Iron-Catalyzed Selective Conjugate Addition of Aryl Grignard Reagents to 2,4-Alkadienoates: 
*tert*-Butyl (Z)-5-Phenyl-3-hexenoate

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**Procedure**

A. *tert*-Butyl (2E,4E)-2,4-hexadienoate (1). An oven-dried, 500-mL, single-necked, round-bottomed flask equipped with an egg-shaped magnetic stirring bar (3 cm x 1.5 cm) is charged with sorbic acid (18.5 g, 165 mmol, 1.00 equiv) (Note 1). After being fitted with a rubber septum and evacuated by a needle connected to the manifold inserted through the septum, the flask is flushed with argon. The flask is then charged with dry dichloromethane (150 mL) (Note 2) by syringe through the septum, oxalyl chloride (28.3 mL, 330 mmol, 2.00 equiv) (Note 3) is added dropwise by syringe pump through the septum over 10 min at room temperature. The septum is removed and three drops of DMF (Note 4) are added using a
pipette. A drying tube filled with calcium chloride is attached. After the evolution of gas ceases (about 30 min) and the resulting solution is stirred at room temperature for an additional 2 h, the solvent and excess oxalyl chloride are removed first on a rotary evaporator (in a water bath maintained at 40 °C) (Note 5) and finally with a vacuum pump (3.6 mmHg at room temperature for 5 min) to afford the desired sorbic acid chloride (Note 6) as a crude oil, which is directly used in the next step.

A separate, oven-dried, 1-L, three-necked, round-bottomed flask equipped with an octagonal magnetic stirring bar (4 cm x 1 cm) is fitted with an internal thermometer and two rubber septa. After the flask is evacuated by a needle connected to the manifold inserted through the side septum, the flask is flushed with argon. This operation is repeated twice. A solution of tert-butyl alcohol (12.2 g, 165 mmol, 1.00 equiv) (Note 7) in dry tetrahydrofuran (150 mL) (Note 8) is added through the septum via syringe. The septum in the middle neck is quickly removed and exchanged for a 200-mL pressure-equalizing addition funnel, the top of which is capped with a septum, and the flask is then cooled in an ice bath. n-Butyllithium (114 mL, 1.46 M in hexane, 165 mmol, 1.00 equiv) (Note 9) is transferred to the pressure-equalizing funnel by syringe and then is added to the reaction flask dropwise in ca. 5 min at the same temperature. After the ice-bath is removed and the mixture is stirred at room temperature for 1 h, it is cooled again in an ice bath and the crude sorbic acid chloride prepared above in dry tetrahydrofuran (100 mL) (Note 8) is added through the septum in one portion via syringe. After the mixture is stirred at room temperature for 1 h, the reaction is terminated by the addition of H₂O (300 mL) slowly in one portion while stirring at room temperature. The contents of the flask are transferred to a 1 L separatory funnel. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (once with 150 mL and twice with 100 mL each). The combined organic layers are washed with brine (100 mL), dried over Na₂SO₄ (40 g), filtered, and concentrated by rotary evaporation to give a crude oil, which is chromatographed on silica gel (Note 10) to afford the isomerically pure tert-butyl (2E,4E)-2,4-hexadienoate (1) (26.4–26.7 g, 95–96% overall yield from sorbic acid) as a colorless oil (Notes 11 and 12).

B. tert-Butyl (Z)-5-phenyl-3-hexenoate (2). An oven-dried 500-mL, three-necked, round-bottomed flask is equipped with an egg-shaped magnetic stirring bar (3 cm x 1.5 cm) and a 200 mL pressure-equalizing addition funnel, the top of which is fitted with a rubber septum. The other necks of the flask are fitted with an internal thermometer and a rubber septum. The
A flask is charged with iron(II) chloride (1.01 g, 8.0 mmol, 0.1 equiv) (Note 13). A needle, which is connected to a manifold, is inserted through the septum, the flask is evacuated, and then argon is flushed through the flask. This evacuation and flush process is repeated twice. After tert-butyl (2E,4E)-2,4-hexadienoate (1) (13.5 g, 80.0 mmol) in dry tetrahydrofuran (80 mL) (Note 8) is added through the septum all at once via syringe at room temperature, the resulting suspension is stirred and cooled in a bath maintained at ca. –45 °C (Note 14). Phenylmagnesium bromide (144 mL, 1.0 M solution in THF, 144 mmol, 1.80 equiv) (Note 15) is added dropwise to the cold suspension through the pressure-equalizing addition funnel over 90 min. A cooling bath is used to maintain the mixture between –45 and –30 °C (Note 14) for 4 h, after which the reaction is terminated at the same temperature by the addition of 1 M HCl solution (150 mL) by means of an addition funnel over ca. 10 min. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3 x 100 mL). The combined organic layers are washed successively with aqueous saturated NaHCO₃ solution (150 mL) and brine (100 mL), dried over Na₂SO₄ (60 g), filtered, and concentrated by rotary evaporation under reduced pressure at 40 °C to give a crude oil. Analysis by ¹H NMR does not reveal the presence of regio- or alkene stereoisomers. The crude product is chromatographed on silica gel (Note 16) to afford tert-butyl (Z)-5-phenyl-3-hexenoate (2) (16.5–16.6 g, 84%) as a colorless oil (Notes 17 and 18).

