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Stereoselective Catalytic Synthesis of Tetrasubstituted Olefins from the Intermolecular Conjugate Addition of Simple Alkenes to α,β -Unsaturated Carbonyl Compounds**

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Abstract

Recent efforts in designing expeditious catalytic synthesis of tetrasubstituted olefins have in part been stimulated by growing needs for developing generally applicable methods for tamoxifen analogs (anti-breast cancer drug) as well as for photo-responsive organic materials and molecular devices.^[1] A number of different catalytic methods have been developed to synthesize tetrasubstituted olefins, including: Suzuki-type Pd-catalyzed coupling reactions,^[2] Ni- and Rh-catalyzed exocyclization methods,^[3] Ni- and Pd-catalyzed nucleophilic coupling reactions of alkynes^[4] and of alkyne-to-arylboronic acids,^[5] Ti-catalyzed tandem alkyne-epoxide-ethyl acetate coupling,^[6] and the ring-closing olefin metathesis by using Grubbs catalyst.^[7] Though catalytic conjugate addition of alkenes has been recognized as a potentially powerful synthetic methodology in forming tetrasubstituted olefins, generally applicable conjugate addition of simple olefins to α,β -unsaturated carbonyl compounds has been hampered by lack of reactivity of the olefin substrates and due to the formation of homocoupling and other byproducts. Chelate-assisted C–H insertion^[8] and cross coupling methods^[9] are among the most notable advances in catalytic coupling reaction of enones with simple alkenes. Ni-catalyzed conjugate addition and allylic substitution reactions of simple alkenes have also been reported recently.^[10] We recently discovered that the cationic complex $[(C_6H_5)(CO)(PCy_3)RuH]^+BF_4^-$ (**1**) is a highly effective catalyst precursor for the coupling reactions of arylketones and alkenes involving C–H activation.^[11] Herein we report a novel catalytic synthesis of tetrasubstituted olefins from the intermolecular conjugate addition reaction of simple olefins to α,β -unsaturated carbonyl compounds.

(1)

Initial feasibility of the conjugate addition reaction was screened by using a cinnamic acid derivative and an α -olefin (eq 1). Thus, the treatment of ethyl cinnamate (0.58 mmol) with

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propene (2.9 mmol) in the presence of a Ru catalyst (3 mol %) in CH_2Cl_2 was stirred at 70 °C for 2 h, after which the product conversion was analyzed by GC.^[12] Among the selected ruthenium catalysts, the complex **1**, both in isolated form and *in-situ* formed from the treatment of the tetranuclear complex $\{[(\text{PCy}_3)(\text{CO})\text{RuH}]_4(\mu\text{-O})(\mu\text{-OH})_2\}$ with $\text{HBF}_4\cdot\text{OEt}_2$, exhibited uniquely high activity in yielding the coupling product **2a** (Table 1).

The scope of the coupling reaction was examined by using the catalyst **1** (Table 2). Enones and α,β -unsaturated esters and amides were found to react smoothly with simple α -olefins to give the tetrasubstituted olefin products. In general, cinnamic esters and amides with *para*-electron donating group were found to promote the coupling reaction, but neither cyclic enones nor pyrrolinones gave the coupling products under the similar reaction conditions. Highly (*Z*)-selective tetrasubstituted olefin products **2r–2u** was resulted from the coupling reaction of *N*-methyl cinnamide with 1-alkenes (entries 18–22). The fact that both 1- and 2-butenes gave the same product **2r** suggested that the rate of olefin isomerization is much faster than the coupling reaction rate (entries 18, 19). It should be emphasized that the α -olefins with sterically non-demanding group were found to give similar (*Z*)-selective tetrasubstituted olefins (entries 20–22), whereas the coupling reaction with cyclopentene afforded a highly diastereoselective formation of the coupling product **2v** (entry 23). For activated olefins, a mixture of linear and branched olefin products **2w** and **2x** was produced with styrene (entry 24), while ethyl acrylate gave an exclusive formation of the (*Z*)-selective linear coupling product **2y** (entry 25). α -Substituted α,β -unsaturated carbonyl compounds with propene also gave the tetraolefin coupling products **2bb–2dd**, though a cyclic lactone resulted in a modest yield of the coupling product **2bb** (entries 28–30). The coupling reaction of β -alkyl-substituted α,β -unsaturated carbonyl substrates in general was found to be very sluggish resulting in low yields with low selectivity. The most salient feature of the coupling reaction is that tri- and tetrasubstituted olefins are efficiently synthesized in highly stereo- and regioselective fashion from the intermolecular conjugate addition of unactivated olefins to α,β -unsaturated carbonyl compounds without employing any reactive reagents or additives.

