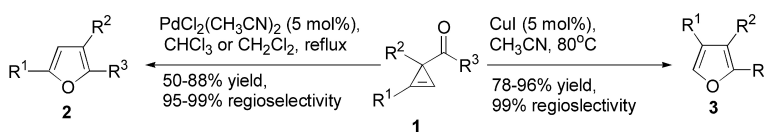


2,3,4- or 2,3,5-Trisubstituted Furans: Catalyst-Controlled Highly Regioselective Ring-Opening Cycloisomerization Reaction of Cyclopropenyl Ketones

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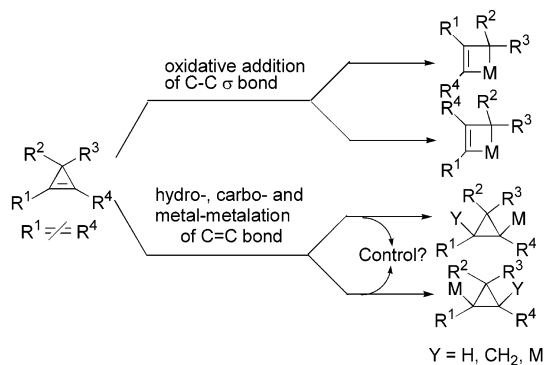
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Cyclopropenes,¹ highly strained but readily accessible carbocyclic molecules, have been shown to possess useful reactivity in organic synthesis.² In the past several years, more and more attention has been paid to the transition metal-catalyzed reaction of cyclopropenes. Two kinds of reaction patterns of cyclopropenes, that is, the direct oxidative addition of the C–C σ bond^{2b,3c} and metalation (hydrometalation,^{3a,b} carbometalation,^{4,5} and bismetalation^{3b}) of the C=C bond, have been disclosed for their interaction with transition metals (Scheme 1). It is obvious that there is an attractive but often troublesome regioselectivity issue when R¹ is different from R⁴.^{5,6}

Scheme 1



After observing some interesting chemistry with methylenecyclopropanes (MCPs),⁷ we showed high interest in the transition metal halide-mediated reaction of cyclopropenes, which also have an active C=C bond in the three-membered ring. Although the chloropalladation of cyclopropenes with a stoichiometric amount of PdCl₂(CH₃CN)₂ leading to an allylpalladium species has been disclosed,⁸ no catalytic reaction has been reported. Herein, we wish to report a highly regioselective ring-opening cycloisomerization of cyclopropenyl ketones **1**, in which the subtle application of CuI and PdCl₂(CH₃CN)₂ addressed the issue of regioselectivity leading to corresponding 2,3,4- or 2,3,5-trisubstituted furans, respectively.

Initially, we tested the halometalation of cyclopropenyl ketone **1a**⁹ in the presence of a number of transition metal halides (MX_n) (Table 1). NiBr₂ and CoCl₂ are less effective with low regioselectivity (entries 2–3, Table 1), while FeCl₃ showed high regioselectivity with a low yield (entry 4, Table 1). RhCl₃·3H₂O, RuCl₃·3H₂O, PdBr₂(PhCN)₂, and PdCl₂ showed higher activity to give **2a** in good yields with high regioselectivities (entries 5–8, Table 1). After numerous screenings, we were pleased to find that the reaction applying 5 mol % PdCl₂(CH₃CN)₂ as the catalyst and CHCl₃ as the solvent (Conditions A) gave **2a** in 71% yield with very high regioselectivity (98:2) (entry 13, Table 1). Both yields and regioselectivities in other solvents such as CH₃CN, AcOEt, and ClCH₂CH₂Cl are lower (entries 10–12, Table 1). After further

Table 1. MX_n-Catalyzed Cycloisomerization of Cyclopropenyl Ketone **1a**^a

entry	catalyst	solvent/ <i>T</i> (°C)	<i>t</i> (h)	2/3 ^b	yield (%) ^c
1	no	acetone/reflux	19		0
2	CoCl ₂	acetone/reflux	24	65:35	7
3	NiBr ₂	acetone/reflux	24	20:80	20
4	FeCl ₃	acetone/reflux	12	99:1	25
5	RuCl ₃ ·3H ₂ O	acetone/reflux	14	98:2	61
6	RhCl ₃ ·3H ₂ O	acetone/reflux	12	98:2	58
7	PdCl ₂	acetone/reflux	11	94:6	60
8	PdBr ₂ (PhCN) ₂	acetone/reflux	17	94:6	53
9	PdI ₂	acetone/reflux	12		trace
10	PdCl ₂ (CH ₃ CN) ₂	CH ₃ CN/80	17	88:12	25
11	PdCl ₂ (CH ₃ CN) ₂	AcOEt/reflux	17	94:6	64
12	PdCl ₂ (CH ₃ CN) ₂	Cl(CH ₂) ₂ Cl/80	11	96:4	66
13	PdCl ₂ (CH ₃ CN) ₂	CHCl ₃ /reflux	18	98:2	71 ^d
14	CuCl ₂	acetone/reflux	12	12:88	75
15	CuI	CH ₃ CN/80	9	<1:99	91 ^d

^a The reaction was carried out using **1a** (0.5 mmol) and catalyst (5 mol %) in solvent (2.0 mL). ^b The ratio was determined by ¹H NMR analysis of the crude reaction mixture. ^c Unless otherwise specified, isolated yields of two isomers. ^d Isolated yield of the major isomer.

