Ring Expansion

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Synthesis of Cyclobutenes by Highly Selective Transition-Metal-Catalyzed Ring Expansion of Cyclopropanes**

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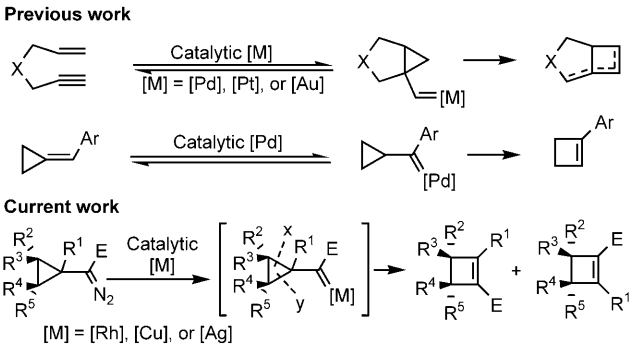
The four-membered ring is an important structural motif, present in many bioactive natural products[1] and key intermediates in the synthesis of structurally complex targets by facile ring-opening reactions.[2] Several selective methods have been developed for the synthesis of cyclobutanes and cyclobutenes.[3] However, highly substituted four-membered-ring natural products, such as sceptrin, welwitindolinone A, and their diverse derivatives still represent a demanding synthetic challenge, and stimulate the development of new selective methods.[4] We wish to explore the use of cyclopropanes, for which stereoselective preparations have been well documented,[5] as precursors for the synthesis of complex four-membered rings.

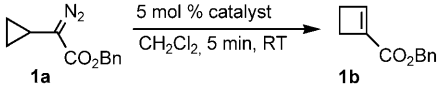
Cyclopropyl carbenes, generated from thermal decomposition of diazo compounds, can undergo a rearrangement to give cyclobutenes but the thermal process requires harsh conditions, and affords low yields and poor selectivities.[6] The profound effect of transition-metal catalysts, such as complexes of rhodium and copper, on the reactivity of metal carbenes has been widely recognized in cyclopropanations, C–H insertions, and dipolar cycloadditions.[7] We envision that transition-metal catalysts may offer unusual selectivity for the ring expansion of cyclopropyl metal carbenes to cyclobutenes. Cyclopropyl metal carbenes have been proposed as intermediates in the formation of various isomeric bicyclic cyclobutenes by cycloisomerization of tethered enynes, by the groups of Trost, Echavarren, and Fürstner with palladium, platinum, or gold catalysts (Scheme 1).[8] Alternatively, cyclopropyl metal carbenes may derive from methylenecyclopropanes (MCPs). Monosubstituted cyclobutenes have been prepared from MCP by Shi and co-workers, using palladium(II) catalysts (Scheme 1).[9] A mechanism involving no cyclopropyl metal carbenes was proposed by Fürstner and Aissa for the conversion of MCPs into monosubstituted cyclobutenes, catalyzed by platinum(II).[10] Despite these elegant studies, selective synthesis of highly desirable polysubstituted cyclobutenes[1–3] remains an elusive target, as many issues have arisen regarding reactivity and selectivity. Herein, we report a synthesis of poly-substituted cyclobutenes by transition-metal-catalyzed highly selective ring expansion of readily available cyclopropanes (Scheme 1). The unique chemo-, regio-, and stereoselectivity for the ring expansion of novel cyclopropyl dirhodium(II), copper(I), and silver(I) carbenes are described.



Scheme 1. Ring expansion of cyclopropyl metal carbenes to cyclobutenes by the migration of bond x or y.

