Homogeneous Catalysis

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

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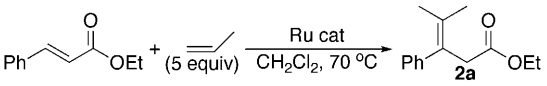
Recent efforts in designing the expeditious catalytic synthesis of tetrasubstituted olefins have in part been stimulated by growing needs for developing generally applicable methods for tamoxifen analogues (antibreast cancer drug) as well as for photoresponsive organic materials and molecular devices.[1] 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 to carbonyl compounds[4] and of alkynes to arylboronic acids,[5] Ti-catalyzed tandem alkyne-epoxide-ethyl acetate coupling,[6] and the ring-closing olefin metathesis by using the Grubbs catalyst.[7] Although catalytic conjugate addition of alkenes has been recognized as a potentially powerful synthetic methodology in forming tetrasubstituted olefins, a generally applicable conjugate addition of simple olefins to α,β-unsaturated carbonyl compounds has been hampered by the lack of reactivity of the olefin substrates and by the formation of homocoupling and other by-products. Chelate-assisted C–H insertion[8] and cross-coupling methods[9] are among the most notable advances in the 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 $[(C_6H_6)(CO)(PCy_3)RuH]^+BF_4^-$ (**1**; Cy = cyclohexyl) 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.

The feasibility of the conjugate addition reaction was determined by screening different ruthenium catalysts for the reaction between a cinnamic acid derivative and an α olefin [Eq. (1)]. Propene (2.9 mmol) was added to a solution of ethyl cinnamate (0.58 mmol) and a ruthenium catalyst (3 mol%) in CH_2Cl_2, and the reaction mixture was stirred at 70°C for 2 hours, after which the product conversion was analyzed by GC methods.[12] Among the selected ruthenium catalysts, complex **1**, both in its isolated form (Table 1, entry 1) and



(1)

Table 1: Catalyst 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	$[\{RuH(CO)(PCy_3)\}_4(O)(OH)_2]$	$HBF_4{\cdot}OEt_2$	94
4	$[RuHCl(CO)(PCy_3)_2]$	–	0
5	$[RuH_2(CO)(PPh_3)_3]$	–	0
6	$[RuCl_2(PPh_3)_3]$	$HBF_4{\cdot}OEt_2$	0
7	$[RuCl_2(PPh_3)_3]$	–	0
8	$[\{(p\text{-cymene})RuCl_2\}_2]$	–	0
9	$[Ru_3(CO)_{12}]$	–	0
10[c]	$[RuH(CO)(PCy_3)_2(S)_2]^+BF_4^-$	–	0
11	$RuCl_3{\cdot}3H_2O$	–	0
12	$HBF_4{\cdot}OEt_2$	–	0

[a] Reaction conditions: ethyl cinnamate (0.58 mmol), propene (2.9 mmol), catalyst (3 mol%), CH_2Cl_2 (1–2 mL), 70°C, 2–5 h. [b] The conversion of cinnamate as determined by GC analysis using C_6Me_6 as an internal standard. [c] S = CH_3CN. p-cymene = 4-isopropyltoluene.

when formed in situ from the treatment of the tetranuclear complex $[\{(PCy_3)(CO)RuH\}_4(\mu\text{-}O)(\mu\text{-}OH)_2]$ with $HBF_4{\cdot}OEt_2$ (entry 3), exhibited uniquely high activity in yielding the coupling product **2a**.

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 with *para* electron-donating groups were found to promote the coupling reaction, but neither cyclic enones nor pyrrolinones gave the coupling products under similar reaction conditions. The coupling reactions of *N*-methyl cinnamide with 1-alkenes furnished the tetrasubstituted *Z*-olefin products **2r**–**2u** selectively (Table 2, entries 18–22). The fact that both 1- and 2-butenes gave the same product, **2r**, suggests that the rate of olefin isomerization is much faster than the rate of the coupling reaction