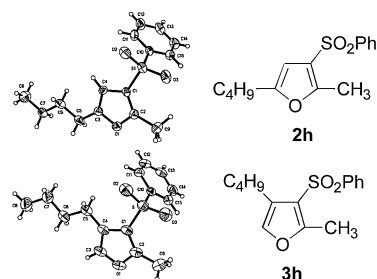
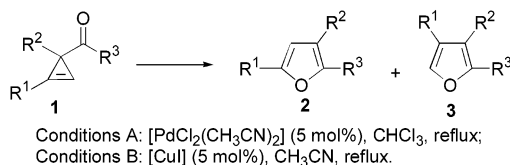


Figure 1.

study, we were excited to find that the reaction of **1a** in CH₃CN at 80 °C under the catalysis of 5 mol % CuI (Conditions B) for 9 h gave **3a** with an excellent regioselectivity (>99:1) in 91% yield (entry 15, Table 1).

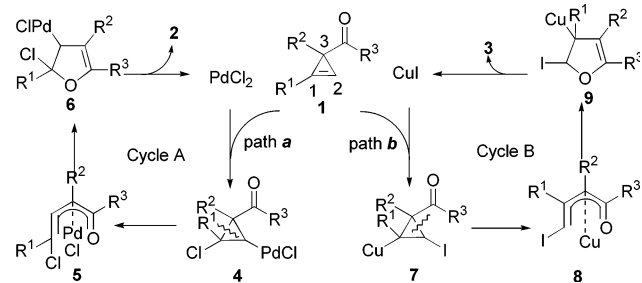
Some typical examples for this regioselective transformation are summarized in Table 2. Several types of substituents such as 1-alkyl, *tert*-butyl, and phenyl groups could be introduced (entries 1–8, Table 2). The introduction of the PhSO₂ group as R² provided us further evidence for the regioselectivity, since we established the structures of **2h**¹⁰ and **3h**¹¹ by X-ray diffraction studies (Figure 1).

A possible rationale for this regioselectivity is depicted in Scheme 2. In the presence of a catalytic amount of PdCl₂(CH₃CN)₂ (cycle A), the regioselective chloropalladation⁸ of the C=C bond of the

Table 2. Regioselective Cycloisomerization of Cyclopropene Ketones **1** under Conditions A and B

entry	cyclopropenyl ketones 1 R ¹ /R ² /R ³	cond./t(h)	yield ^a (2:3) ^b
1	TBSO(CH ₂) ₂ /CO ₂ Et/CH ₃ (1b)	A ^c /3	(2b) 65 (95:5)
2	1b	B/10	(3b) 85 (<1:99)
3	TBSOCH ₂ /CO ₂ Et/CH ₃ (1c)	A/3	(2c) 60 (96:4)
4	1c	B/10	(3c) 83 (<1:99)
5	<i>t</i> -Bu/CO ₂ Et/CH ₃ (1d)	A/13	(2d) 66 (98:2)
6	1d	B/4.5	(3d) 80 (<1:99)
7	Ph/CO ₂ Et/CH ₃ (1e)	A/10	(2e) 73 (99:1)
8	1e	B/2.5	(3e) 89 (1:99)
9	<i>n</i> -C ₅ H ₁₁ /CO ₂ Et/Ph (1f)	A ^c /24	(2f) 50 (98:2) ^d
10	1f	B/10	(3f) 80 (<1:99)
11	<i>n</i> -C ₄ H ₉ /COMe/CH ₃ (1g)	A ^c /3	(2g) 78 (95:5)
12	1g	B/6	(3g) 80 (<1:99)
13	<i>n</i> -C ₄ H ₉ /SO ₂ Ph/CH ₃ (1h)	A ^c /5	(2h) 88 (99:1)
14	1h	B/10	(3h) 96 (<1:99)

^a Isolated yield of the major isomer. ^b The ratio was determined by ¹H NMR analysis of the crude reaction mixture. ^c CH₂Cl₂ was used as the solvent. ^d Unidentified product was also formed.

Scheme 2

cyclopropenyl ketone **1** (path *a*) would afford the palladium intermediate **4**, which would undergo β -decarbopalladation to afford delocalized intermediate **5**. Subsequent intramolecular *endo*-mode insertion of the C=C bond into the oxygen–palladium bond of intermediate **5** would afford a cyclic palladium intermediate **6**, which would undergo β -halide elimination to afford **2** and regenerate palladium(II) species. On the other hand, in the presence of a catalytic amount of CuI, it would proceed according to cycle B. The opposite regioselective iodocupration of the C=C bond of **1** (path *b*) and subsequent β -decarbocupration gave delocalized intermediate **8**. The intramolecular *endo*-mode insertion of the C=C bond into the oxygen–copper bond of intermediate **8** and subsequent β -halide elimination of intermediate **9** afforded **3** and regenerated CuI.

In conclusion, we have developed a regioselective cycloisomerization of cyclopropenyl ketones **1** leading to 2,3,4-trisubstituted furans or 2,3,5-trisubstituted furans by using the catalyst CuI or PdCl₂(CH₃CN)₂, respectively. Further studies into the scope, mechanism, and synthetic applications of this transformation are being carried out in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data of all new compounds (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (11) X-ray data for compound **3h**: C₁₅H₁₈O₃S, Mw = 278.35, triclinic, Space group P-1, Mo K α , final R indices [*I* > 2 σ (*I*)], R1 = 0.0488, wR2 = 0.1119, *a* = 7.9303 (11) Å, *b* = 9.6961 (13) Å, *c* = 11.1246 (11) Å, α = 68.445 (2)°, β = 81.980 (3)°, γ = 66.606 (2)°, *V* = 730.16 (17) Å³, *T* = 293 (2) K, *Z* = 2, reflections collected/unique: 4497/3261 (*R*_{int} = 0.0589), No Observation [*I* > 2 σ (*I*)] 2119, parameters 245. CCDC 211696 contains the supplementary crystallographic data.

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