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

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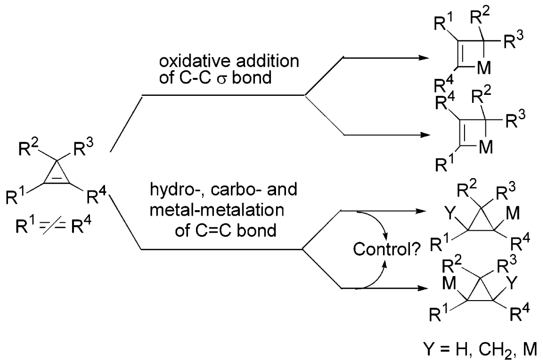
Cyclopropenes,[1] highly strained but readily accessible carbocyclic molecules, have been shown to possess useful reactivity in organic synthesis.[2] In the past several years, more and more attention has been paid to the transition metal-catalyzed reaction of cyclopropenes. Two kinds of reaction patterns of cyclopropenes, that is, the direct oxidative addition of the C−C $\sigma$ 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 $R^1$ is different from $R^4$.[4,5,6]

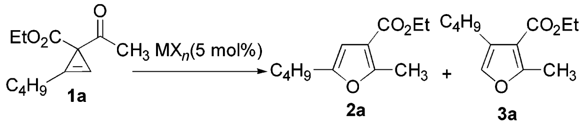
***Scheme 1***



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 $PdCl_2(CH_3CN)_2$ 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 $PdCl_2(CH_3CN)_2$ 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). $NiBr_2$ and $CoCl_2$ are less effective with low regioselectivity (entries 2−3, Table 1), while $FeCl_3$ showed high regioselectivity with a low yield (entry 4, Table 1). $RhCl_3 \cdot 3H_2O$, $RuCl_3 \cdot 3H_2O$, $PdBr_2(PhCN)_2$, and $PdCl_2$ 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 % $PdCl_2(CH_3CN)_2$ as the catalyst and $CHCl_3$ 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 $CH_3CN$, AcOEt, and $ClCH_2CH_2Cl$ are lower (entries 10−12, Table 1). After further study, we were excited to find that the reaction of **1a** in $CH_3CN$ 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).

***Table 1.*** $MX_n$-Catalyzed Cycloisomerization of Cyclopropenyl Ketone **1a**[a]



| entry | catalyst | solvent/*T* (°C) | *t* (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 | $RuCl_3 \cdot 3H_2O$ | acetone/reflux | 14 | 98:2 | 61 |
| 6 | $RhCl_3 \cdot 3H_2O$ | 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 | $PdCl_2(CH_3CN)_2$ | $CH_3CN$/80 | 17 | 88:12 | 25 |
| 11 | $PdCl_2(CH_3CN)_2$ | AcOEt/reflux | 17 | 94:6 | 64 |
| 12 | $PdCl_2(CH_3CN)_2$ | $Cl(CH_2)_2Cl$/80 | 11 | 96:4 | 66 |
| 13 | $PdCl_2(CH_3CN)_2$ | $CHCl_3$/reflux | 18 | 98:2 | 71[d] |
| 14 | $CuCl_2$ | acetone/reflux | 12 | 12:88 | 75 |
| 15 | CuI | $CH_3CN$/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.

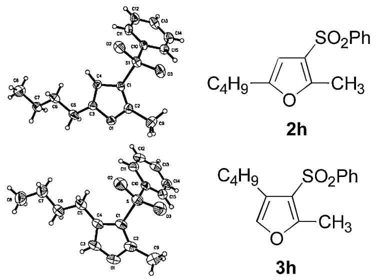


***Figure 1.***

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 $PhSO_2$ group as $R^2$ 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 $PdCl_2(CH_3CN)_2$ (cycle A), the regioselective chloropalladation[8] of the C═C bond of the

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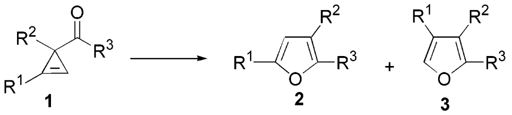
***Table 2.*** Regioselective Cycloisomerization of Cyclopropene Ketones **1** under Conditions A and B

