Synthesis of 2-alkylidenetetrahydrofurans by Ru-catalyzed regio- and stereoselective codimerization of dihydrofurans with α,β-unsaturated esters†

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2-(1-Alkoxycarbonyl)alkylidenetetrahydrofurans were readily synthesized by the codimerization of 2,3- or 2,5-dihydrofurans with α,β-unsaturated esters using a zerovalent Ru catalyst, Ru(cod)(cot), with high regio- and stereoselectivity.

2-Alkylidenetetrahydrofurans are versatile synthetic building blocks for natural products such as macrotetrolide antibiotics[1] and for artificial biologically active substances.[2] A large number of preparative methods for 2-(1-alkoxycarbonyl)alkylidenetetrahydrofurans have been reported so far, and are roughly classified into the following categories: acid or base-mediated cyclizations,[3,4] cross-Claisen condensation by nucleophilic reactions of ester enolates with lactones,[5] selenium[6] or iodine[7]-involved cyclizations, and transition metal-catalyzed reactions.[8–10] Most of these methods, however, have an essential drawback inasmuch as undesirable byproducts such as inorganic salts are produced. On the other hand, codimerization of unsaturated hydrocarbons is an attractive carbon–carbon bond forming method with high atom efficiency. In the course of our investigation on ruthenium-catalyzed selective codimerization of alkenes,[11] we found a highly regio- and stereoselective codimerization of dihydrofurans with α,β-unsaturated esters catalyzed by low-valent ruthenium complexes, which provides a novel and unique synthetic route to 2-(1-alkoxycarbonyl)alkylidenetetrahydrofurans.[12]

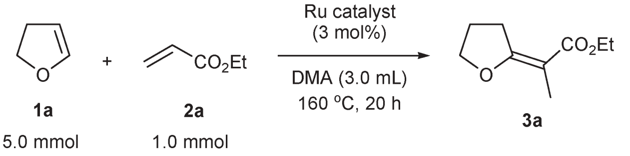
The reaction of 2,3-dihydrofuran (**1a**) with ethyl acrylate (**2a**) was first examined. A zerovalent ruthenium catalyst, Ru(cod)(cot) [cod = 1,5-cyclooctadiene, cot = 1,3,5-cyclooctatriene], was found to catalyze the codimerization efficiently in a polar solvent, *N*,*N*-dimethylacetamide (DMA) at 160 °C, affording 2-(1-ethoxycarbonyl)ethylidenetetrahydrofuran (**3a**) exclusively in 70% yield. Catalytic activity of several low-valent ruthenium complexes for the codimerization of **1a** with **2a** was then surveyed (Table 1). Another zerovalent ruthenium complex, $Ru(cot)(dmfm)_2$ [dmfm = dimethyl fumarate],[13] was also effective to give **3a** (run 3). $Ru(cyclooctadienyl)_2$, $Ru_3(CO)_{12}$ and $RuHCl(CO)(PPh_3)_3$ showed moderate catalytic activity (runs 4, 5 and 6). $CpRuCl(PPh_3)_2$, Cp*RuCl(cod) [Cp* = pentamethylcyclopentadienyl], $RuH_2(PPh_3)_4$, $[RuCl_2(CO)_3]_2$ and $Ru(CO)_3(PPh_3)_2$ were ineffective for the present codimerization. With 8–10 group transiton metal catalysts such as $Fe_3(CO)_{12}$, $Co_2(CO)_8$, $RhCl(PPh_3)_3$, $IrCl(CO)(PPh_3)_2$ and $Pd(PPh_3)_4$, **3a** was not obtained at all.

The effect of the reaction temperature on the codimerization of **1a** with **2a** was examined, and 160 °C was revealed to be suitable. The yield of **3a** was decreased at over 160 °C (60% at 170 °C and 51% at 180 °C). The use of other solvents with high boiling point such as diglyme and mesitylene resulted in a lower yield of **3a** (32 and 35%).

Under the optimized reaction conditions, the scope of the codimerization of dihydrofurans with α,β-unsaturated esters was investigated (Table 2). The reaction of **1a** with 2-aryl-2,3-dihydrofurans proceeded nicely to give the corresponding codimers (runs 2 and 3). Remarkably, β-substituted unsaturated esters such as methyl cinnamate (**2b**), methyl crotonate (**2c**) and dimethyl fumarate (**2d**) were also applicable to the present catalytic system (runs 5–7). Dimethyl maleate worked as well as **2d** to afford the identical codimer **3g** in 68% yield. The use of 2,5-dihydrofuran instead of **1a** in the codimerization with **2a** gave **3a** in 62% yield. In this case, isomerization of the substrate prior to the codimerization would occur. On the other hand, the codimerization of **1a** with α-substituted and β,β-disubstituted acrylates, 2(5*H*)-furanone, vinylketones, acrylonitrile and acrylamides, did not proceed under the present reaction conditions. Six-membered unsaturated cyclic ethers such as 3,4-dihydro-2*H*-pyran and 1,4-dioxene, and *n*-butyl vinyl ether did not give the corresponding codimers in the reaction with **2a**, either.

