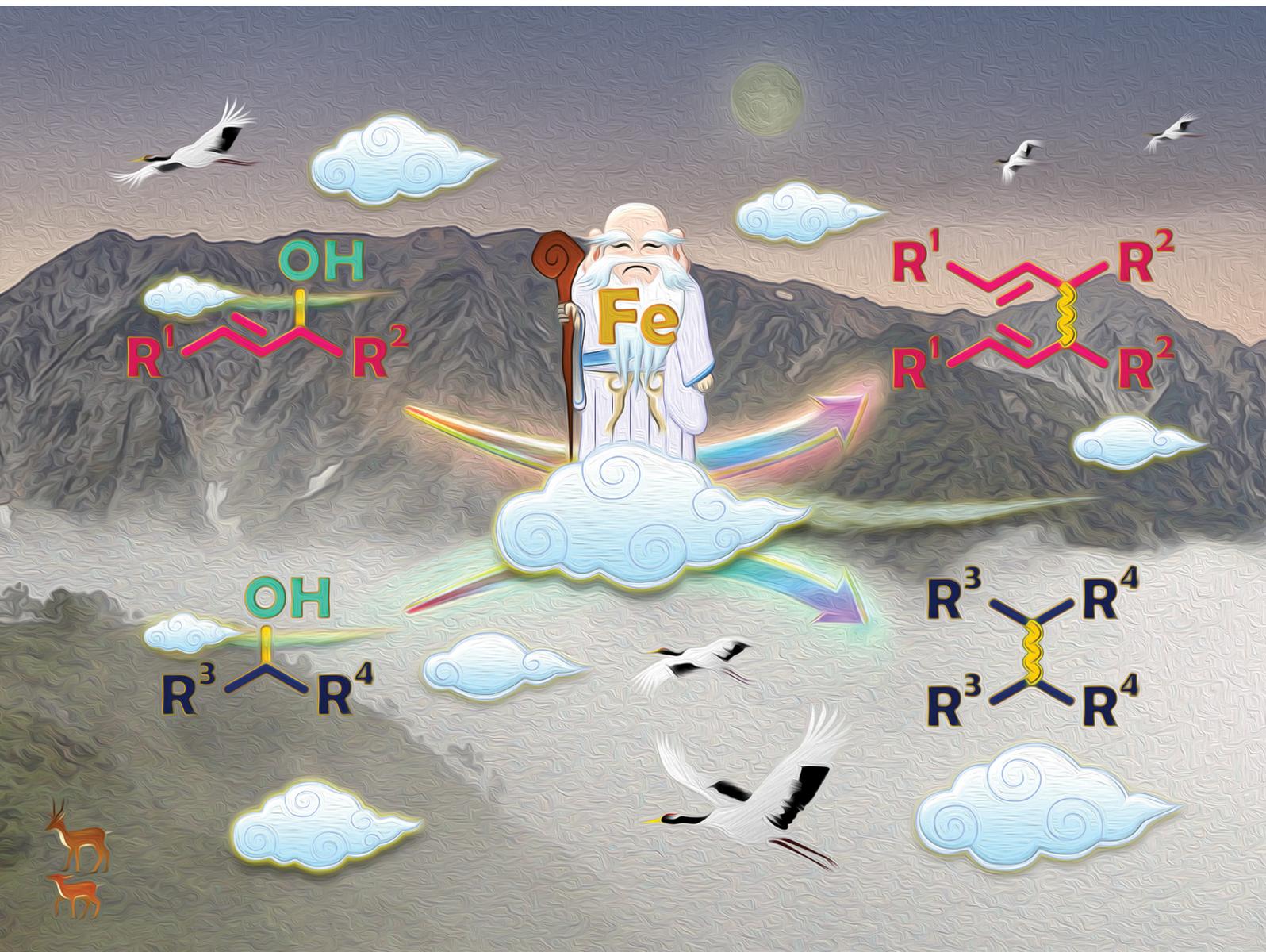


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Toshiyuki Moriuchi *et al.*
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Catalytic dehydroxylative homo-coupling reaction of alcohols by using iron/L-ascorbic acid system

