Organic LETTERS

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Catalytic, Formal Homo-Nazarov-Type Cyclizations of Alkylidene Cyclopropane-1,1-Ketoesters: Access to Functionalized Arenes and Heteroaromatics

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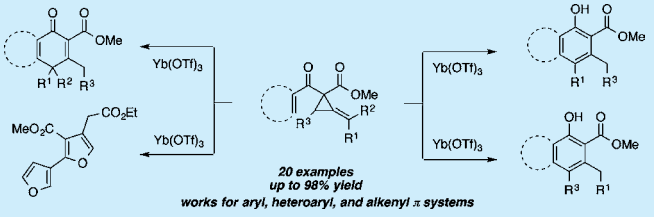
Supporting Information

ABSTRACT: A catalytic, formal homo-Nazarov-type cyclization of alkylidene cyclopropanes (ACPs) to give functionalized arenes and heteroaromatics is reported. In the presence of a Lewis acid catalyst, the ACP 1,1-ketoesters undergo distal bond cleavage to afford an allyl cation intermediate. Adjacent π-attack on the allyl cation then provides a six-membered ring that undergoes rapid aromatization. In these cases, benzenoid products are formed in up to 98% yield. Strategic choice of the substitution about the ACP allows for the generation of other useful isomeric products in good yields.



Alkylidene cyclopropanes (ACPs) serve as versatile building blocks in organic synthesis due to their interesting reactivity.[1] These substrates can readily participate in alkene addition reactions, including H-Nuc additions, hydrometalations, dimetalations, and cycloadditions.[2] Furthermore, due to their inherent ring strain,[3] they undergo a variety of ring-opening reactions in the presence of nucleophiles, transition metal catalysts, and acids.[1] The most intriguing ring-opening pathways are acid-promoted and are categorized into two general patterns: heterolytic cleavage of the C(1)/C(3) distal bond and heterolytic breakage of the C(2)/C(3) proximal bond (Figure 1A). Due to this distinct reactivity, within the past decade, ACPs have been the subject of several focused and comprehensive reviews.[1,2]

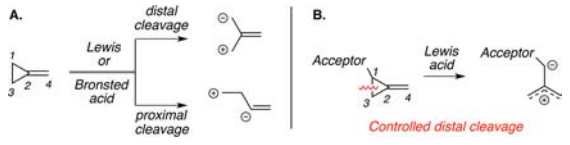


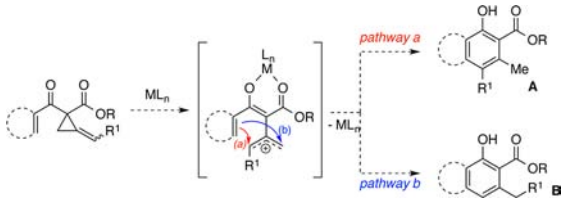
Figure 1. Heterolytic reactivity of alkylidene cyclopropanes (ACPs).

Regiocontrol of ring opening poses a unique opportunity for ACP utility. By altering the substitution pattern about the cyclopropane and by choosing appropriate metal reagents or catalysts, ring-opening selectivity can be achieved. For example, distal cleavage (C(1)/C(3) cleavage) is preferentially observed when ACPs are substituted with acceptors on C(1) of the cyclopropyl ring (Figure 1B).

Despite the growing interest in the reactivity of 1-acceptor-substituted ACPs, examples of their intramolecular ring-opening cyclization reactions have only recently begun to surface. Surprisingly, only a handful of examples of this reaction class have been reported, starting with a seminal contribution by Ma in 2003.[4] Lautens et al. explored Lewis acid catalyzed cycloisomerizations to form cyclic diazadienes.[5] Wang et al. later demonstrated the first intramolecular Friedel–Crafts-type alkylation initiated by distal cleavage of alkylidene cyclopropane-1,1-diesters to afford indenes or dihydronaphthalene derivatives.[6] Oshima similarly demonstrated the efficient synthesis of indene from the tetrasubstituted benzylidenecyclopropane using Wang's protocol.[7]

