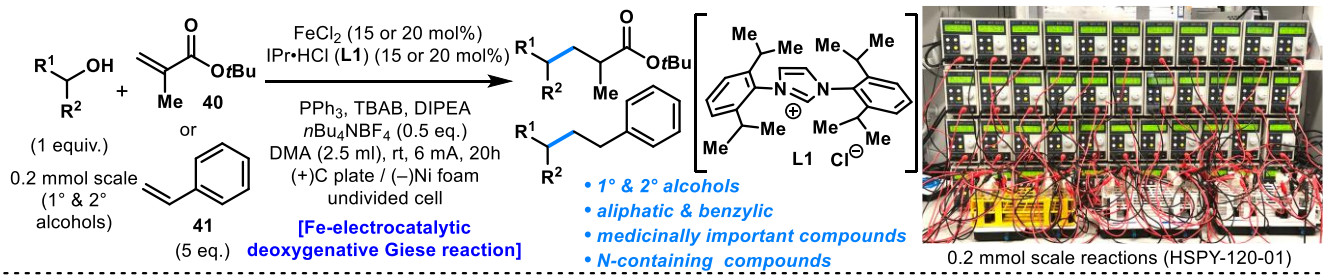
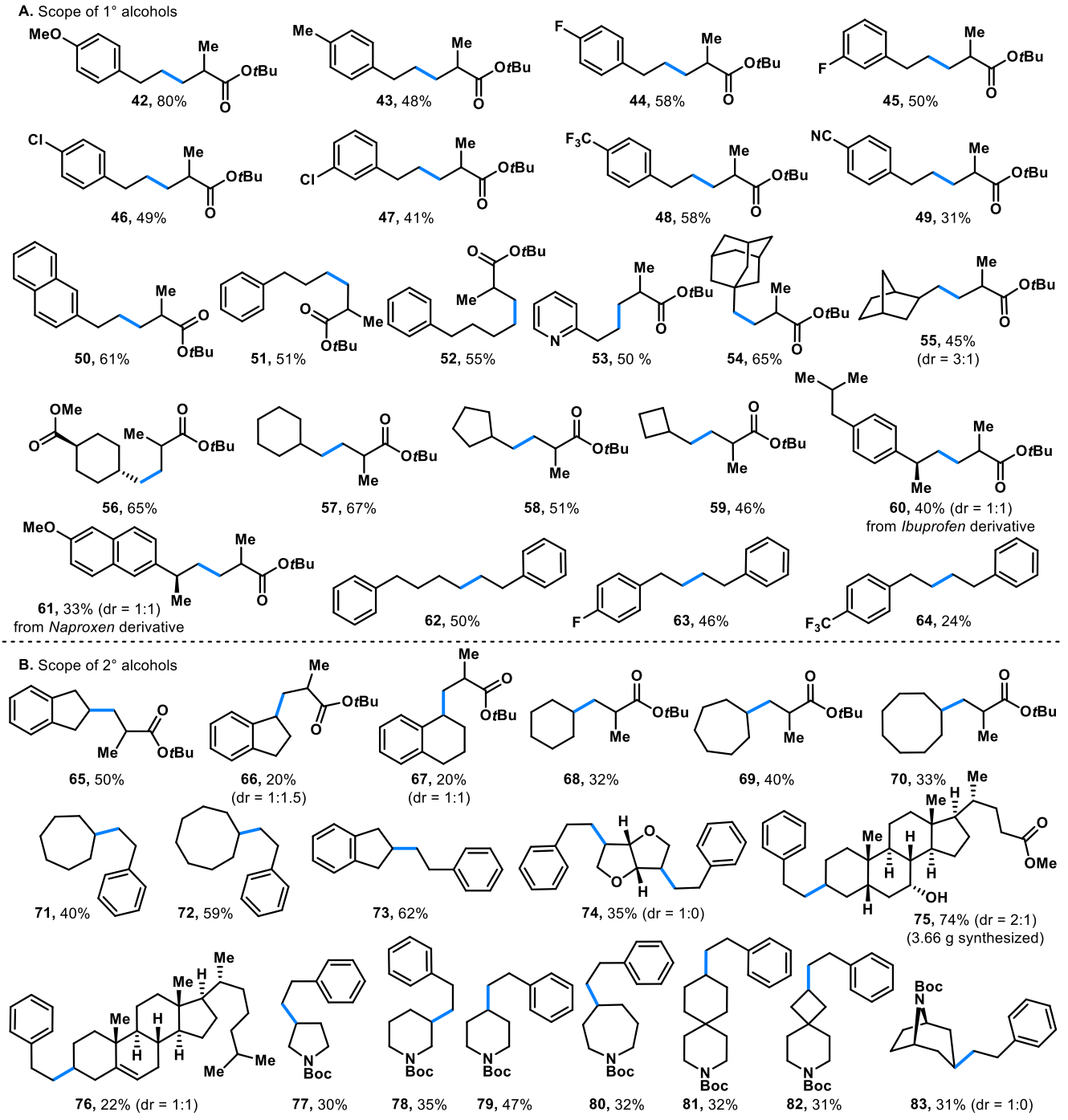
Table 2. Substrate scope of Fe-catalyzed electrochemical deoxygenative Giese reaction[a,b]





