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Synthesis of α-methyl ketones by a selective, iridium-catalyzed cyclopropanol ring-opening reaction

Daniel T. Ziegler, Andrew M. Steffens, Timothy W. Funk *

Department of Chemistry, Gettysburg College, 300 N Washington St., Gettysburg, PA 17325, USA

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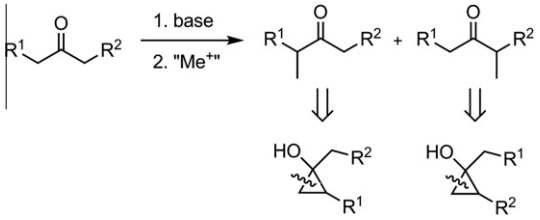
ABSTRACT

A mild method for synthesizing α-methyl ketones from substituted cyclopropanols is reported. This process, catalyzed by $[Cp^*IrCl_2]_2$, cleaves cyclopropanol rings regioselectively and more efficiently than the other conditions examined. While tertiary cyclopropanols afford α-methyl ketones, secondary cyclopropanols and cyclopropyl silyl ethers are less reactive and yield other isomerization products.

Cyclopropanes are versatile synthetic intermediates and a large number of ring-opening processes affording a wide variety of products have been reported. Within the broad field of cyclopropane chemistry lies the reactions of cyclopropanes substituted with electron-donating heteroatoms[1]; the most common substituents are alkoxy and silyloxy presumably because they are easily synthesized from vinyl ethers by Simmons–Smith cyclopropanations.[2] Ring-opening reactions of these substituted cyclopropanes generally occur regioselectively. The development of a titanium-mediated coupling of esters and Grignard reagents to access substituted cyclopropanols in a single step has been followed by explorations of their ring-opening reactions.[1a,3] In particular, we were interested in the ring-opening isomerization of cyclopropanols to α-methyl ketones because they are common structural features in organic molecules. Traditionally α-methyl ketones have been synthesized by C-methylations of enolates, but this method can lead to mixtures of regioisomers when an unsymmetrical ketone is used.[4] To avoid this issue, the α-methyl ketone could be accessed from the appropriate cyclopropanol by a ring-opening isomerization (Scheme 1).

We were interested in developing a simple, mild, regioselective, transition metal-catalyzed synthesis of α-methyl ketones from cyclopropanols. In order to take full advantage of this approach, the cyclopropanol ring-opening must occur selectively at the less substituted carbon–carbon bond. The conditions most commonly used to afford the desired regioisomer are strongly basic (hydroxide in alcohol), which may destroy sensitive functionality in the molecule.[1a,b,5] Two metal-catalyzed reactions have been reported: a Pd/C process done under a hydrogen atmosphere[6] and a platinum-catalyzed ring-opening using Zeise's dimer ($[Pt(C_2H_4)Cl_2]_2$).[7] Both methods have been applied only to the opening of the cyclopropanol ring of substituted bicyclo[4.1.0]heptanes. We chose to use the latter process as a starting point largely due to its mild reaction conditions and procedural simplicity.



Scheme 1. Synthesis of α-methyl ketones from unsymmetrical ketones or cyclopropanols.

The 1,2-disubstituted cyclopropanol **1a** was synthesized as a racemate using a modified Kulinkovich reaction[8] and was treated with Zeise's dimer using the published reaction conditions (Table 1, entry 1).[7] The desired α-methyl ketone product **2a** formed with none of the linear regioisomer **3a** was observed in the crude ^1H NMR spectrum. The linear ketone **3a** would form if cleavage occurred at the more substituted C–C bond (bond *b*). In addition to **2a**, a small amount of alkene **4a** was present.[9,10] Encouraged by these results, we examined other transition metal dimers for reactivity and selectivity in the ring-opening of **1a**. The two ruthenium

* Corresponding author. Tel.: +1 717 337 6348; fax: +1 717 337 6270.
E-mail address: tfunk@gettysburg.edu (T.W. Funk).

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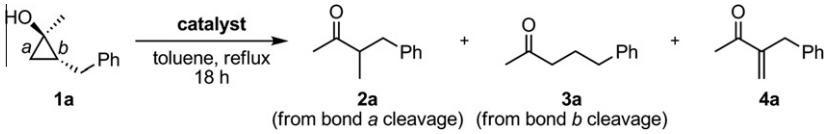
Table 1
Potential catalysts for regioselective cyclopropanol ring-opening