Over the past several years, we have exploited intramolecular ring-opening cyclizations of strained carbocycles to generate functionalized (hetero)arenes.[8] For example, we published examples of catalytic, formal homo-Nazarov cyclizations of alkenyl[8a] and heteroaryl[8b] cyclopropyl ketones to form functionalized six-membered rings. Inspired by these successes, we sought to explore the compatibility of ACP-1,1-dicarbonyls within our mechanistic regime. Here, we disclose the catalytic, formal homo-Nazarov-type intramolecular ring-opening cyclizations of ACP-1,1-ketoesters (Scheme 1). Mechanistically, the

Scheme 1. Formal Homo-Nazarov-Type Cyclizations of ACPs



reaction involves Lewis acid catayzed heterolytic distal cleavage of the ACP to afford a 1,3-dipole containing an allyl cation. Intramolecular π-attack can occur at either end of the delocalized allyl cation (pathways *a* and *b*) to afford a six-membered ring. Proton loss and alkene isomerization provide

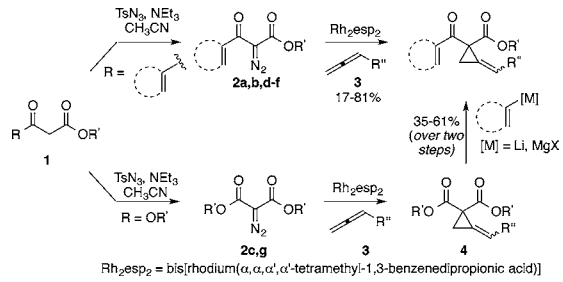
Received: June 10, 2014
Published: July 8, 2014

   dx.doi.org/10.1021/ol501676q | Org. Lett. 2014, 16, 3788–3791

two isomeric *o*-phenolic ester derivatives **A** and **B**, whose ratios are dependent upon the nature of R^1. In most cases, product **A**, arising from the thermodynamically preferred pathway *a*, is expected to be the major product formed.

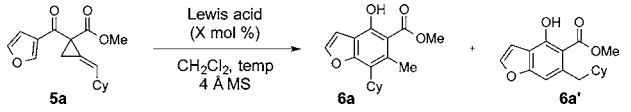
To evaluate our hypothesis, alkylidene cyclopropanes were prepared[9] in one of two ways using the Rh(II)-catalyzed cyclopropanation of allenes with *α*-diazo dicarbonyl compounds as a benchmark (Scheme 2).[10]

Scheme 2. Preparation of ACPs



Due to the commercial availability of cyclohexyl allene **3a** and the large amount of the corresponding *α*-diazo compound on hand, 3-furyl ACP **5a** was chosen as the model system for reaction optimization (Table 1). Various metal triflates were

Table 1. Reaction Optimization



entry[a]	Lewis acid	loading (mol %)	temp (°C)	time (h)	% yield[b]	6a:6a'[c]
1	$In(OTf)_3$	15	rt	8	66	98:2
2	$Sc(OTf)_3$	15	rt	8	68	98:2
3	$Al(OTf)_3$	15	rt	20	74	98:2
4	$Ga(OTf)_3$	15	rt	9	70	99:1
5	$Cu(OTf)_2$	15	rt	48	20	99:1
6	$Zn(OTf)_2$	15	rt	48	–[d]	99:1
7	$Yb(OTf)_3$	15	rt	19	57	98:2
8	**$Yb(OTf)_3$**	**15**	**40**	**12**	**91**	**95:5**
9	$In(OTf)_3$	15	40	4	77	99:1
10	$Sc(OTf)_3$	15	40	4	74	99:1
11	$Al(OTf)_3$	15	40	8	80	99:1
12	$Ga(OTf)_3$	15	40	4	77	99:1
13	$Yb(OTf)_3$	20	40	10	74	97:3
14	$Yb(OTf)_3$	10	40	14	81	97:3