We first screened a variety of transition-metal catalysts for the ring expansion of simple monosubstituted cyclopropane **1a**, and observed complete conversion of diazo compound **1a** into cyclobutenoate **1b** in less than five minutes at ambient temperature with a range of catalysts (Table 1, entries 1–3).[11] Notably, some of the metal catalysts known to promote the formation of the proposed cyclopropyl metal carbene intermediates from enynes or MCPs were inactive in this reaction. Electrophilic metal carbenes were presumably generated from diazo compound **1a** following dissociation of dinitrogen in the presence of dirhodium(II), copper(I), or silver(I) catalysts.[7] Ring expansion of cyclopropyl metal carbenes by a

Table 1: Screening of metal catalysts.[a]



1a **1b**

Entry	Catalyst	Yield
1	$[Rh_2(OAc)_4]$	88%[b]
2	$[Cu(CH_3CN)_4]PF_6$	80%[b]
3	AgOTf	90%[b] (87%[c])
4[d]	$[Cu(acac)_2]$	91%[b]

[a] No product was detected by thin-layer chromatograpy after 5 h for the following catalysts: $Pd(OAc)_2$, $[Ni(cod)_2]$, $[AuClPPh_3]$, and $[RuCl_2(PPh_3)_3]$. [b] Yield determined by ^1H NMR spectroscopy in $CDCl_3$, using CH_2Br_2 as the internal standard. [c] Yield of isolated product. [d] 5 h, room temperature. cod = cycoocta-1,5-diene.

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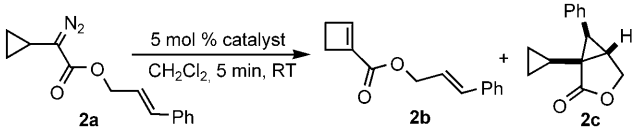
1,2-migration of one of the cyclopropane C–C σ bonds then led to cyclobutenoate **1b**.

We then set out to investigate the reactivity and selectivity of cyclopropyl dirhodium(II), copper(I), and silver(I) carbenes, which are not easily accessible from other methods. Metal carbenes are well known to cyclopropanate olefins.[5,7] Indeed, a mixture of ring-expansion product **2b** and intramolecular cyclopropanation product **2c** was detected after diazo compound **2a** was treated with a $[Rh_2(OAc)_4]$ catalyst (Table 2, entry 1). Surprisingly, both $[Cu(CH_3CN)_4]PF_6$ and

Table 2: Chemoselectivity of metal catalysts.



Entry	Catalyst	**2b**/**2c**[a]	Yield
1	$[Rh_2(OAc)_4]$	3:1	91%[a]
2	$[Cu(CH_3CN)_4]PF_6$	1:0	89%[b]
3	AgOTf	1:0	87%[b]

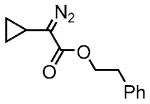
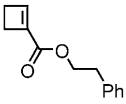
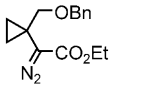
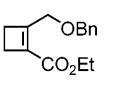
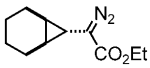
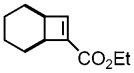
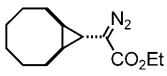
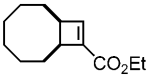
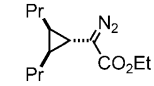
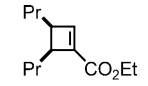
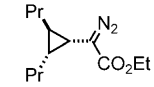
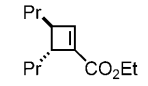
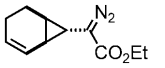
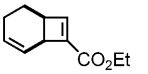
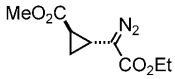
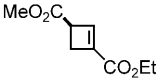
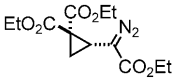
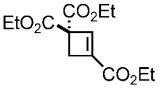
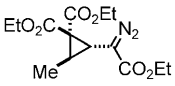
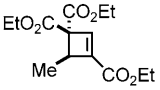
[a] The isomeric ratio was determined by ^{1}H NMR spectroscopy. [b] Yield of isolated product.

AgOTf catalysts exhibited excellent chemoselectivity for the selective formation of cyclobutenoate **2b** (Table 2, entries 2 and 3) even though the copper(I)- and silver(I)-catalyzed cyclopropanation of alkenes is well-documented.[12]

The scope of the silver(I)-catalyzed ring expansion was explored for various substituted 2-cyclopropyl-2-diazoacetates (Table 3), which are generally chromatographically stable and prepared in three steps by a sequence of alkene-cyclopropanation, tosylhydrazone formation, and base-mediated α elimination. Ring expansion occurred smoothly for substrate **3a** despite the presence of two relatively reactive benzylic C–H bonds towards 1,5-insertion. The 1,2-disubstituted cyclobutene **4b** and bicyclic cyclobutenes **5b** and **6b** were synthesized efficiently under the standard conditions (Table 3). Ring expansion took place stereospecifically using the AgOTf catalyst, as demonstrated by the conversion of *cis*-cyclopropane **7a** into *cis*-cyclobutene **7b**, and *trans*-cyclopropane **8a** into *trans*-cyclobutene **8b**, respectively. These results indicate that the migrating carbon atom retains its configuration during the AgOTf-catalyzed ring expansion.