Entry	Catalyst (mol %)	Conversion (%)[a]	Product distribution[a]			
			1a (%)	**2a** (%)	**3a** (%)	**4a** (%)
1[b]	**$[Pt(C_2H_4)Cl_2]_2$ (2.5)**	**>99**	**0**	**97**	**0**	**3**
2	Shvo's catalyst (4)	>99	0	73	27	0
3	$[(p\text{-Cymene})RuCl_2]_2$ (2.5)	>99	0	79	21	0
4	$[Cp^*RhCl_2]_2$ (2.5)	>99	0	83	13	4
5	**$[Cp^*IrCl_2]_2$ (2.5)**	**>99**	**0**	**97**	**3**	**0**
6	$[Cp^*IrCl_2]_2$ (2.5) + PPh_3 (5)	>99	0	91	9	0
7	$[Cp^*IrCl_2]_2$ (2.5) + pyridine (5)	74	26	56	18	0
8[c]	**$[Cp^*IrCl_2]_2$ (2.5)**	**>99**	**0**	**96**	**4**	**0**
9	HCl (10)	>99	0	58	42	0
10	—	74	26	62	12	0
11[c]	—	15	85	7	8	0

[a] Determined by ^1H NMR spectroscopy of the crude reaction mixture; no other compounds were observed.
[b] Reaction run in Et_2O at rt.
[c] Reaction run at 80 °C. Shvo's catalyst = $\{[Ph_4(\eta^5\text{-}C_4CO)]_2H\}Ru_2(CO)_4(\mu\text{-}H)$; Cp* = pentamethylcyclopentadienyl.

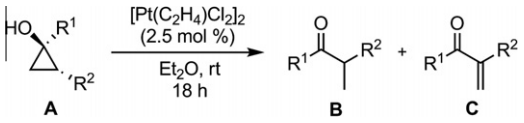
compounds examined isomerized **1a** but with lower selectivity for the desired regioisomer (Table 1, entries 2 and 3). Selectivity for **2a** increased when a rhodium dimer was used (Table 1, entry 4) and was excellent in the presence of $[Cp^*IrCl_2]_2$ (Table 1, entry 5). The addition of ligands to $[Cp^*IrCl_2]_2$ decreased the formation of **2a** (Table 1, entries 6 and 7). Decreasing the temperature to 80 °C had an insignificant effect on the selectivity of the ring-opening reaction (Table 1, entry 8). With the exception of Shvo's catalyst, all the transition metal dimers explored contained chloride ligands. We treated cyclopropanol **1a** with HCl to determine if residual HCl formed in solution was catalyzing the reaction (Table 1, entry 9), and the ring opening was largely unselective. At elevated temperature there was a background reaction that generated **2a** preferentially, but at 80 °C that process was slowed significantly (Table 1, entries 10 and 11).

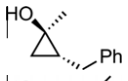
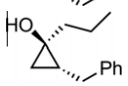
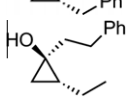
Based on the results presented in Table 1, the ring-opening isomerization was most selective when Zeise's dimer or $[Cp^*IrCl_2]_2$ was used. We initially proceeded forward with Zeise's dimer but discovered that the reaction was not as efficient as with other cyclopropanols (Table 2, entries 2 and 3). While none of the linear regioisomer was observed in either reaction, unreacted cyclopropanol **A** was present in addition to the alkene product from oxidative ring-opening (**C**). Presumably **C** formed by β-hydrogen elimination from a platinum(II)-alkyl species, which generated an unreactive platinum(0) species upon reductive elimination of HCl.[11] The formation of a catalytically inactive platinum compound explains the incomplete conversions.

Fortunately when other cyclopropanols were treated with $[Cp^*IrCl_2]_2$, the ring-openings occurred cleanly and selectively to form the desired α-methyl ketones (Table 3). Only the cyclopropanol ring of a cyclopropyl-substituted compound was opened (Table 3, entry 2), illustrating the selectivity and mildness of the reaction conditions. A variety of other substituents on the cyclopropanol ring were tolerated, including protected alcohols (Table 3, entries 6–8) and alkyl bromides (Table 3, entries 9 and 10). Toluene was ultimately selected as the reaction solvent, but it also occurred cleanly in ethanol and acetonitrile at 80 °C with 2.5 mol % of the iridium dimer. When the catalyst loading was decreased to 0.5 mol %, the reaction did not go to completion in toluene (94% conversion for substrate **1b**), and unidentified impurities and large amounts of unreacted cyclopropanol were present in ethanol and acetonitrile. The successful ring-opening isomerization of tertiary cyclopropanols to α-methyl ketones encouraged us to explore secondary cyclopropanols (Table 3, entry 11). While the desired α-methyl aldehyde **2k** was the major product, a large amount of unreacted cyclopropanol **1k** remained in addition to small amounts of the linear regioisomer **3k** and the alkene **4k**. Silyl cyclopropyl ether **1l** afforded no 2-methylcyclohexanone; instead, an undetermined mixture of unreacted **1l** and alkene **2l** was formed (Table 3, entry 12). Alkene **2l** was generated in high yield when **1l** was treated with Zeise's dimer.[7,12]