[a]Isolated yield. [b]$FeCl_2$ (15 mol%), IPr·HCl (15 mol%), PPh_3 (4 eq.), TBAB (4 eq.), and DIPEA (4 eq.) was used for **40**. $FeCl_2$ (20 mol%), IPr·HCl (20 mol%)), PPh_3 (6 eq.), TBAB (4 eq.), and DIPEA (2 eq.) was used for **41**.

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other heterocycles (**18**-**21**). Interestingly, the reaction also proceeded for ferrocene in 23% isolated yield (**22**).

Next, acrylate derivatives and other Michael acceptors were investigated (Table 1B). The results showed that various acrylate derivatives, including methyl methacrylate, could be applied in the Giese reaction (**23**-**29**). To confirm the applicability of functional groups, this reaction was also tested in Michael acceptors with amino groups, and it was found that the reaction was applicable to Michael acceptors such as 2-(diethylamino)ethyl methacrylate and 2-(dimethylamino)ethyl methacrylate (**30**, **31**). Furthermore, the reaction proceeded well with various acrylate derivatives, including cyclic and acyclic acrylates (**32**-**37**). To our delight, the electrochemical deoxygenative Giese reaction also works well for amide (**38**). Further investigation of different Michael acceptors revealed that the reaction also proceeds well with diethyl vinyl phosphonate (**39**), which is of great significance for diversity synthesis.

Various primary alcohols with tert-butyl methacrylate (**40**) and styrene (**41**) as Michael acceptors were investigated (Table 2A). As a result, the reaction proceeded well with primary alcohols regardless of various functional groups such as electron donating and electron-withdrawing groups on the aromatic ring (**42**-**52**). The deoxygenative Giese reaction proceeded well with alcohols containing heterocycles such as pyridine rings and other aliphatic primary alcohols (**53**-**59**). The reaction was also effective with primary alcohols derived from important pharmaceuticals such as ibuprofen and naproxen. And when various primary alcohols were applied in this reaction, the desired product was obtained (**62**-**64**).