A deuterium-labeling experiment was conducted to elucidate the reaction mechanism with deuterium-incorporated dimethyl

Table 1 Codimerization of 2,3-dihydrofuran with ethyl acrylate catalyzed by several ruthenium complexes[a]



Run	Catalyst	Yield[b] (%)
1	None	0
2	Ru(cod)(cot)	70
3[c]	$Ru(cot)(dmfm)_2$	70
4	$Ru(cyclooctadienyl)_2$	50
5	$Ru_3(CO)_{12}$	45
6	$RuHCl(CO)(PPh_3)_3$	31
7	$CpRuCl(PPh_3)_2$	5

[a] Ru catalyst (0.030 mmol as a metal atom). [b] GLC yields. [c] dmfm = dimethyl fumarate.

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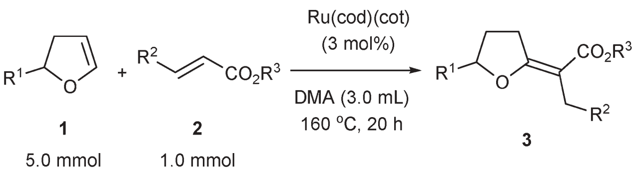
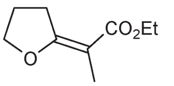
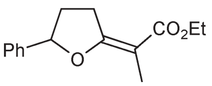
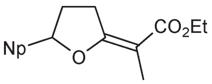
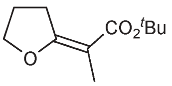
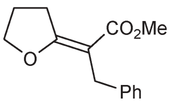
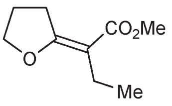
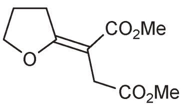
† Electronic supplementary information (ESI) available: Experimental section. See http://dx.doi.org/10.1039/b509578f

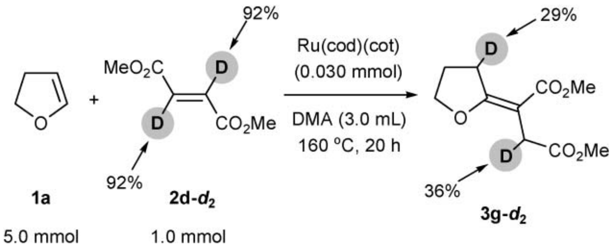
Table 2 Ru(cod)(cot)-catalyzed codimerization of 2,3-dihydrofurans with α,β-unsaturated esters



Run	R^1	R^2	R^3	Product		Yield[a] (%)
1	H	H	Et		**3a**	70 (59)
2	Ph	H	Et		**3b**	39 (26)
3[b,c]	Np	H	Et		**3c**	79 (65)
4	H	H	^{t}Bu		**3d**	72 (55)
5	H	Ph	Me		**3e**	44 (19)
6	H	Me	Me		**3f**	(11)
7	H	CO$_2$Me	Me		**3g**	64 (55)

[a] GLC yields. Isolated yields are shown in parentheses. [b] Np = 1-Naphthyl. [c] 48 h.