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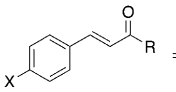
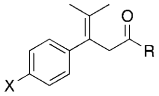
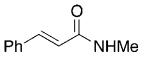
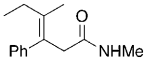
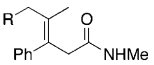
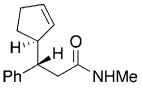
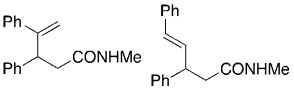
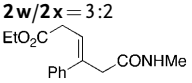
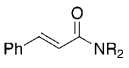
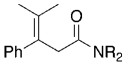
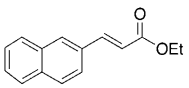
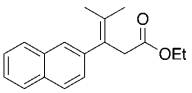
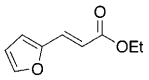
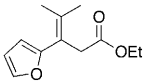
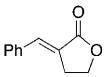
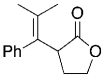
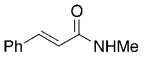
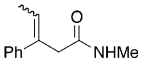
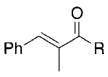
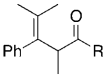
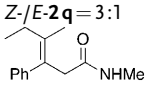
Table 2: Conjugate addition reaction of simple olefins to α,β-unsaturated carbonyl compounds.[a]

Entry	Carbonyl compound	Alkene	Product(s)	*t* [h]	*T* [°C]	Yield [%][b]	Entry	Carbonyl compound	Alkene	Product(s)	*t* [h]	*T* [°C]	Yield [%][b]
													
1	X = H, R = OEt		**2a**	2	70	95	19			**2r**	14	50	65
2	X = Me, R = OEt		**2b**	2	70	94							
3	X = OEt, R = OEt		**2c**	2	70	95	20		R = *n*Pr	**2s**	14	50	90
4	X = Cl, R = OEt		**2d**	2	70	93	21		R = Cy	**2t**	14	50	90
5	X = CF_3, R = OEt		**2e**	2	70	92	22		R = CH_2Ph	**2u**	14	50	85
6	X = H, R = OMe		**2f**	2	70	95							
7	X = H, R = OBn		**2g**	2	70	93	23			**2v**	14	20	89
8	X = H, R = Me		**2h**	2	70	92							
9	X = H, R = Ph		**2i**	2	70	92	24			**2w**/**2x** = 3:2	14	50	70
10	X = Me, R = Me		**2j**	2	70	95							
							25			**2y**	14	50	50
11	R = H, Me		**2k**	2	70	93							
12	R = H, Ph		**2l**	2	70	94	26			**2z**	2	70	90
13	R = H, Bn		**2m**	2	70	95							
14	R = Me, Me		**2n**	2	70	94	27			**2aa**	2	70	95
15	R = *i*Pr, *i*Pr		**2o**	2	70	94							
16	R = Me, Ph		**2p**	2	70	94	28			**2bb**	2	70	15
													
17			*Z*-/*E*-**2q** = 3:1	14	50	82	29	R = OEt		**2cc**	14	70	94
							30	R = NHMe		**2dd**	14	70	90
18			**2r**	14	50	64							

[a] Reaction conditions: carbonyl compound (0.58 mmol), alkene (2.9 mmol), 1 (10 mg, 3 mol%), CH2Cl2 (2 mL). [b] Yield reported for isolated product.

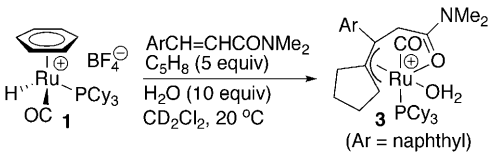
(Table 2, entries 18 and 19). It should be emphasized that the less bulky α olefins were found to give similar tetrasubstituted *Z* olefins selectively (Table 2, entries 20–22), whereas the coupling reaction with cyclopentene resulted in the formation of the highly diastereoselective coupling product **2v** (Table 2, entry 23). For the activated olefins, styrene gave a mixture of the branched and linear olefin products **2w** and **2x**, respectively (Table 2, entry 24), whereas ethyl acrylate gave exclusive formation of the linear coupling product **2y** (*Z* olefin; Table 2, entry 25). α-Substituted α,β-unsaturated carbonyl compounds reacting with propene gave the tetrasubstituted olefin coupling products **2bb**–**2dd**, even though the reaction of the cyclic lactone resulted in only a modest yield of the coupling product **2bb** (Table 2, entries 28–30). The coupling reaction of β-alkyl-substituted α,β-unsaturated carbonyl substrates in general was found to be very slow, thus resulting in low yields and low selectivity. The most salient feature of the coupling reaction is that tri- and tetrasubstituted olefins are efficiently synthesized in a 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 the H/D exchange pattern on the carbonyl substrate, a mixture of (*E*)-$C_6D_5CD{=}CDCONMe_2$ (0.58 mmol), propene (2.9 mmol), and **1** (3 mol%) in CH_2Cl_2 (2 mL) was stirred at 70 °C for 2 hours. The isolated product **2n** was found to contain

approximately 55% D on the α-methylene position, but with only 7% D on the δ-methyl positions (see Figure S1 in the 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 atom of (*E*)-C_6H_5CH=$CHCONEt_2$; the ^{13}C ratio of the recovered substrate to that of the virgin sample [(^{13}C(recovered)/^{13}C(virgin)] was $C_\beta = 1.018$ (average of 3 runs, at 75%–80% conversion; see Table S1 in the Supporting Information). These results indicate that the olefin insertion into an α,β-unsaturated carbonyl substrate is the rate-limiting step of the coupling reaction.