The proposed mechanism for the reaction is illustrated in Scheme 2. The cyclopropanol coordinates to a monomeric iridium species and loses H^+ to form **D**. Regioselective β-carbon elimination cleaves the less sterically hindered cyclopropanol C–C bond and affords an iridium-alkyl species (**E**) that is protonated to yield the α-methyl ketone and regenerate the catalyst. We believe that the reaction does not occur through a radical mechanism because an

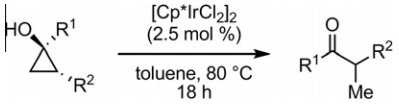
Table 2
Product distribution of cyclopropanol ring-openings using $[Pt(C_2H_4)Cl_2]_2$

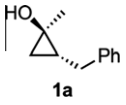
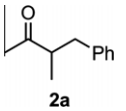
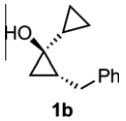
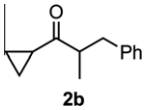
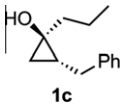
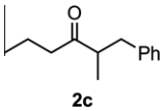
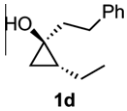
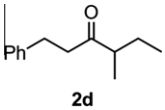
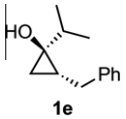
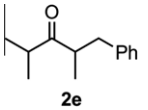
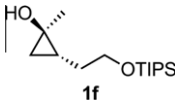
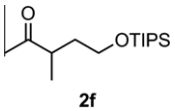
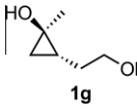
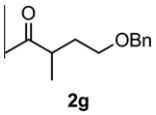
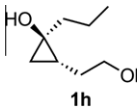
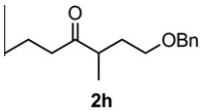
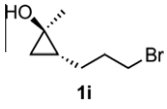
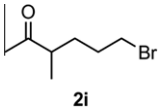
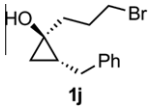
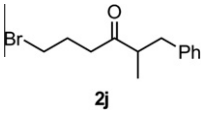
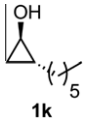
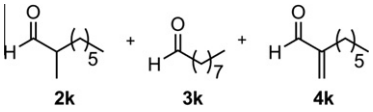
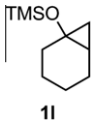
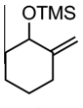


Entry	Cyclopropanol	Conversion (%)[a]	Product distribution[a]		
			Unreacted **A** (%)	**B** (%)	**C** (%)
1		>99	0	(94)	3
2		95	5	90	5
3		79	21	76	3

[a] Determined by ^1H NMR spectroscopy of the crude reaction mixture; no other compounds were observed. Values in parentheses are isolated yields.

Table 3
Substrate scope of iridium-catalyzed cyclopropanol ring-opening

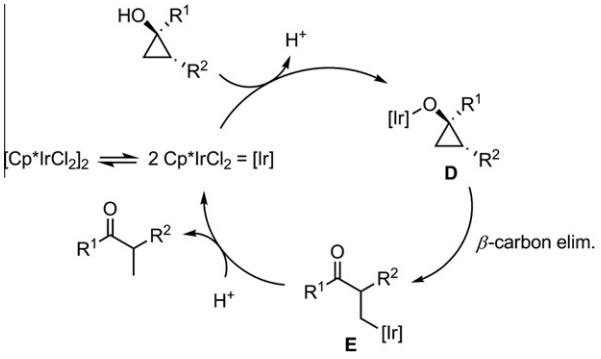


Entry	Substrate	Product(s)	Isolated yield (%)[a]
1	 **1a**	 **2a**	84
2	 **1b**	 **2b**	93
3	 **1c**	 **2c**	86
4	 **1d**	 **2d**	90
5	 **1e**	 **2e**	86
6	 **1f**	 **2f**	72
7	 **1g**	 **2g**	71
8	 **1h**	 **2h**	78
9	 **1i**	 **2i**	71
10	 **1j**	 **2j**	92
11[b]	 **1k**	 **2k** **3k** **4k**	**1k**: (77) **2k**: (17) **3k**: (4) **4k**: (2)
12[c]	 **1l**	 **2l**	nd

Reaction conditions: cyclopropanol (1 equiv) and $[Cp^*IrCl_2]_2$ (0.025 equiv) in toluene (0.25 M in cyclopropanol) heated to 80 °C for 18 h.
[a] Values in parentheses are product distributions determined by ^1H NMR spectroscopy.
[b] From the ^1H NMR spectrum of the crude reaction mixture.
[c] nd = not determined.