Various secondary alcohols were then investigated (Table 2B). The reaction was also found to be applicable to a wide range of different secondary alcohols, when 2-hydroxyindan was used in this reaction, the target product (**65**) was obtained in 50% isolated yield. On the other hand, 1-hydroxyindan and 1,2,3,4-tetrahydro-1-naphthol, which have an alcohol at the benzoivc position, gave the target compounds in lower yields (**66**, **67**). The deoxygenative Giese reaction also proceeded with substrates such as cyclohexanol, cycloheptanol, and cyclooctanol (**68**-**70**). Further investigation of the range of substrates for this reaction demonstrated that the desired compounds could also be obtained by coupling secondary alcohols with styrene (**41**) (**71**-**74**). In addition, the reaction was also applicable to steroidal skeletons, which have a variety of biological activities and are important for drug development (**75**, **76**). It is worth noting that compound **75** could be synthesized on a gram scale. Finally, we confirmed the substrate applicability of the present reaction to heterocyclic compounds, which are extremely important building blocks in the field of medicinal chemistry and found that the reaction was applicable to a wide range of compounds (**77**-**83**). These results indicate that this reaction can introduce a wide range of Michael acceptors to a variety of primary and secondary alcohols (Tables 1 and 2).

Mechanistic studies were attempted to elucidate the reaction mechanism of this reaction (Figure 2A). First, cyclopropylmethanol (**84**) and 4-vinyltoluene (**85**) were reacted using the standard conditions for this reaction (Table 1). In consequence, the ring opening radical **86** was obtained. The Giese reaction of the chiral compound **87** with styrene (**41**) gave the racemic compound **77**. From these experimental results, it is clear that this reaction is a radical reaction mechanism.

At the same time, control experiments were performed with (3-iodobutyl)benzene (**88**), a putative intermediate of this reaction (Figure 2B). First, we tried the standard condition of this reaction using **88** and 4-tert-butylstyrene (**2**) without electrodes and current, and using Zn dust (10 eq.) and Mn dust (10 eq.) as chemical reductants. Consequently, the desired compound **3** was not obtained at all. In addition, we tried the standard condition of this reaction with (+)C plate / (-)Ni foam and no current flow (0 mA). However, the desired compound **3** was not obtained. Based on these results and the aforementioned control experiments (Figure 1C, entry 1), it can be concluded that the application of electrochemistry is essential for this reaction. A further control experiment was then performed to investigate the effect of $FeCl_2$ in this reaction (Figure 2B, bottom). Sacrificial anodes ((+)Zn plates) were used instead of (+)C plates in the standard reaction conditions. As a result, the desired compound **3** was isolated in 24% yield under the conditions without $FeCl_2$ and IPr ligand. On the other hand, the yield was improved (42% isolated yield) under the condition with $FeCl_2$ and IPr ligand. These experimental results indicated that the $FeCl_2$ and IPr ligands are crucial in this reaction system. It is interesting to note that in the Giese reaction of 4-phenyl-2-butanol (**1**) and 4-tert-butylstyrene (**2**), the isolated yield under standard conditions was 60% (Figure 1C). This yield is higher than that of (3-iodobutyl)benzene (**88**) in a sacrificial anode ((+)Zn plate) (Figure 2B, bottom). This is probably due to the fact that this reaction does not use alkyl halide as a starting material, but alcohol as a starting material, which allows the gradual formation of alkyl halide in the reaction system and keeps the concentration of radicals at a reasonable level. From these experimental results, it can be concluded that $FeCl_2$ is essential for this reaction. In addition, the importance of keeping the radical concentration in the reaction system at a reasonable value is evident.

Based on the above mechanistic studies and control experiments, the proposed mechanism of this reaction is shown below (Figure 2C). First, as reported by Li *et al.*,[8] X^- (X = Br or I) is oxidized to Br_2 or I_2 by anodic oxidation. Subsequently, the resulting Br_2 or I_2 reacts with PPh_3, and the Appel reaction proceeds in the presence of alcohol as substrate. The alcohol substrate is then converted to the Mitsunobu intermediate **89** to give the alkyl halide **90**. The resulting alkyl halide **90** undergoes XAT (halogen atom transfer) through the Fe complex to form the radical intermediate **91**. **91** reacts readily with the Michael acceptor to form **92**, which is then derivatized by SET (single electron transfer) to give the desired product **93** (path A). The Fe^n species produced after XAT and SET are expected to be converted to Fe^{n-1} by cathodic reduction and used in the next catalytic cycle. The process of **92** to **93** may also be mediated by the HAT