Kento Okabayashi, Masumi Itazaki  and Toshiyuki Moriuchi *

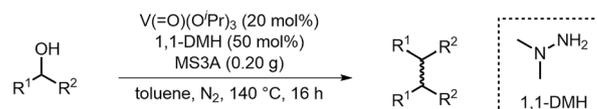
The development of catalytic transformation systems using alcohol as a carbon source is an important research topic. Herein, we report an iron catalyzed-dehydroxylative homo-coupling reaction of allyl alcohols. The catalytic homo-coupling reaction of 1,3-diphenylprop-2-en-1-ol in the presence of FeBr₂ and L-ascorbic acid proceeded smoothly to provide the corresponding 1,5-diene in good yield. This catalytic system could also be applied to benzyl alcohols. Furthermore, a gram-scale catalytic dehydroxylative homo-coupling reaction of alcohols was successfully achieved to validate the scalability of this transformation of alcohols as carbon sources.

Introduction

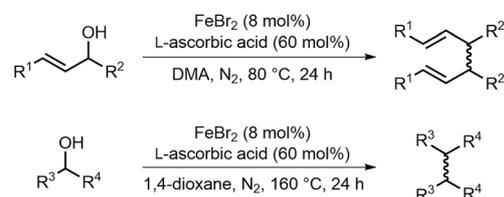
1,5-Dienes are biologically active compounds and valuable building blocks for natural products,¹ so the development of synthetic methodologies for 1,5-dienes is one of the most important research topics.² Conventionally, 1,5-dienes have been synthesized by C(allyl)-C(allyl) coupling reactions using various allylating reagents.³ However, in such reactions, allylating reagents had to be synthesized in advance, and stoichiometric amounts of by-products were produced. Since allyl alcohols are stable and readily available compounds, direct conversion of allyl alcohols to 1,5-dienes, in other words, a dehydroxylative homo-coupling reaction of allyl alcohols, has attracted much attention as one of the best synthetic methods. Only a few such reactions have been demonstrated by using TiCl₃,^{2a} NbCl₅^{2b} or La.^{2f,2g} However, these reactions require more than stoichiometric amounts of metal salts. The Ni/B₂pin₂⁴ and Pd/H₂⁵ catalytic systems have been reported to synthesize 1,5-dienes using allyl alcohol as a substrate. These methods have some disadvantages including the use of difficult-to-handle and precious reagents. The Nicholas group reported the dehydroxylative homo-coupling reaction of alcohols by using vanadium catalysts with oxophilicity and redox properties, giving the corresponding coupling compounds with the concomitant production of ketones as the oxidation compounds of the alcohol as by-products.⁶ We also reported dehydroxylative homo-coupling reactions of alcohols in the presence of hydrazine derivatives using a vanadium catalyst different from that used by the Nicholas group (Scheme 1a).⁷ This reaction had the advantage of suppressing

the production of the by-product ketones and improving the selectivity of the coupling product by using a hydrazine derivative as an organic reductant, but the catalytic activity was moderate. Taking into account the results reported so far, we have developed catalytic dehydroxylative homo-coupling reactions for the synthesis of 1,5-dienes directly from allyl alcohols using a ubiquitous iron compound as a catalyst. This paper reports that the desired catalytic reactions were achieved by the combination of FeBr₂ and L-ascorbic acid and this catalytic system could be extended from allyl alcohols to benzyl alcohols (Scheme 1b).

a) Our previous work



b) This work



- ✓ Commercially available catalyst and additive
- ✓ Up to 91% isolated yield
- ✓ Gram-scale homo-coupling reaction
- ✓ Direct transformation of alcohols

Scheme 1 (a) Our previous work: oxovanadium-catalyzed dehydroxylative homo-coupling reaction of alcohols in the presence of 1,1-DMH. (b) This work: iron-catalyzed dehydroxylative homo-coupling reaction of alcohols in the presence of L-ascorbic acid.