unpaired electron on the alcohol carbon of substrate **1b** would fragment the appended cyclopropane ring.[13] There is no evidence of cyclopropane ring-opening in the crude ^1H NMR spectrum of the reaction of $[Cp^*IrCl_2]_2$ with **1b**. While we propose the above mechanism because of its similarity to alcohol oxidations with $[Cp^*IrCl_2]_2$,[14] we cannot rule out a mechanism involving oxidative addition of a cyclopropyl C–C bond to afford a metallacyclobutane intermediate.[15]

In summary, we have developed a selective, simple, mild synthesis of α-methyl ketones from cyclopropanols using $[Cp^*IrCl_2]_2$. This



Scheme 2. Proposed mechanism involving β-carbon elimination.

method could be used as an alternative to unselective enolate methylations of nearly symmetrical ketones and to the strongly basic conditions commonly used to transform 1,2-disubstituted cyclopropanols into α-methyl ketones. The method using Zeise's dimer proved to be less efficient than the Ir-catalyzed process due to incomplete conversions that may be attributed to the reductive generation of a catalytically inactive platinum species. The Ir-catalyzed reactions afforded the desired products with high selectivity and in high conversion under neither oxidizing nor reducing conditions.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures and spectral data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.067.

References and notes

1. For reviews see: (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597; (b) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605; (c) Rinderhagen, H.; Waske, P. A.; Mattay, J. *Tetrahedron* **2006**, *62*, 6589; (d) Murai, S.; Ryu, I.; Sonoda, N. *J. Organomet. Chem.* **1983**, *250*, 121; (e) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733; (f) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321; (g) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165; (h) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151; For other reports see: (i) Epstein, O. L.; Lee, S.; Cha, J. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 4988; (j) Lysenko, I. L.; Oh, H.-S.; Cha, J. K. *J. Org. Chem.* **2007**, *72*, 7903; (k) Lee, H. G.; Lysenko, I. L.; Cha, J. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3326.
2. (a) Charette, A. B.; Beauchemin, A. *Org. React.* **2004**, 1; (b) Conia, J. M. *Pure Appl. Chem.* **1975**, *43*, 317; (c) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53.
3. For recent examples of cyclopropanol ring-opening reactions, see: (a) Churykau, D. H.; Kulinkovich, O. G. *Synlett* **2006**, 3427; (b) Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 2717; (c) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708; (d) Trost, B. M.; Xie, J.; Maulide, N. *J. Am. Chem. Soc.* **2008**, *130*, 17258; (e) Nomura, K.; Matsubara, S. *Chem. Eur. J.* **2010**, *16*, 703.
4. (a) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965; (b) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361; (c) Hatakeyama, T.; Ito, S.; Yamane, H.; Nakamura, M.; Nakamura, E. *Tetrahedron* **2007**, *63*, 8440; For more details see Ref. 1 in (d) Saito, S.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 611.
5. Silyl cyclopropyl ethers also afford α-methyl ketones under basic hydrolysis conditions; see Ref. 2b.
6. (a) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3381; (b) Shan, M.; O'Doherty, G. A. *Synthesis* **2008**, 3171.
7. (a) Hoberg, J. O.; Jennings, P. W. *Organometallics* **1996**, *15*, 3902; For an application in total synthesis, see: (b) Epstein, O. L.; Cha, J. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 121.
8. (a) Kim, S.-H.; Sung, M. J.; Cha, J. K. *Org. Synth.* **2003**, *80*, 111; (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.
9. The peaks in the crude ^{1}H NMR spectrum matched those published for alkene **4a**: Lu, S.-M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8920.
10. Palladium-catalyzed oxidative ring-openings of cyclopropanols are known: (a) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147; (b) Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629.
11. This would be a platinum analogue of the known palladium-catalyzed oxidative ring-opening of cyclopropanols. See Ref. 10.
12. (a) Ikura, K.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 1520; (b) Ikura, K.; Ryu, I.; Ogawa, A.; Sonoda, N.; Harada, S.; Kasai, N. *Organometallics* **1991**, *10*, 528.
13. (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317; (b) Mąkosza, M.; Kwast, A. *Eur. J. Org. Chem.* **2004**, 2125; (c) Newcomb, M.; Glenn, A. G.; Williams, W. G. *J. Org. Chem.* **1989**, *54*, 2675; (d) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687.
14. (a) Fujita, K.-I.; Yamaguchi, R. *Synlett* **2005**, 560; (b) Fujita, K.-I.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289; (c) Jiang, B.; Feng, Y.; Ison, E. A. *J. Am. Chem. Soc.* **2008**, *130*, 14462.
15. For a proposed Ir(V) metallacyclobutane intermediate, see: (a) Anstey, M. R.; Yung, C. M.; Du, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 776; For Ir(III) metallacyclobutanes, see: (b) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241.