We performed the following kinetic experiments to probe the mechanism of the coupling reaction. To examine H/D exchange pattern on the carbonyl substrate, the reaction mixture of (*E*)- $\text{C}_6\text{D}_5\text{CD}=\text{CDCONMe}_2$ (0.58 mmol) with propene (2.9 mmol) in the presence of **1** (3 mol %) in CH_2Cl_2 (2 mL) was stirred at 70 °C for 2 h. The isolated product **2n** was found to contain ~55% D on the α -methylene position, but with only 6% of D on the δ -methyl positions (Figure S1, Supporting Information).

The carbon isotope effect of the coupling reaction was measured by employing Singleton's NMR technique at natural abundance.^[13] The most pronounced carbon isotope effect was observed on the β -carbon of (*E*)- $\text{C}_6\text{H}_5\text{CH}=\text{CHCONEt}_2$ when the ^{13}C ratio of recovered substrate at 75–80% conversion was compared to that of the virgin sample ($^{13}\text{C}(\text{recovered})/^{13}\text{C}(\text{virgin})$ at $C_\beta = 1.018(7)$; average of 3 runs)(Table S1, Supporting Information). These results indicate that the olefin insertion to α,β -unsaturated carbonyl substrate is the rate-limiting step of the coupling reaction.

(2)

In an effort to trap/isolate catalytically relevant species, the reaction mixture of complex **1** (5.0 mmol) with a naphthyl-substituted amide (25 mmol), cyclopentene (5 equiv) and H₂O (10 equiv) in CD₂Cl₂ was followed by NMR (eq 2). The formation of the Ru-allyl complex **3** was detected after 5 h at room temperature. In a preparatory scale reaction, the complex **3** was most conveniently isolated from the reaction of the tetrameric complex $\{[(PCy_3)(CO)RuH]_4(\mu-O)(\mu-OH)_2\}$ with the amide, HBF₄·OEt₂ and cyclopentene in wet CH₂Cl₂, and its structure was unequivocally established by X-ray crystallography (Figure S2, Supporting Information).^[12]

The complex **3** was found to exhibit virtually same activity as **1** in mediating the coupling reaction of benzamide and propene under the conditions stipulated in eq 1. The analogous reaction in the presence of 1.5 equiv of H₂O resulted in a substantially lower product conversion (75 % after 2 h).^[14] To further establish catalytic relevance of the complex, the reaction of **3** with 1.0 equiv of (*E*)-PhCH=CHCONHMe was monitored by ¹H NMR. The reversible coordination of the amide substrate was observed at room temperature to form a 2:1 ratio of **3** and carbonyl-coordinated complex, but no new Ru–H species has been detected even after heating at 60 °C. While a more careful study is needed to establish the exact mechanism, the preliminary results suggest that both amide and excess alkene substrates are required for the conversion of the complex **3** to catalytically active species.^[15]

These results support a mechanism involving a cationic Ru–H species **4**, which is initially formed from the ligand exchange reaction of **1** with the carbonyl substrate (Scheme 1). We propose that the chelate-directed regioselective alkene insertion and β-H elimination steps would form the cationic Ru-alkene-hydride species **5**. It has been well established that both olefin bond polarity and the chelation of the carbonyl group are important in directing regioselective insertion of enamides and α,β-unsaturated carbonyl compounds.^[16] In our case, an electrophilic Ru center should also promote the regioselective olefin insertion in forming the carbonyl-chelated species **5**. The carbon isotope effect study provides a strong support for the rate-limiting olefin insertion step. In light of the recent deuterium labeling study on the alkene dimerization and isomerization reactions,^[17] the olefin isomerization step is expected to be facile in yielding the tetrasubstituted olefin product **2** with the regeneration of **4**. The successful isolation of the catalytically active Ru-allyl complex **3** can also be inferred from the Ru-alkene-hydride species **5** via dehydrogenation and the trapping of the Ru-allyl species by a water molecule. An alternative oxidative coupling mechanism has also been considered for the coupling reaction. Though we cannot rigorously rule out the mechanism at this time, the oxidative coupling mechanism cannot readily explain both deuterium labeling pattern and (*Z*)-stereoselective formation of the tetrasubstituted olefin products.^[18]

In summary, a novel catalytic method for tetrasubstituted olefins has been developed from the conjugate addition of unactivated olefins to α,β-unsaturated carbonyl compounds. The preliminary kinetic and spectroscopic studies provide supporting evidences for a mechanistic pathway involving a rate-limiting olefin insertion to α,β-unsaturated carbonyl substrates and rapid olefin isomerization steps. Efforts are currently underway to establish the detailed mechanism as well as to extend the scope of the coupling reaction.

