

Reaction of trisubstituted alkenes with iron porphyrin carbenes: facile synthesis of tetrasubstituted dienes and cyclopentadienes†

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The unprecedented reaction of trisubstituted alkenes with iron porphyrin carbenes has been successfully developed. Both multiply substituted 1,3-butadiene and cyclopentadiene products are readily accessible with high efficiency and selectivity in good yields.

Reactions of metal carbenes/carbenoids with alkenes are a type of fundamental transformation in organic chemistry.^{1,2} However, the reaction type, reactivity and selectivity of these transformations strongly depend on the properties of the metal carbenes (carbenoids) and the alkenes.^{1,2} Accordingly, in contrast to the great success achieved with terminal olefins,^{1–3} the reactions of electron-deficient alkenes and sterically hindered olefins are far less reported.⁴ For example, iron-porphyrins have proved to be a type of powerful catalysts for the cyclopropanation of terminal alkenes, but they are inactive toward α,β -unsaturated carbonyl compounds and tri- or tetra-substituted alkenes.⁵ This could be ascribed to the electrophilic nature of iron carbenes and their strict shape selectivity. Recently, we realized a formal sp^2 C–H insertion reaction of crotonate-derived α,β -unsaturated esters with Fe-carbenes *via* cyclopropanation/ring-opening by introducing an ylide group to improve the electron density of the double bond.^{6,7} This result suggests that the electronic nature of the substrates might be the main cause of their low reactivity in the case of α,β -unsaturated esters.⁷ Inspired by this success, we became curious about whether this strategy could also be employed for the reaction of “dead” trisubstituted alkenes with iron carbenes. Herein, we wish to report our effort toward this goal and the realization of the reactions of trisubstituted alkenes with iron porphyrin carbenes where both multiply substituted 1,3-butadiene and cyclopentadiene products are accessible with high efficiency and selectivity by using different carbene sources (Scheme 1).

Initially, the substituent effect on trisubstituted allylic phosphonium salts **1** was first investigated with LiHMDS as a base. As shown in Table 1, the reactions of phosphonium salts **1a** and **1b** with



Scheme 1 Iron mediated reactions of ylide-activated trisubstituted alkenes.

Table 1 Substituted group effects on the cyclopropanation/ring-opening reaction

Entry ^a	R	Yield ^b (%)	(3E, 5E)/(3E, 5Z) ^c
1	MeO ₂ C-(1a)	ND	—
2	Ph-(1b)	ND	—
3	Me-(1c)	13 (3a)	69/31
4	MeO-(1d)	49 (4a)	83/17
5 ^d	MeO-(1d)	NR	—

^a Phosphonium salt **1** (0.5 mmol), LiHMDS (0.6 mL, 1.0 M in THF, 0.6 mmol), MDA (50 μ L, 0.6 mmol), PCBA (56 mg, 0.4 mmol), Fe(TCP)Cl (1.7 mg, 0.002 mmol), PhCH₃ (4.0 mL). ^b Isolated yield. ^c Determined by ¹H NMR. ^d Without LiHMDS.

methyl diazo acetate (MDA) in the presence of a catalytic amount of tetra(4-chlorophenyl)porphyrin iron chloride (Fe(TCP)Cl) only led to dimerization of MDA and the direct Wittig reaction of **1a–b** with *p*-chlorobenzaldehyde (entries 1 and 2, Table 1). Increasing the electron density of the C=C double bond by installing a methyl group, to our delight, delivered a 13% yield of desired 1,3-butadiene products with a selectivity of 69 to 31, (3E, 5E)/(3E, 5Z). Upon replacing the methyl group with a methoxy group, the yield of 1,3-butadiene derivative **4a** was improved to 49% with a better selectivity of 83 to 17 (entry 3 vs. entry 4, Table 1). As expected, this reaction did not work at all in the absence of the base (entry 5, Table 1).

Based on these results, an extensive screening of the reaction conditions was conducted next by using phosphonium bromide **1d**, MDA and 4-chlorobenzaldehyde (PCBA) in the presence of a catalytic amount of [Fe(TCP)Cl].⁸ To our delight, the 1,3-butadiene products could be obtained in 89% yield with an excellent selectivity (99/1) finally, when using *t*-BuOK as a base in CH₃CN media

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Table 2 Synthesis of tetrasubstituted dienes