Department of Chemistry, Graduate School of Science, Osaka Metropolitan University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan.
E-mail: moriuchi@omu.ac.jp



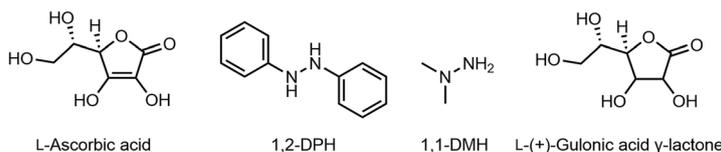
Results and discussion

We initially examined whether iron compounds could act as catalysts for the dehydroxylative homo-coupling reaction of allyl alcohols (Table 1). Heating 1,3-diphenylprop-2-en-1-ol (**1a**) at 80 °C in 1,4-dioxane for 24 h in the presence of FeCl₂ (8 mol%) and L-ascorbic acid (60 mol%) produced the corresponding homo-coupling product **2a** in 82% NMR yield (*dl/meso* = 1:1) (entry 1). The yield and *dl/meso* selectivity were the same even when using quite high-purity FeCl₂ (99.99% purity) (entry 2), indicating that the catalytic activity in entry 1 was not due to the impurities in the purchased FeCl₂. The catalytic reaction with FeBr₂ instead of FeCl₂ as a catalyst slightly improved the yield of **2a** (entry 3). The homo-coupling reaction proceeded scarcely under aerobic conditions (entry 4). Other iron species such as Fe(OAc)₂, Fe(acac)₂ and FeBr₃ did not work as a catalyst or showed poor catalytic activity (entries 5–7). In addition, other chloride transition metal salts, CoCl₂, NiCl₂, CuCl₂, or PdCl₂(MeCN)₂ were not effective for this catalytic reaction, indicating that iron plays a crucial role in promoting this

transformation (entries 8–11). In our reaction, L-ascorbic acid is considered to act as a reducing reagent. Therefore, other additives besides L-ascorbic acid, such as *o*-dihydroxybenzene, *p*-dihydroxybenzene, *o*-phenylenediamine, 1,2-diphenylhydrazine (1,2-DPH), 1,1-dimethylhydrazine (1,1-DMH) and L-(+)-gulonic acid γ -lactone, were investigated, but all of them did not show favourable results (entries 12–17). This catalytic transformation of allyl alcohol **1a** requires both FeBr₂ and L-ascorbic acid; if either one is missing, the reaction does not proceed (entries 18 and 19). We now speculate that L-ascorbic acid may serve as a ligand in the catalytically active iron complex in addition to its reducing activity, but the role of L-ascorbic acid in the reaction system is currently under investigation. The effect of the solvent on this catalytic reaction was also examined. The reaction proceeded effectively in polar solvents, among which DMA (dimethylacetamide) showed the best result (NMR yield: 93%; isolated yield: 90%) (entries 20–23). In contrast, the reactions were significantly suppressed when a non-polar solvent was used, which may come from the low solubility of the catalyst (entries 24 and 25).

Table 1 The optimization of reaction conditions for the dehydroxylative homo-coupling reaction of 1,3-diphenylprop-2-en-1-ol (**1a**)^a

Entry	Catalyst	Additive	Temp. (°C)	Solvent	NMR yield of 2a ^b (%)	<i>dl/meso</i>
1	FeCl ₂	L-Ascorbic acid	80	1,4-Dioxane	82	1:1
2 ^c	FeCl ₂	L-Ascorbic acid	80	1,4-Dioxane	82	1:1
3	FeBr ₂	L-Ascorbic acid	80	1,4-Dioxane	84	1:1
4 ^d	FeBr ₂	L-Ascorbic acid	80	1,4-Dioxane	4	1:1
5	Fe(OAc) ₂	L-Ascorbic acid	80	1,4-Dioxane	0	—
6	Fe(acac) ₂	L-Ascorbic acid	80	1,4-Dioxane	0	—
7	FeBr ₃	L-Ascorbic acid	80	1,4-Dioxane	17	1:1
8	CoCl ₂	L-Ascorbic acid	80	1,4-Dioxane	2	1:1
9	NiCl ₂	L-Ascorbic acid	80	1,4-Dioxane	2	1:1
10	CuCl ₂	L-Ascorbic acid	80	1,4-Dioxane	12	1:1
11	PdCl ₂ (MeCN) ₂	L-Ascorbic acid	80	1,4-Dioxane	1	1:1
12	FeBr ₂	<i>o</i> -Dihydroxybenzene	80	1,4-Dioxane	0	—
13	FeBr ₂	<i>p</i> -Dihydroxybenzene	80	1,4-Dioxane	15	1:1
14	FeBr ₂	<i>o</i> -Phenylenediamine	80	1,4-Dioxane	0	—
15	FeBr ₂	1,2-Diphenylhydrazine (1,2-DPH)	80	1,4-Dioxane	8	1:1
16	FeBr ₂	1,1-Dimethylhydrazine (1,1-DMH)	80	1,4-Dioxane	0	—
17	FeBr ₂	L-(+)-Gulonic acid γ -lactone	80	1,4-Dioxane	0	—
18	FeBr ₂	—	80	DMA	0	—
19	—	L-Ascorbic acid	80	DMA	0	—
20	FeBr ₂	L-Ascorbic acid	80	DMA	93 (90) ^e	1:1
21	FeBr ₂	L-Ascorbic acid	80	DMSO	89	1:1
22	FeBr ₂	L-Ascorbic acid	80	<i>t</i> -Amyl alcohol	77	1:1
23	FeBr ₂	L-Ascorbic acid	80	MeCN	57	1:1
24	FeBr ₂	L-Ascorbic acid	80	Xylene	9	1:1
25	FeBr ₂	L-Ascorbic acid	80	CPME	23	1:1
26	FeBr ₂	L-Ascorbic acid	50	DMA	43	1:1