**Notes**

1. Sorbic acid was purchased from Sigma-Aldrich Co. (USA), and was observed to be isomerically pure and used as received.
2. Anhydrous dichloromethane was purchased from Sigma-Aldrich Co. (USA) and used as received.
3. Oxalyl chloride was purchased from Sigma-Aldrich Co. and used without purification.
4. Anhydrous DMF was purchased from Sigma-Aldrich Co. (USA) and used as received.
5. The stirring bar must be removed from the flask with a teflon-coated magnet before this operation.
6. As the boiling point of sorbic acid chloride is 74 °C/14 mmHg (Ongoka, P.; Mauze, B.; Miginic, L. J. Organomet. Chem. 1987, 322, 131–139), exhaustive evaporation may result in the decrease of product quantity.

7. tert-Butyl alcohol was purchased from Sigma-Aldrich Co. (USA) and used without purification.

8. Anhydrous tetrahydrofuran was purchased from Sigma-Aldrich Co. (USA) and used as received.

9. A 1.6 M solution of n-BuLi in hexane was purchased from Sigma-Aldrich Co. (USA) and the concentration was determined by titration to be 1.46 M prior to use according to a reported method: Ireland, R. E.; Meissner, R. S. J. Org. Chem. 1991, 56, 4566–4568.

10. The crude oil is charged onto a column of 5.5-cm diameter, which is packed with 100 g of silica gel (P60 from SiliCycle Inc., 230-400 mesh (40-63 µm)). Fractions were collected with Fisherbrand disposable culture tubes (Borosilicate Glass 16 x 50 mm). Approximately 1300 mL of the eluent (hexane/ethyl acetate: initially 100:0 (100 mL) and then 99:1 (1200 mL)) is required.

11. The product (1) has the following physicochemical properties: 

   
   \[ R_f = 0.70 \] (hexane/ethyl acetate = 90:10, TLC: Silica gel 60 F254 obtained from Merck and visualized with 254 nm UV lamp); 
   
   \[ ^1H \text{NMR (400 MHz, CDCl}_3 \]: 1.47 (s, 9 H), 1.83 (d, \( J = 6.2 \) Hz, 3 H), 5.69 (d, \( J = 15.2 \) Hz, 1 H), 6.07 (dq, \( J = 15.2, 6.2 \) Hz, 1 H), 6.16 (dd, \( J = 15.2, 10.4 \) Hz, 1 H), 7.14 (dd, \( J = 15.2, 10.4 \) Hz, 1 H). The \( E,E \)-diene stereochemistry is confirmed by \( ^1H \text{NMR coupling constants.} \)
   
   \[ ^13C \text{NMR (100 MHz, CDCl}_3 \]: 18.6, 28.2, 80.0, 120.9, 129.8, 138.5, 143.9, 166.7; IR (neat) 2962, 2932, 1708 (C=O), 1646, 1617, 1455, 1367, 1330, 1280, 1249, 1170, 1135, 999 cm\(^{-1}\); HRMS (FTMS + p NSI) [M + H] calcd for C\(_{10}\)H\(_{17}\)O\(_2\): 169.1223. Found: 169.1221. Anal. Calcd for C\(_{10}\)H\(_{16}\)O\(_2\): C, 71.39; H, 9.59. Found: C, 71.05; H, 9.55.

12. The checkers found the product to be >95% pure by GC (HP 5890 SERIES II, column: HP-5; 5% phenyl methyl siloxane; 30 m x 320 µm x 0.25 µm); Injection temperature: 150 °C; Oven program: Starting temperature, 50 °C for 5 min; heating to 250 °C by a rate of 10 °C per min; 250 °C for 10 min. Retention time of the product was 11.42 min and gave a single peak.