Entry ^a	R	t (h)	3 <i>E</i> , 5 <i>E</i> -4 ^b (%)	3 <i>E</i> , 5 <i>E</i> /3 <i>E</i> , 5 <i>Z</i> ^c
1	4-ClC ₆ H ₄ -	6	89 (4a)	99/1
2	4-BrC ₆ H ₄ -	9	86 (4b)	96/4
3	2-NO ₂ C ₆ H ₄ -	6	78 (4c)	97/3
4	3-NO ₂ C ₆ H ₄ -	6	83 (4d)	97/3
5	4-NO ₂ C ₆ H ₄ -	6	90 (4e)	97/3
6	C ₆ H ₅ -	36	90 (4f)	95/5
7	2-CH ₃ C ₆ H ₄ -	31	71 (4g)	99/1
8	3-CH ₃ C ₆ H ₄ -	31	77 (4h)	97/3
9	4-CH ₃ C ₆ H ₄ -	31	77 (4i)	97/3
10	4-CH ₃ OC ₆ H ₄ -	32	55 (4j)	98/2
11	2,4-Cl ₂ C ₆ H ₃ -	8	95 (4k)	97/3
12	1-Naphthyl-	15	86 (4l)	96/4
13	<i>E</i> -PhCH=CH-	24	64 (4m)	97/3
14	PhC ₂ H ₄ -	24	72 (4n)	92/8
15	<i>n</i> -Octyl-	36	49 (4o)	95/5

^a Phosphonium salt **1d** (235.5 mg, 0.5 mmol), *t*BuOK (67.2 mg, 0.6 mmol), MDA (50 μ L, 0.6 mmol), aldehyde (0.4 mmol), Fe(TCP)Cl (1.7 mg, 0.002 mmol), CH₃CN (4.0 mL). ^b Isolated yield of the single isomer. ^c Determined by ¹H NMR.

(entry 1, Table 2). Notably, the catalyst loading can be further lowered to 0.1 mol% without apparent reduction of the catalytic efficiency (Table S1 in the ESI[†]). The successful activation of the trisubstituted C=C double bond by introducing two electron-donating groups (the ylidic and methoxy groups) suggests that the steric factor in the metal carbene-involved reactions could be overcome, at least partially, by increasing the electron density of the C=C double bond.

Under the optimized conditions, a series of aldehydes bearing aryl and aliphatic groups was examined. As shown in Table 2, the corresponding 1,3-butadienes (3*E*, 5*E*)-**4** can be obtained generally in high yields with excellent selectivities (entries 1–10). Different substituted aryl aldehydes provided the desired products with a similar selectivity (entries 3–6, and entries 7–9, Table 2). Compared with the sterically hindered *ortho*-substituted aryl aldehydes, an apparent increase in yield was observed in the reactions of *para*- or *meta*-substituted aryl aldehydes (entry 3 vs. entries 4 and 5, entry 7 vs. entries 8 and 9, Table 2). On the other hand, electron-rich aryl aldehydes were converted generally in lower yields, compared with the electron-deficient ones. To our delight, aliphatic aldehydes are also suitable substrates, although the selectivity and yield were slightly lower under the same conditions (entries 14 and 15, Table 2). Notably, in all cases excellent (*E,E*)-selectivities were observed (up to 99:1) and only (3*E*, 5*E*)-**4** was isolated using column chromatography. The configuration of the product (3*E*, 5*E*)-**4e** was further confirmed by X-ray analysis (for details, see the ESI[†]).⁸

Interestingly, when using 2-diazo-1-phenylethanone in place of methyl diazoacetate in DCM, cyclopentadiene derivative **5a**⁹ was isolated in 9% yield. After further optimization of the reaction parameters such as reaction time, base, solvent *etc.*, we were pleased to find that the yield of the desired cyclopentadiene derivative **5c** can be improved to 76% in the reaction of ethyl ester **2c** with 1.4 equivalents of 2-diazo-1-phenylethanone and 1,1-dichloroethane (DCE) as the solvent.⁸ The generality of this formal C–H insertion–Wittig cascade reaction was further investigated under the optimized

Table 3 Synthesis of cyclopentadiene derivatives

Entry ^a	R ¹	R ²	R ³	Yield ^b (%)
1	Me	Me	Ph	65 (5a)
2	Et	Me	Ph	74 (5b)
3	Et	Et	Ph	76 (5c)
4	Et	<i>t</i> -Bu	Ph	50 (5d)
5	Et	CH ₂ =CHCH ₂ CH ₂	Ph	40 (5e)
6	Et	Et	<i>p</i> -CH ₃ OC ₆ H ₄	45 (5f)
7	Et	Et	<i>p</i> -CH ₃ C ₆ H ₄	50 (5g)
8	Et	Et	<i>p</i> -FC ₆ H ₄	57 (5h)
9	Et	Et	<i>p</i> -ClC ₆ H ₄	48 (5i)
10	Et	Et	<i>p</i> -BrC ₆ H ₄	48 (5j)
11	Et	Et	<i>m</i> -BrC ₆ H ₄	70 (5k)
12	Et	Et	<i>E</i> -PhCH=CH	46 (5l)
13	Et	Et	2-Furyl	73 (5m)

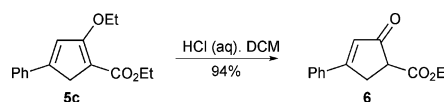
^a Conditions: ylide **2** (0.4 mmol), R₃COCHN₂ (0.56 mmol), Fe(TCP)Cl (1.7 mg, 0.002 mmol), DCE (4.0 mL), 20 °C. ^b Isolated yield.