^a Reaction conditions: 1,3-diphenylprop-2-en-1-ol (**1a**, 0.25 mmol), catalyst (8 mol%) and additive (60 mol%) in solvent (1 mL) under N₂ for 24 h. ^b Triphenylmethane was used as an internal standard. ^c FeCl₂ (99.99% purity) was used as a catalyst. ^d The homo-coupling reaction was conducted under aerobic conditions. ^e Isolated yield.



Reducing the reaction temperature to 50 °C caused a decrease in the yield of **2a** (entry 20 vs. entry 26). The *dl/meso* selectivity of **2a** for each condition did not change at all.

Since the optimized reaction conditions were found to be those mentioned in entry 20 in Table 1, the reaction of allyl alcohols other than **1a** was examined (Table 2). When allyl alcohols with a methyl group at the *para* (**1b**) and *meta* (**1c**) positions were used,

the corresponding products **2b** and **2c** were obtained in 91% and 84% yields, respectively (entries 1 and 2). Allyl alcohols with Br (**1d**) and F (**1e**) substituents at the *para* position were converted to the corresponding 1,5-dienes **2d** and **2e** in good yields (entries 3 and 4). Starting from **1f**, the direct homo-coupling reaction product **2f** (*dl/meso* = 1 : 1) was formed in 52% yield and its isomer **2f'** was not obtained (entry 5). In addition to the formation of **2f**, **1f'** was also

Table 2 Substrate scope of the iron-catalyzed dehydroxylative homo-coupling reaction of various allyl alcohols **1**^a

Entry	Starting material	Product: isolated yield
1	 1b	 2b : 91% (<i>dl/meso</i> = 1:1)
2	 1c	 2c : 84% (<i>dl/meso</i> = 1:1)
3	 1d	 2d : 73% (<i>dl/meso</i> = 1:1)
4	 1e	 2e : 83% (<i>dl/meso</i> = 1:1)
5	 1f	 2f : 52% (<i>dl/meso</i> = 1:1) 2f' : 0%
6	 1f'	 2f : 0% 2f' : 0%
7	 1g	 2g : 51% (<i>dl/meso</i> = 1:1)

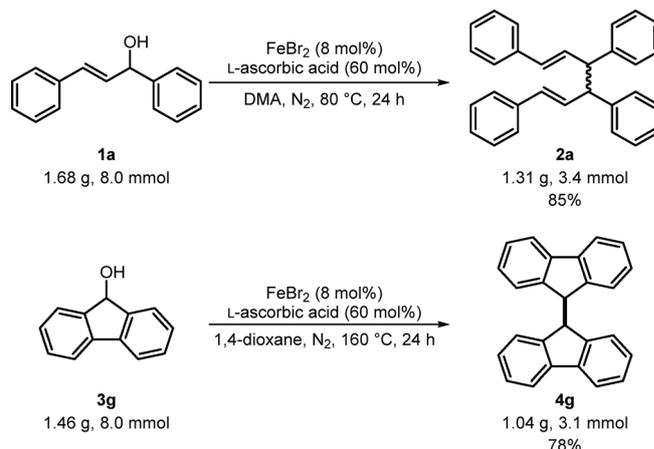
^a Reaction conditions: **1** (0.25 mmol), FeBr₂ (8 mol%) and L-ascorbic acid (60 mol%) in DMA (1 mL) under N₂ at 80 °C for 24 h.