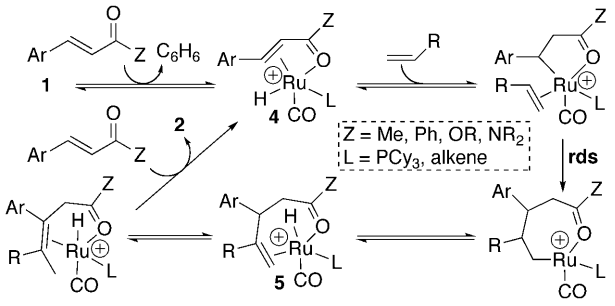
In an effort to trap catalytically relevant species, the reaction of complex **1** (5.0 mmol) with a naphthyl-substituted amide (25 mmol), cyclopentene (5 equivalents), and H_2O (10 equivalents) in CD_2Cl_2 was monitored by ^1H and ^{31}P NMR spectroscopy [Eq. (2)]. The formation of the Ru/allyl complex **3** was detected after 5 hours at room temperature. In a preparatory scale reaction, the complex **3** was isolated from the reaction of the tetrameric complex [{$(PCy_3)(CO)RuH$}$_4$-(μ-O)(μ-OH)$_2$] with the naphthyl-substituted amide, $HBF_4{\cdot}OEt_2$, and cyclopentene in wet CH_2Cl_2, and its structure was unequivocally established by X-ray crystallography (see Figure S2 in the Supporting Information).[12]



(2)

The complex **3** was found to exhibit virtually the same activity as **1** in mediating the coupling reaction of (E)-PhCH=CONHMe and propene under the conditions stipulated in Equation (1); the reaction gave **2k** in a >90% yield after 2h. When this reaction was performed in the presence of 1.5 equivalents of H_2O, a substantially lower product conversion (75% after 2 hours) was observed.[14] To further establish catalytic relevance of the complex, the reaction of **3** with 1 equivalent of (*E*)-PhCH=CHCONHMe was monitored by ^1H NMR spectroscopy. The reversible coordination of the α,β-unsaturated carbonyl substrate was observed at room temperature to form a 2:1 ratio of **3** and the carbonyl-coordinated complex, but no new Ru–H species was detected, even after heating at 60 °C. Although a more careful study is needed to establish the exact mechanism, the preliminary results suggest that both the α,β-unsaturated carbonyl compound and excess alkene substrates are required for the conversion of the complex **3** into a catalytically active species.[15]

These results support a mechanism involving the 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-hydride elimination steps would form the cationic Ru/alkene/hydride species **5**. It has been



Scheme 1. Proposed mechanism of the formation of the tetrasubstituted olefin. rds = rate-determining step.

well established that both the 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 the formation of the carbonyl-chelated species **5**. The carbon isotope effect study provides 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** suggests species **5** as a possible intermediate, which can undergo dehydrogenation and then trapping by a water molecule. An alternative oxidative coupling mechanism has also been considered for the coupling reaction. Although we cannot rule out this mechanism at this time, the oxidative coupling mechanism cannot readily explain both the deuterium labeling pattern and the stereoselective formation of the tetrasubstituted *Z*-olefin products.[18]

In summary, a novel catalytic method for the synthesis of 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 evidence for a mechanistic pathway that involves a rate-limiting olefin insertion to the α,β-unsaturated carbonyl substrate 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 CH_2Cl_2 (2.0 mL) in a 25 mL Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar. The Schlenk 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 by a vacuum transfer, and the reaction mixture was stirred in an oil bath for 2 h at 70 °C. The reaction mixture was cooled to room temperature and then opened to air. After filtering through a small pad of silica gel (hexanes/EtOAc = 2:1), the solution was analyzed by GC methods. Analytically pure product **2a** was isolated after column chromatography (hexanes/EtOAc = 20:1 to 4:1).

Spectroscopic data for **2a**: ^{1}H NMR (400 Hz, $CDCl_3$, 20 °C, TMS): $\delta = 7.32$ (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): $\delta = 171.2$, 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^+].

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[12] See the Supporting Information for the experimental details. CCDC 805621 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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