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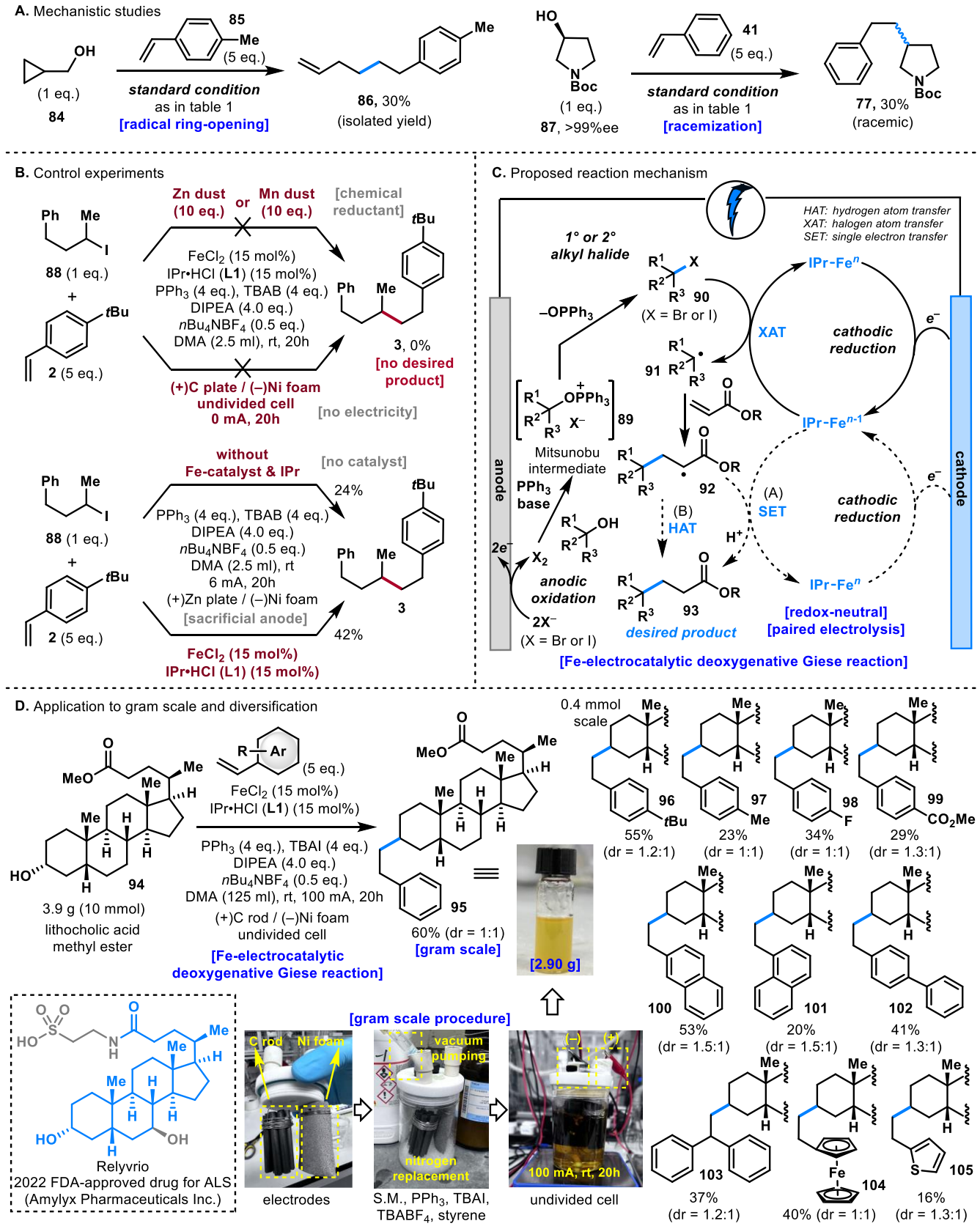

Figure 2. (A) Mechanistic studies; (B) Control experiments; (C) Proposed reaction mechanism; (D) Application to gram scale and diversification.