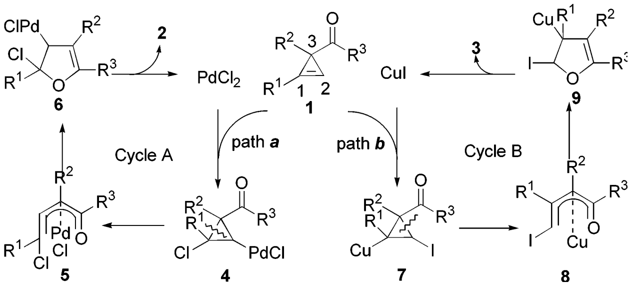


Conditions A: [$PdCl_2(CH_3CN)_2$] (5 mol%), $CHCl_3$, reflux;
Conditions B: [CuI] (5 mol%), $CH_3CN$, reflux.

| entry | cyclopropenyl ketones **1** $R^1/R^2/R^3$ | cond./*t*(h) | yield[a] (**2**:**3**)[b] |
|---|---|---|---|
| 1 | $TBSO(CH_2)_2/CO_2Et/CH_3$ (**1b**) | A[c]/3 | (**2b**) 65 (95:5) |
| 2 | **1b** | B/10 | (**3b**) 85 (<1:99) |
| 3 | $TBSOCH_2/CO_2Et/CH_3$ (**1c**) | A/3 | (**2c**) 60 (96:4) |
| 4 | **1c** | B/10 | (**3c**) 83 (<1:99) |
| 5 | *t*-$Bu/CO_2Et/CH_3$ (**1d**) | A/13 | (**2d**) 66 (98:2) |
| 6 | **1d** | B/4.5 | (**3d**) 80 (<1:99) |
| 7 | $Ph/CO_2Et/CH_3$ (**1e**) | A/10 | (**2e**) 73 (99:1) |
| 8 | **1e** | B/2.5 | (**3e**) 89 (1:99) |
| 9 | *n*-$C_5H_{11}/CO_2Et/Ph$ (**1f**) | A[c]/24 | (**2f**) 50 (98:2)[d] |
| 10 | **1f** | B/10 | (**3f**) 80 (<1:99) |
| 11 | *n*-$C_4H_9/COMe/CH_3$ (**1g**) | A[c]/3 | (**2g**) 78 (95:5) |
| 12 | **1g** | B/6 | (**3g**) 80 (<1:99) |
| 13 | *n*-$C_4H_9/SO_2Ph/CH_3$ (**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] $CH_2Cl_2$ 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 $PdCl_2(CH_3CN)_2$, 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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(10) X-ray data for compound **2h**: $C_{15}H_{18}O_3S$, MW = 278.35, orthorhombic, space group *Pca*2(1), Mo Kα, final R indices [$I > 2\sigma(I)$], R1 = 0.0446, wR2 = 0.0598, $a = 12.0416$ (9) Å, $b = 15.7116$ (11) Å, $c = 15.1600$ (11) Å, α = 90°, $\beta = 90°$, $\gamma = 90°$, $V = 2868.2$ (4) $Å^3$, $T = 293$ (2) K, $Z = 8$, reflections collected/unique: 16 943/6492 ($R_{int} = 0.0555$), no observation [$I > 2\sigma(I)$] 3776, parameters 425. CCDC 211695 contains the supplementary crystallographic data.

(11) X-ray data for compound **3h**: $C_{15}H_{18}O_3S$, Mw = 278.35, triclinic, Space group P-1, Mo Kα, final R indices [$I > 2\sigma(I)$], 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)°, $\beta = 81.\ 980$ (3)°, $\gamma = 66.606$ (2)°, $V = 730.16$ (17) $Å^3$, $T = 293$ (2) K, $Z = 2$, reflections collected/unique: 4497/3261 ($R_{int} = 0.0589$), No Observation [$I > 2\sigma(I)$] 2119, parameters 245. CCDC 211696 contains the supplementary crystallographic data.

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