When substrate **9a** was treated with AgOTf, a regioisomeric ratio of 10:1 favoring cyclobutene **9b** was obtained by migration of the carbon atom next to the double bond, which may stabilize the partial positive charge developed on the migrating allylic carbon atom during ring expansion. From ester-substituted cyclopropane **10a**, a mixture of regioisomeric cyclobutenes was obtained in a 6:1 ratio at ambient temperature, and a 10:1 ratio at −20 °C, favoring the less sterically congested 1,3-disubstituted cyclobutene **10b**. The formation of **10b** is also electronically favored, because the migrating carbon atom with a partial positive charge is further removed from the electron-withdrawing ester group in **10a**. The mutual reinforcement of steric and electronic effects may contribute to the exclusive formation of 1,3,3-trisubstituted

Table 3: Scope of the AgOTf-catalyzed ring expansion.[a]

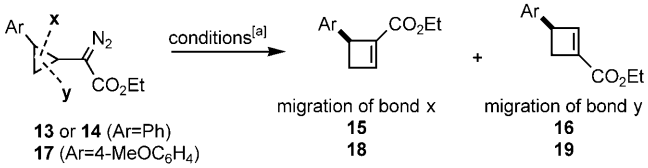
Cyclopropane	Cyclobutene	Yield	Ratio[b]
3a 	**3b** 	91%	–
4a 	**4b** 	77%	–
5a 	**5b** 	72%	–
6a 	**6b** 	90%	–
7a 	**7b** 	71%	single isomer
8a 	**8b** 	92%	single isomer
9a 	**9b** 	73%	10:1
10a 	**10b** 	70%	10:1[c]
11a 	**11b** 	87%	single isomer
12a 	**12b** 	77%	single isomer

[a] Conditions: CH_2Cl_2, room temperature, 5 min, 5 mol% AgOTf, unless noted otherwise. Yields given are yields of isolated product. [b] The isomeric ratio was determined by ^{1}H NMR spectroscopy. [c] −20 °C, 30 min.

cyclobutene **11b** and 1,3,3,4-tetrasubstituted cyclobutene **12b**, from **11a** and **12a**, respectively. Notably, this reaction, which involves metal carbene intermediates, is compatible with a variety of functional groups, such as relatively reactive benzylic C–H bonds, aromatic rings, ethers, olefins, and esters. The resulting cyclobutenoates can be further functionalized by hydrogenation or conjugated addition, to afford saturated cyclobutanes.[13]

When cyclopropane **13** or **14** (Ar = Ph) was treated with AgOTf, a mixture of cyclobutenes **15** and **16** was obtained with low regioselectivity (Table 4, entries 2 and 10). After some tailoring of reaction conditions, both cyclobutenes were prepared with good selectivity, by judicious selection of cyclopropanes and metal catalysts (Table 4, entries 4 and 9). The formation of the less-congested 1,3-disubstituted cyclobutene **16** is favored sterically, but the formation of cyclobutene **15** is favored electronically, as the phenyl group can stabilize the partial positive charge on the migrating benzylic carbon atom, induced by metal catalysts during ring expansion. From either *trans*-**13** or *cis*-**14**, the ratio of products **15**/**16** is dependent on the metal catalyst, decreasing in the order copper(I), silver(I), dirhodium(II). These results may reflect

Table 4: Catalyst-dependent regioselectivity.