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(hydrogen atom transfer) mechanism (path B) in addition to the SET mechanism (path A).

To demonstrate the usefulness of this reaction, application to the gram scale and diversification were conducted (Figure 2D). We tried to diversify the compound and scale up this reaction using lithocholic acid methyl ester (**94**), which contains the Relyvrio™ scaffold in its molecule.[11] As expected, the reaction proceeded well at the 10 mmol scale (3.9 g of **94**) and the target compound **95** was successfully obtained in 60% yield (dr = 1:1, 2.9 g). Further attempts were made to diversify **94** on the 0.4 mmol scale. It was found that various Michael acceptors could be introduced into **94** in a single step (**96**-**105**). This diversification method could be applied to various bioactive and medically important compounds with hydroxyl groups.

CONCLUSION

The redox-neutral Fe-electrocatalytic deoxygenative Giese reaction elucidated herein represents a powerful approach for the one-step installation of Michael acceptors into both primary and secondary alcohols. The key feature of this reaction is its independence from scarce metals or highly toxic reagents, allowing the use of readily available commercial reagents to effortlessly form C–C bonds from alcohols at ambient temperature. In addition, the previously unreported achievement of cathodic reduction, which facilitates the electrochemical reduction of the Fe-catalyst, has been realized. Coupled with the Appel reaction via anodic oxidation, a redox-neutral Giese reaction was achieved, providing tremendous efficiency for small molecule diversification. This methodology represents a pioneering investigation into the fusion of Fe-catalysis and electrochemistry in the field of redox-neutral reactions. In the near future, the exploration of diverse innovative reactions utilizing this redox cycle holds promising prospects. In addition, the application of this approach in the field of medicinal chemistry is expected to further advances in medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data (^{1}H and ^{13}C NMR, MS) for all new compounds as well as optimization tables. This material is available free of charge *via* the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

Hugh Nakamura; email: hnakamura@ust.hk

Author Contributions

§L.Y., S.L. and H.O. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support for this work was provided by start-up funds from HKUST (Project No. R9820) and the Interstellar Initiative Early Career Program 2022 from AMED and the New York Academy of Sciences to H.N.

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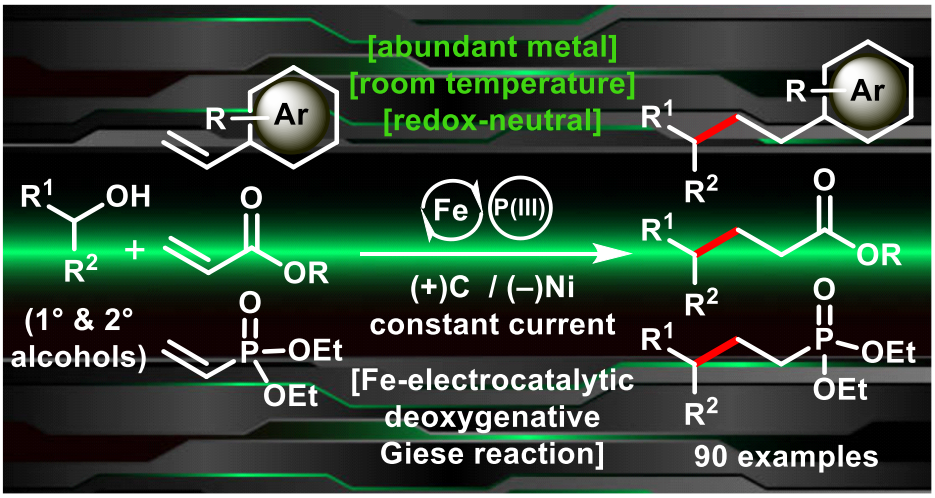

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