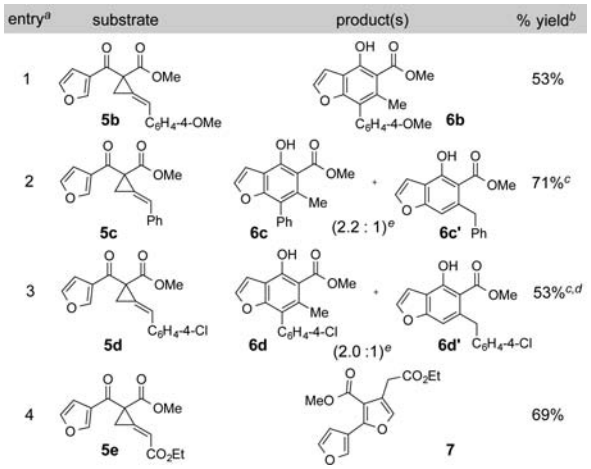
[a]Reactions run with Lewis acid, cyclopropane **5a**, and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) at the indicated temperature. [b]Combined yield of **6a** and **6a′** after column chromatography. [c]Product ratios determined by ^1H NMR of isolated mixture. [d]~15% conversion observed as determined by crude ^1H NMR.

examined at 15 mol % in CH_2Cl_2 (Table 1). For ACP **5a**, the reactions proved to be regioselective for the favored benzofuran **6a** (>88:12 in all cases). For $In(OTf)_3$, $Sc(OTf)_3$, $Al(OTf)_3$, and $Ga(OTf)_3$, each reaction went to completion and afforded **6a** in 66–74% yield (entries 1–4). In contrast, $Cu(OTf)_2$ and $Zn(OTf)_2$ proved to be inefficient catalysts for the transformation as low yields/conversions (<20%) of **6a** were obtained (entries 5 and 6).

Interestingly, although the reaction with $Yb(OTf)_3$ did not reach completion,[11] benzofuran **6a** was obtained in 57% yield along with ~40% unreacted starting material (entry 7). When the reaction was run at reflux, the reaction went to completion in ~12 h and the product yield increased to 91% (entry 8). Similar yield improvements were obtained for the other Lewis acids in CH_2Cl_2 at reflux (entries 9–12); however, none of the catalysts gave higher yields than $Yb(OTf)_3$. When the $Yb(OTf)_3$ loading was changed to either 20 and 10 mol %, the yields decreased to 74% and 81%, respectively (entries 13 and 14).[12] Therefore, 15 mol % $Yb(OTf)_3$ in CH_2Cl_2 at reflux was chosen as the conditions for the examination of substrate scope.[13]

Next, the effects of the alkylidene substituents were examined (Table 2). When the alkylidene was substituted with a

Table 2. Alkylidene Substituent Effects

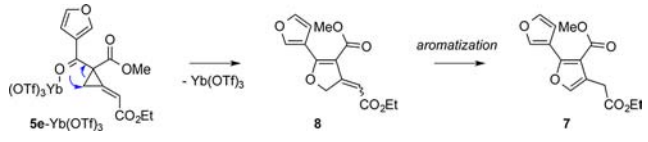


[a]Reactions run with Lewis acid (15 mol %), cyclopropane **5**, and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) at 40 °C. [b]Isolated yield after column chromatography. [c]Combined isolated yield of **6** and **6′**. [d]Reactions performed in 1,2-dichloroethane at reflux. [e]Product ratios determined by ^1H NMR of isolated mixture.

4-methoxyphenyl group (as in **5b**), the expected benzofuran **6b** was formed in 53% as the only product (entry 1). In contrast, when the substituent is phenyl (as in **5c**), a 2.2:1 mixture of **6c** and its isomer **6c′** was obtained in 71% combined yield (entry 2). A similar result was observed with ACP **5d** (bearing a 4-chlorophenyl group) as a 53% yield of a 2.0:1 mixture of **6d**:**6d′** was formed (entry 3). These observations suggest activation barriers that are closer in energy for the intramolecular cyclization at either terminus of the allyl cation as compared to ACP **5b**.[14]

When the alkylidene substituent was an electron-withdrawing group, an alternative reaction outcome was observed. For instance, when the alkylidene substituent was an ester group, the 2,3′-bifuran derivative **7** was generated in 69% yield and none of the benzofuran product(s) were seen (Table 2, entry 4).[15] Bifuran **7** arises from an intramolecular attack of the enolate oxygen on the alkylidene cyclopropane to form a transient dihydrofuran intermediate that undergoes aromatization to the furan (Scheme 3). The regiochemical outcome suggests that