Table 3 Substrate scope of the iron-catalyzed dehydroxylative homo-coupling reaction of various benzyl alcohols **3**^a

Entry	Starting material	Product: isolated yield
1		 4a : 67% (0%) ^b
2		 4b : 59%
3		 4c : 59%
4		 4d : 62% (<i>dl/meso</i> = 1:1)
5		 4e : 71% (<i>dl/meso</i> = 1:1)
6		 4f : 73%
7		 4g : 90%

^a Reaction conditions: **3** (0.25 mmol), FeBr₂ (8 mol%) and L-ascorbic acid (60 mol%) in 1,4-dioxane (1 mL) under N₂ at 160 °C for 24 h.
^b DMA was used as a solvent.

**Scheme 2** Gram-scale iron-catalyzed homo-coupling reactions of 1,3-diphenylprop-2-en-1-ol (**1a**) and 9H-fluoren-9-ol (**3g**).

in this catalytic reaction. The utilization of bis-allyl alcohol **1g** resulted in the formation of the homo-coupling product **2g** in 51% yield (entry 7).

To extend the utility of our synthetic method, the applicability of the dehydroxylative homo-coupling reaction to benzyl alcohols was examined (Table 3). The homo-coupling reaction of benzhydryl alcohol (**3a**) in the presence of FeBr₂ (8 mol%) and L-ascorbic acid (60 mol%) did not occur in DMA at 160 °C. The reaction using 1,4-dioxane instead of DMA provided the desired dehydroxylative homo-coupling product **4a** in 67% yield (entry 1). In 2017, Tang and his coworkers discovered that **4a** showed the aggregation-induced emission (AIE) phenomenon.⁹ The catalytic system we developed in this paper is a valuable method that enables the synthesis of useful compounds from commercially available benzhydryl alcohol (**3a**) in a single step. Benzyl alcohols **3b** and **3c** could be converted to the corresponding coupling products in 59% yields (entries 2 and 3). When using benzyl alcohols **3d** and **3e** featuring a methyl substituent at the *para* and *ortho* position of one phenyl moiety, the desired coupling products **4d** (*dl/meso* = 1:1) and **4e** (*dl/meso* = 1:1) were obtained in 62% and 71% yields, respectively (entries 4 and 5). Benzyl alcohol derivative **3f** was converted to the desired coupling product **4f** in 73% yield (entry 6). Furthermore, the catalytic dehydroxylative homo-coupling reaction of 9H-fluoren-9-ol (**3g**) proceeded smoothly to afford the corresponding coupling product **4g** in 90% yield (entry 7).

To show the usefulness of this iron-catalyzed dehydroxylative homo-coupling reaction system, we carried out scale-up reactions using two different alcohols (Scheme 2). A gram-scale catalytic reaction of **1a** was successfully performed to provide the 1,5-diene **4a** in 85% yield (1.31 g). Moreover, the gram-scale reaction of **3g** was completed, producing the desired homo-coupling product **4g** in 79% yield (1.04 g).

Conclusions

A direct dehydroxylative homo-coupling reaction of allyl alcohols was successfully implemented by using a commercially available FeBr₂ catalyst in the presence of L-ascorbic acid,

observed in 47% yield. The isomerization reaction of allyl alcohol **1f** to **1f'** is expected to occur in parallel with the dehydroxylative homo-coupling reaction.⁸ In contrast, the homo-coupling product 1,5-diene was not detected in the catalytic reaction of allyl alcohol **1f'** (entry 6). These results indicate that allyl alcohol **1f'** is inactive



providing the corresponding 1,5-dienes. This catalytic system could be applied to the dehydroxylative homo-coupling reaction of benzyl alcohols, greatly expanding the range of applications of this catalytic system. Notably not only a wide range of substrate applicability but also gram-scale homo-coupling reactions were realized in this catalytic system. Investigation into the reaction mechanism of this catalytic system and the potential applications to other reactions is ongoing.

Author contributions

Kento Okabayashi: formal analysis, investigation, methodology, funding acquisition and writing – original draft. Masumi Itazaki: methodology and writing – review and editing. Toshiyuki Moriuchi: conceptualization, formal analysis, investigation, methodology, funding acquisition, resources, supervision, writing – original draft and writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data that support the findings of this study are available in the article and in its online supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5nj03299g>.

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