13. Iron(II) chloride (anhydrous, beads, ~10 mesh, 99.99% purity) was purchased from Sigma-Aldrich Co. (USA) and used as received.
14. The temperature of the acetone bath is maintained by a cryogenic reactor.

15. A 1.0 M solution of PhMgBr in THF was purchased from Sigma-Aldrich Co. (USA) and used as received.

16. Column chromatograph is carried out on a column of 5.5-cm diameter and packed with 225 g of silica gel (P60 from SiliCycle Inc., 230-400 mesh (40-63 μm)). Fractions were collected with Fisher-brand disposable culture tubes (Borosilicate Glass 16 x 50 mm). Approximately 2.0 L of the eluent (hexane/ethyl acetate: initially 100:0 (500 mL), 99:1 (500 mL), 98:2 (500 mL), and finally 96:4 (500 mL)) is used.

17. The product (2) has the following physicochemical properties: $R_f = 0.62$ (hexane/ethyl acetate = 90:10, TLC: Silica gel 60 F254 obtained from Merck and visualized with 254 nm UV lamp); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.33 (d, $J = 6.8$ Hz, 3 H), 1.42 (s, 9 H), 3.00 (ddd, $J = 16.8$, 7.2, 1.6 Hz, 1 H), 3.10 (ddd, $J = 16.8$, 7.2, 1.6 Hz, 1 H), 3.71 (dq, $J = 9.2$, 6.8 Hz, 1 H), 5.55 (dt, $J = 10.8$, 7.2 Hz, 1 H), 5.68 (b dd, $J = 10.8$, 9.2 Hz, 1 H), 7.15-7.30 (m, 5 H); The Z-stereochemistry is confirmed by the $^1$H NMR coupling constants and listed above (Z:E = >99:<1) and also by the $^1$H NMR NOESY experiments showing the correlation between the peaks at $\delta$: 5.55 and 5.68 ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 22.0, 28.1, 34.5, 37.5, 80.6, 120.5, 126.0, 126.9, 128.5, 137.7, 145.8, 171.0. IR (neat) 2974, 2930, 1729 (C=O), 1601 (C=C), 1452, 1392, 1367, 1328, 1144, 950, 843, 698 cm$^{-1}$; HRMS (FTMS + p NSI) [M + Na] calcd for C$_{16}$H$_{22}$O$_2$Na: 269.1512. Found: 269.1507. Anal. Calcd for C$_{16}$H$_{22}$O$_2$: C, 78.01; H, 9.00. Found: C, 78.09; H, 9.09.

18. The checkers found the product to be >95% pure by GC (HP 5890 SERIES II, column: HP-5; 5% phenyl methyl siloxane; 30 m x 320 μm x 0.25 μm); Injection temperature: 150 °C; Oven program: Starting temperature, 50 °C for 5 min; heating to 250 °C by a rate of 10 °C per min; 250 °C for 10 min. Retention time of the product was 17.58 min and gave a single peak.

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Discussion

The transition metal-catalyzed conjugate addition of organometallic reagents to electron-deficient olefins is one of the most versatile methods for selective C-C bond formation. Nonetheless, the selective addition to α,β,γ,δ-unsaturated carbonyl compounds has not been amply solved, because they have multiple reaction sites (e.g., 1,2-, 1,4-, and 1,6-addition) and there are additional issues on the regio- and stereoselectivities of the remaining olefinic bond as shown in Scheme 1.
Although copper salts have been mainly used as the catalysts in these reactions, we reported a notable role of an iron catalyst in the 1,6-selective addition of aryl Grignard reagents to 2,4-dienoates or dienamides, giving stereo-defined cis-4-aryl-2-alkenoates or -amides (Scheme 2). We proposed that the reaction involves the intermediary formation of the s-cis-diene-iron complex, which effects the aryl transfer from iron to the terminal position of the dienoate to give the observed cis-product after hydrolysis. The magnesium dienolate, most likely generated in situ, could be also used for the reactions with other electrophiles (El'). Table 1 summarizes the products prepared from various 2,4-dienoates, aryl Grignard reagents, and electrophiles. In all cases, the corresponding 1,6-addition products are obtained virtually as a single isomer. The cis stereoselectivity regarding the ester group and the incoming aryl group is always exclusively high.
A recent report claimed that the iron-catalyzed reactions might be actually catalyzed by copper impurities involved in the iron reagents. We have confirmed that the present 1,6-addition was actually catalyzed by iron on the following basis: (i) Several representative copper catalysts did not furnish the desired products at our hands; (ii) Other groups reported that copper-catalyzed 1,6-additions gave the products exclusively with trans-olefin; (iii) The use of 99.998%-pure iron chloride, rather than the routinely used iron chloride (99.9% purity), did not alter the above outcome, giving virtually the same yield and regio- and stereoselectivities of the 1,6-adduct.