Scheme 3. Formation of 2,3′-Bifuran 7

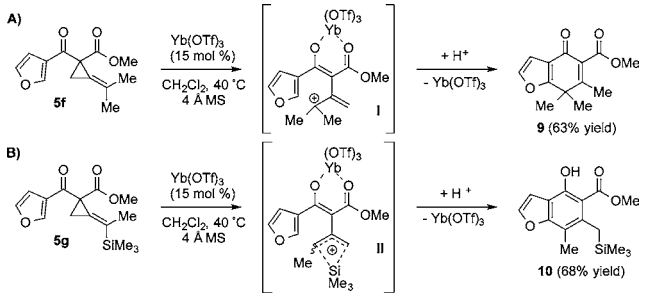


dx.doi.org/10.1021/ol501676q | Org. Lett. 2014, 16, 3788–3791

the allyl cation is not formed which is in agreement with the destabilizing effect of an electron-withdrawing substituent on an allyl cation.

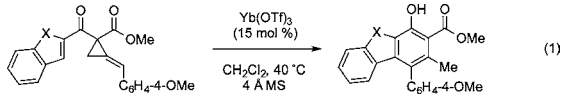
In hopes of generating more functionalized/functionalizable products, ACPs bearing a second substituent on the alkylidene were employed (Scheme 4). In one example, the ACP (**5f**) had

Scheme 4. Effects of Alkylidene Disubstitution



two methyl alkylidene substituents and gave the 4-oxo-4,7-dihydrobenzofuran derivative **9** in 63% yield (Scheme 4A). **9** contains both a quaternary center and an alkylidene β-ketoester moiety, which can serve as a site for further reactivity.[16] In another example, the alkylidene was substituted with a methyl and a trimethylsilyl group (Scheme 4B). **10** was formed in 68% yield and presumably arises via formation of a silyl-stabilized[17] methyl allyl cation **II** followed by Friedel–Crafts-type cyclization and subsequent aromatization. This approach offers potential for functionalization, as the proper choice of silyl group would allow for facile C–C[18] and C–O[19] bond formation.

To further explore the reaction scope, the reactive π-systems on the ACP were modified in three different ways and the resulting reactivities were cataloged. First, other heteroaryl π-systems were employed under the reaction conditions (eq 1).[8b,20] The

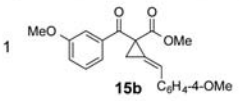
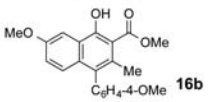
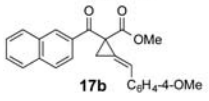
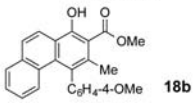
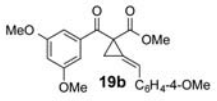
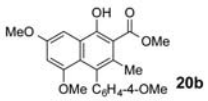
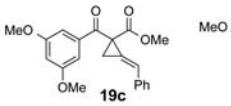
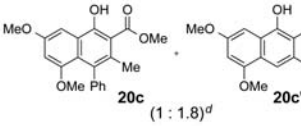
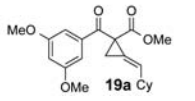
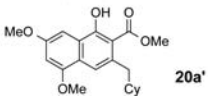


(1)

2-benzofuryl ACP **11b** (bearing an 4-methoxyphenyl alkylidene substituent) gave the corresponding dibenzofuran product **12b** in 78% yield. Similarly, 2-indolyl ACP **13b** smoothly afforded carbazole **14b** in 69% yield.