Experimental Section

Representative Procedure of the Catalytic Reaction

In a glove box, complex **1** (10 mg, 17.4 μmol) and ethyl cinnamate (0.58 mmol) were dissolved in CH₂Cl₂ (2.0 mL) in a 25 mL Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar. The tube was brought out of the box, and was cooled in a dry ice-acetone bath. Excess propene (2.9 mmol) was condensed into the reaction tube via a vacuum

transfer, and the tube was stirred in an oil bath which was preset at 70 °C for 2 h. The tube was cooled to room temperature and was open to air. After filtering through a small silica gel column (hexanes/EtOAc = 2:1), the solution was analyzed by GC. Analytically pure product **2a** was isolated after a silica gel column chromatography (hexanes/EtOAc = 20:1 to 4:1).

Spectroscopic data for **2a**: ^1H NMR (400 Hz, CDCl_3 , 20 °C, TMS): δ =7.32 (m, 2H; Ar), 7.18 (m, 2H; Ar), 4.07 (q, J =7.1 Hz, 2H; CH_2), 3.39 (s, 2H; CH_2), 1.85 (s, 3H; CH_3), 1.64 (s, 3H; CH_3), 1.16 ppm (t, J =7.1 Hz, 3H; CH_3). ^{13}C NMR (100.5 Hz, CDCl_3 , 20 °C): δ =171.2, 143.2, 132.1, 128.8, 127.9, 127.8, 126.2, 60.3, 40.1, 22.2, 20.6, 14.1 ppm. GC-MS m/z : 218 [M^+].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- The coupling reaction with D_2O did not give any deuterium incorporation in the coupling product.
- A plausible way to form catalytically active Ru–H species from **3** could involve a η^3 - η^1 allyl shift and β -hydrogen elimination of the σ -allyl ligand.

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Scheme 1.
Proposed Mechanism of the Tetrasubstituted Olefin Formation.

Table 1Catalyst Survey for the Coupling Reaction of Ethyl Cinnamate and Propene.^[a]

entry	catalyst	additive	yield (%) ^[b]
1	1		95
2	[RuH(CO)(PCy ₃) ₄ (O)(OH) ₂]		0
3	[RuH(CO)(PCy ₃) ₄ (O)(OH) ₂]	HBF ₄ ·OEt ₂	94
4	RuHCl(CO)(PCy ₃) ₂		0
5	RuH ₂ (CO)(PPh ₃) ₃		0
6	RuCl ₂ (PPh ₃) ₃	HBF ₄ ·OEt ₂	0
7	RuCl ₂ (PPh ₃) ₃		0
8	[(p-cymene)RuCl ₂] ₂		0
9	Ru ₃ (CO) ₁₂		0
10 ^[c]	[RuH(CO)(PCy ₃) ₂ (S) ₂] ⁺ BF ₄ ⁻		0
11	RuCl ₃ ·3H ₂ O		0
12	HBF ₄ ·OEt ₂		0

^[a] Reaction conditions: ethyl cinnamate (0.58 mol), propene (2.9 mmol), catalyst (3 mol %), CH₂Cl₂ (1–2 mL), 70 °C, 2–5 h.^[b] The conversion of innamate as determined by GC.^[c] S = CH₃CN.

Table 2
Conjugate Addition Reaction of Simple Olefins to α,β -Unsaturated Carbonyl Compounds.^[a]

entry	carbonyl compd	alkene	product (s)	t (h)	temp (°C)	yd (%)

1	X = H	R = OEt	2a	2	70	95
2	X = Me	R = OEt	2b	2	70	94
3	X = OEt	R = OEt	2c	2	70	95
4	X = Cl	R = OEt	2d	2	70	93
5	X = CF ₃	R = OEt	2e	2	70	92
6	X = H	R = OMe	2f	2	70	95
7	X = H	R = OBz	2g	2	70	93
8	X = H	R = Me	2h	2	70	92
9	X = H	R = Ph	2i	2	70	92
10	X = Me	R = Me	2j	2	70	95

11	R = H, Me		2k	2	70	93
12	R = H, Ph		2l	2	70	94
13	R = H, Bz		2m	2	70	95
14	R = Me, Me		2n	2	70	94
15	R = i-Pr, i-Pr		2o	2	70	94
16	R = Me, Ph		2p	2	70	94
17				14	50	82

(Z)/(E)-**2q** = 3:1

entry	carbonyl compd	alkene	product (s)	t (h)	temp (°C)	yd (%)
18				14	50	64
19				14	50	65
20				14	50	90
21				14	50	90
22				14	50	85
23				14	20	89
24				14	50	70
25				14	50	50
26				2	70	90
27				2	70	95
28				2	70	15

entry	carbonyl compd	alkene	product (s)	t (h)	temp (°C)	yd (%)
29				14	70	94
30				14	70	90

[a] Reaction conditions: carbonyl compound (0.58 mmol), alkene (2.9 mmol), **1** (10 mg, 3 mol %), CH₂Cl₂ (2 mL).