In addition to esters, 2,4-dienamides are also good substrates for this iron-catalyzed 1,6-addition, the results of which are shown in Table 2.
Table 2. Iron-catalyzed 1,6-addition to 2,4-dienamides

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<td>68</td>
<td>97:3</td>
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*For entries 6-13, d.s. refers to the ratio of two major diastereoisomers. Two other minor isomers, which were formed in trace amounts and could not be isolated nor characterized, are omitted.
When the reaction was started with optically active amides derived from (2S,5S)-2,5-diphenylpyrrolidine, both the iron-catalyzed 1,6-addition and the subsequent alkylation of the intermediate enolate took place in a highly diastereoselective manner to afford the corresponding optically active three component-coupling products (Table 2, entries 6-13). A proposed stereochemical course giving the observed products 8 from 7 is shown in Scheme 3, where the s-cis-diene-iron intermediate appears to play an important role to control the stereochemistry of the first aryl addition at the remote position from the chiral auxiliary.

Scheme 3. Proposed stereochemical course of the reaction

The nature of iron to effect the selective 1,6-addition is also found in the conjugate addition to 2-en-4-ynoates and -amides. The results are summarized in Table 3, where methyl as well as aryl Grignard reagents took part in the reaction to give exclusively 3,4-dienoates or -amides after hydrolysis.

In summary, the new iron-catalyzed 1,6-conjugate addition of aryl Grignard reagents to 2,4-dienoates and -amides proceeded in a regio- and stereoselective manner to give virtually single cis-olefinic adducts. As iron is an inexpensive, non-toxic, and ubiquitous metal, this process fulfills the recent demand for an environmentally friendly process.
Table 3. Iron-catalyzed 1,6-addition to 2-en-4-ynoates and -amides

<table>
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<tr>
<th>entry</th>
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<td>11</td>
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*Diastereoselectivity was 67:33. Absolute stereochemistry of the allene part has not been determined. †This reaction was performed at −78 °C for 3 h.*
References

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8. Iron(II) chloride (99.998% pure beads (~10 mesh) purchased from Sigma-Aldrich Co., USA.) afforded the product of the same quality in 82% yield.


Appendix

Chemical Abstracts Nomenclature (Registry Number)

Sorbic acid; (110-44-1)
Oxalyl chloride; (79-37-8)
Sorbic acid chloride; (2614-88-2)
tert-Butyl alcohol; (75-65-0)
n-Butyllithium; (109-72-8)
tert-Butyl (2E,4E)-2,4-hexadienoate; (81838-85-9)
Iron(II) chloride: Ferrous chloride; (7758-94-3)
Phenylmagnesium bromide; (100-58-3)
Hirokazu Urabe was born in 1958 in Kanagawa, Japan. He received his Ph.D. under the supervision of Prof. Isao Kuwajima at Tokyo Institute of Technology in 1985. After he became Assistant Professor at the same institute in 1986, he was a postdoctoral fellow in Prof. B. M. Trost's group at Stanford University during 1988-1990. After he returned to the Department of Biomolecular Engineering, Tokyo Institute of Technology, he was promoted to Associate Professor (2000) and to Professor (2004). His research focuses on the development of new synthetic methods and their application to the synthesis of medicinally important organic compounds and naturally occurring products.

Takeshi Hata was born in 1972 in Kanagawa, Japan. He received his Ph.D. in 2000 from Kyoto University under the supervision of Prof. Tamejiro Hiyama. After he worked as a medicinal chemist at Mitsubishi Pharma Corporation from 2000 to 2005, he joined the faculty at Tokyo Institute of Technology in 2005 as Assistant Professor and was promoted to Associate Professor in 2013. He is interested in development of new methodologies for synthetic reactions and synthesis of biologically important natural products.

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Liangbing Fu was born in Hubei, China. He earned his B.Sc. in Pharmacy from Tongji Medical College, Huazhong University of Science and Technology in 2008. He moved to Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences and obtained his M.Sc. in Medicinal Chemistry under the guidance of Professor Ke Ding in 2011. In the same year he started his Ph.D. studies at Emory University under the mentorship of Professor Huw M. L. Davies. His current research mainly focuses on the development of novel donor-acceptor carbenoid transformations.