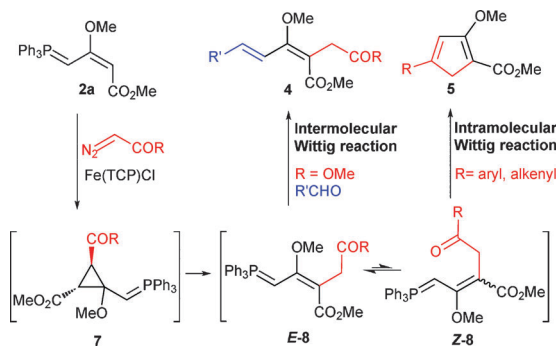
conditions, and the results are presented in Table 3. Replacement of the ethoxy group with a methoxy group decreased the yield to 65% (entry 1, Table 3). On the other hand, bulky *tert*-butyl ester gave a lower yield than methyl and ethyl esters (entry 4, Table 3). The electronic nature of the substituents on diazo arylethanone slightly influenced the yield (entries 6–10), while the *meta* bromo-substituted diazo compound gave a much better yield than the *para*-substituted one (entries 10 and 11). However, no desired product was observed when 1-(2-bromophenyl)-2-diazoethanone was employed. When (*E*)-1-diazo-4-phenylbut-3-en-2-one and 2-diazo-1-(furan-2-yl) ethanone were employed, the desired products were obtained in 46% and 73% yield respectively (entries 12 and 13, Table 3).

The cyclopentadiene derivatives are valuable intermediates in organic synthesis,¹⁰ and by treatment with hydrochloric acid cyclopentadienes can be readily transformed to cyclopentenones which are also a useful type of synthetic intermediate as exemplified with **5c** (Scheme 2).

A plausible mechanism for the formal sp² C–H insertion of trisubstituted allylic phosphorus ylide is proposed in Scheme 3. Cyclopropanation of trisubstituted allylic phosphorus ylide affords highly active cyclopropylmethyl ylide intermediate **7**. The ylide- or MeO-group triggered ring-opening reaction affords a *Z-E* mixture of **8**, which can be further transformed to tetrasubstituted dienes by trapping with aldehydes. According to the configuration of 1,3-butadienes, *E*-**8** should be the major isomer in this process, but can isomerise to *Z*-**8**, which then undergoes an intramolecular Wittig reaction to afford cyclopentadienes **5** when diazo arylethanones are employed.

Unfortunately, many efforts to trap the cyclopropanation intermediates ended with a failure. Using deuterium labelled diazo methyl acetate (*d*₃-MDA), deuterium was detected in both methoxy-carbonyl groups (Scheme 4), which indicates that cyclopropanation should occur. The different contributions of deuterium in different

**Scheme 2** Transformation of cyclopentadiene **5c** to cyclopentenone **6**.



Scheme 3 Proposed mechanism of the formal C-H insertion reaction.



Scheme 4 Deuterium experiment for the mechanism.

methoxycarbonyl groups may be caused by the diastereoselectivity in the cyclopropanation step or the different trigger group governed ring-opening (MeO- vs. $\text{Ph}_3\text{P}=\text{CH}-$), but further mechanistic studies are needed to draw an explicit rationalization for the current reaction.

In summary, a carbene transfer reaction of tri-substituted alkenes mediated by iron-porphyrin catalysis has been successfully realized based on an ylidic activation approach. The reaction with diazo acetate proceeded *via* a formal sp^2 C-H insertion to the double bond and delivered multiply substituted 1,3-butadiene derivatives in moderate to excellent yields with excellent *Z-E* selectivity, while utilization of diazo arylethanone as the substrate allows an efficient construction of cyclopentadiene derivatives. To our knowledge, this reaction represents the first example of the reactions of trisubstituted α,β -unsaturated carbonyl esters with iron carbenes. The current reaction further demonstrated that the low reactivity or inactivity of di- and tri-substituted alkenes toward electrophilic iron carbenes could be partially overcome by increasing the electron density of the double bond.

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