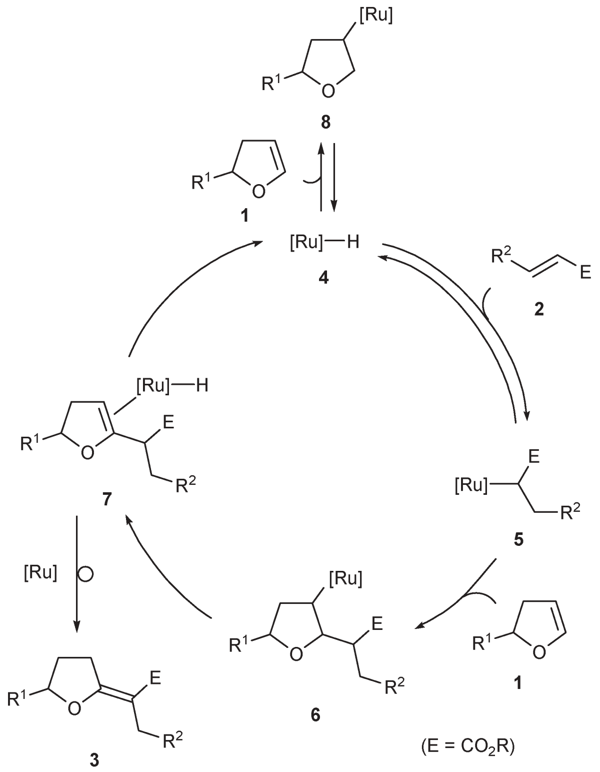
fumarate (**2d**-d_2). The codimer **3g**-d_2 was isolated in 50% yield with 29 and 36% deuterium incorporations as shown in eqn (1). The decrease of the deuterium incorporating ratio in **3g**-d_2 implies that a rapid H/D exchange occurred during the reaction, that is promoted by an *in situ*-generated ruthenium hydride species. We believe that the hydride should be supplied from a cod ligand in Ru(cod)(cot) or an olefinic hydrogen of α,β-unsaturated esters *via* C–H activation.



(1)

A proposed mechanism is shown in Scheme 1. Alkylruthenium complex **5** would be formed by the insertion of α,β-unsaturated ester **2** into the Ru–H bond of the catalytically active ruthenium hydride species **4**. At this stage, an electron-withdrawing alkoxycarbonyl group should be placed at the α-position. Successive insertion of **1** into the Ru–C bond in **5** gives tetrahydrofuranylruthenium species **6**, where an electronic factor seems to be predominant to control the insertion direction. The intermediate **6** is followed by β-hydrogen elimination to afford **7**, and isomerization of the formed dihydrofuran gives 2-alkylidenetetrahydrofuran **3**, along with the regeneration of ruthenium hydride **4**. It is noted that (*E*)-**3h** is more thermally stable than (*Z*)-**3h** by 4.97 kcal mol^{-1}, calculated by a DFT method at the B3LYP/6-31G** level (Fig. 1). The decrease of deuterium incorporation in eqn (1) can be explained by the existence of the rapid equilibria between **4** and **5**, and, **4** and **8**. Under these equilibria, a certain percentage of the deuterium in **2d**-d_2 would be transferred into the dihydrofuran at the early stage of the reaction.

A metallacycle mechanism can be considered as an alternative pathway; in this case, however, linear codimers should be obtained rather than the branched ones such as **3a**–**3d**, because the alkoxycarbonyl group would prefer to occupy the α-position in the metallacycle intermediate. Moreover, the decrease of deuterium incorporation in eqn (1) cannot be explained by this mechanism.



Scheme 1 A possible mechanism.

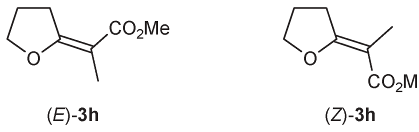


Fig. 1

In summary, we have developed a novel synthetic method for 2-(1-alkoxycarbonyl)alkylidenetetrahydrofurans by a simple codimerization of dihydrofurans with α,β-unsaturated esters. Further mechanistic study and application of the present reaction to organic synthesis are now in progress.‡

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Notes and references

‡ *General procedure*: A mixture of 2,3-dihydrofuran (**1a**, 351 mg, 5.0 mmol), ethyl acrylate (**2a**, 100 mg, 1.0 mmol), Ru(cod)(cot) (9.4 mg, 0.030 mmol) and *N*,*N*-dimethylacetamide (3.0 mL) were placed in a 20 mL Pyrex glass flask equipped with a magnetic stirring bar and a reflux condenser under an argon atmosphere. The reaction mixture was then stirred at 160 °C for 20 h. After removal of the solvent, the crude product was purified by flash column chromatography (ethyl acetate–hexane = 1 : 10) and Kugelrohr distillation (110 °C at 10 Torr) to give the corresponding codimer **3a** (93 mg, 59%) as a colorless oil; IR (neat): 1692, 1646, 1455, 1304 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.14 (t, J = 7.0 Hz, 2H), 4.08 (q, J = 6.8 Hz, 2H), 2.99 (dt, J = 1.5, 7.8 Hz, 2H), 2.03–1.96 (m, 2H), 1.74 (t, J = 1.5, 3H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0 (C), 169.1 (C), 97.5 (C), 71.2 (CH_2), 59.5 (CH_2), 31.0 (CH_2), 24.7 (CH_2), 14.6 (CH_3), 11.4 (CH_3); MS (EI) *m*/*z* 170 (M^+). Anal. Calc. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.33; H, 8.11%.

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