Cyclopropane	Entry	Catalyst	x/y[b]	Yield
	1	$[Cu(CH_3CN)_4]PF_6$	5:1	–
	2	AgOTf	1:2	–
Ph, N_2, CO_2Et	3	$[Rh_2(OAc)_4]$	1:7	–
13	4[c,d]	$[Rh_2(octanoate)_4]$	1:9	89%[e]
	5	$[Rh_2(O_2CCPh_3)_4]$	1:4	–
	6	$[Rh_2(O_2CCF_3)_4]$	1:5	–
	7	$[Rh_2(caprolactam)_4]$	1:7	–
	8	heat[f]	2:1	48%[g]
	9[d]	$[Cu(CH_3CN)_4]PF_6$	17:1	93%[e]
Ph, N_2, CO_2Et	10	AgOTf	3:1	–
	11	$[Rh_2(OAc)_4]$	1:4	–
14	12	heat[f]	1:3	35%[g]
	13	$Ag(O_2CCF_3)$	13:1	–
Ar, N_2, CO_2Et	14	$[Cu(CH_3CN)_4]PF_6$	100% **18**	90%[g]
	15	AgOTf	100% **18**	90%[g]
17	16	$[Rh_2(OAc)_4]$	1:2	–

[a] CH_2Cl_2, room temperature, 5 min, 10 mol% catalyst, isomeric ratio was determined by ^{1}H NMR spectroscopy, unless noted otherwise. [b] Isomeric ratio of products resulting from the migration of bond x or y. [c] −20°C, 30 min. [d] 5 mol% catalyst. [e] Yield of isolated product. [f] 70°C for 24 h in toluene. [g] Yield determined by ^{1}H NMR spectroscopy in $CDCl_3$, using CH_2Br_2 as the internal standard.

the net results of the opposing electronic and steric effects in different cyclopropyl metal carbenes (for example, electronic effects dominate in the case of copper(I) carbene and steric effects dominate in the case of dirhodium(II) carbene). In addition, steric repulsion between the two *cis* substituents in **14** may significantly weaken the C–C bond x (see Table 4) so that a higher proportion of product **15** was obtained from *cis*-**14** than from *trans*-**13**, for each catalyst (for example, Table 4, entries 1 versus 9, 2 versus 10, or 3 versus 11). In sharp contrast to the metal-catalyzed process, the thermally driven reaction proceeded with low regioselectivity and a significant amount of by-products (Table 4, entries 8 and 12). We also discovered that regioselectivity for the ring expansion was not only metal-dependent but also ligand-dependent (Table 4, entries 3–7, 10, and 13).

To further understand this unprecedented catalyst-dependent regioselectivity for the ring expansion of cyclopropanes, we prepared compound **17** (Ar = 4-$MeOC_6H_4$), incorporating an electron-rich *para*-methoxyphenyl substituent. If our hypothesis is correct, the ratio of products **18**/**19** (resulting from the ring expansion of **17**) should be greater than the ratio of compounds **15**/**16**, for any given catalyst. Indeed, cyclobutene **18** was synthesized as a single regioisomer when diazo compound **17** was treated with copper(I) or silver(I) catalysts (Table 4, entries 14 and 15). The dirhodium(II) catalyst provides a 1:2 ratio for compounds **18**/**19** (Table 4, entry 16), which is more in favor of the electronically favored product than the 1:7 ratio for compounds **15**/**16** (Table 4, entry 3).

In summary, we have developed a highly chemoselective, regioselective, and stereospecific synthesis of polysubstituted cyclobutenoates and demonstrated the crucial effect of transition-metal catalysts on the reactivity and selectivity of metal carbenes. The intriguing catalyst-dependent divergence in the chemo- and regioselectivity of metal carbenes may create myriad opportunities for mechanistic investigations, design of new reactions, and target-oriented synthesis. The stereospecificity of this metal-catalyzed ring expansion paves the way for asymmetric synthesis of cyclobutenes from readily available, optically pure cyclopropanes. The electronic and steric effects for the regioselective cleavage of cyclopropane C–C σ bonds illustrated here may find applications in many other metal-catalyzed reactions involving cyclopropanes as building blocks.

Experimental Section

General procedure: Silver triflate (5 mol%) was added to a solution of the diazo compound (0.3–0.5 mmol) in CH_2Cl_2 (3–5 mL, 0.1M) under argon. The reaction mixture was stirred at room temperature for 5 min. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as the eluent.

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