Next, the effect of employing aryl groups[21] as the intramolecular π-nucleophile for the ring-opening cyclization was examined (Table 3). When the ACP was substituted with a 3-methoxyphenyl group as the π-donor and a 4-methoxyphenyl group on the alkylidene (as in **15b**), the expected regioisomeric naphthalene product **16b** was formed in 77% yield (entry 1). If the π-nucleophile is a 2-naphthyl group, two regioisomeric products are possible via Friedel–Crafts-type alkylation at C(1) or C(3) of the naphthalene. The preferred reactivity is expected to occur at C(1) given the relative stability of the resulting Wheland intermediate.[22] Indeed, the only observed cyclization product is phenanthrene **18b**, resulting from C(1) attack, in 44% yield (entry 2). When 3,5-dimethoxyphenyl was the π-donor, regiochemical outcomes were found to be dependent upon the alkylidene substituent. For instance, a 4-methoxyphenyl substituent gives the favored naphthalene product **20b** in 80% yield (entry 3), whereas a phenyl group gives a 1.8:1 preference for the less energetically favorable **20c**′ over **20c** (98% yield, entry 4).

Table 3. Aryl Groups as the Intramolecular π-Nucleophiles

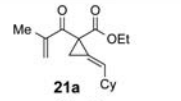
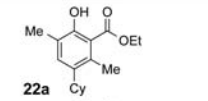
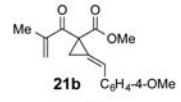
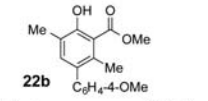
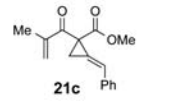
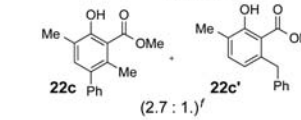
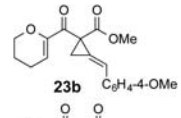
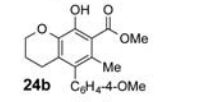
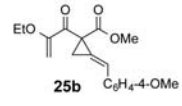
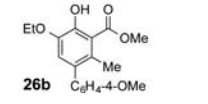
entry[a]	substrate	product(s)	% yield[b]
1			77%
2			44%
3			80%
4			98%[c] (1 : 1.8)[d]
5			39%[e]

[a]Reactions run with $Yb(OTf)_3$ (15 mol %), ACP (**15b**, **17b**, or **19a–c**), and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) at 40 °C. [b]Isolated yield after column chromatography. [c]Combined yield of **20c** and **20c**′. [d]Product ratios determined by ^1H NMR of isolated mixture. [e]Reaction performed in 1,2-dichloroethane at reflux.

This outcome is seemingly the result of a combination of electronic and steric effects in the transition state for cyclization. To assess the steric influence on the regiooutcome, ACP **19a** (bearing the cyclohexyl alkylidene substituent) was prepared. As anticipated, the only observed product was naphthalene derivative **20a**′ in 39% yield (entry 5). Thus, sterics directly influence the cyclization pathways and product outcomes.

Next, the ACP π-nucleophilic moiety was changed to alkenyl groups and evaluated for performance (Table 4).[8a,20a,23] For the

Table 4. Performance of Alkenyl Ketone Substituents

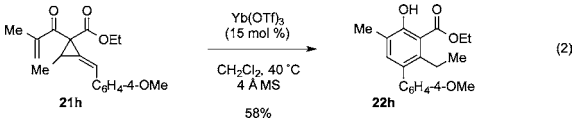
entry[a]	substrate	product	% yield[b]
1			66%[c]
2			49%
3		 (2.7 : 1.)[f]	59%[d,e]
4			26%[d]
5			51%[d]

[a]Reactions run with $Yb(OTf)_3$ (15 mol %), ACP (**21a–c**, **23b**, or **25b**), and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) at 40 °C. [b]Isolated yield after column chromatography. [c]Reactions performed with 30 mol % $Yb(OTf)_3$. [d]Reaction performed in 1,2-dichloroethane at reflux. [e]Combined yield of **22c** and **22c**′. [f]Product ratios determined by NMR of isolated mixture.

dx.doi.org/10.1021/ol501676q | Org. Lett. 2014, 16, 3788–3791

isopropenyl π-donor, similar reactivity trends were observed for ACPs bearing either a cyclohexyl (**21a**)[24] or a 4-methoxyphenyl (**21b**) alkylidene substituent, as phenols **22a** and **22b** were formed in 66% and 49% yield, respectively (entries 1 and 2). For **21c**, bearing the phenyl group, an unsurprising 2.7:1 mixture of phenols **22c** and **22c′** was observed in 59% yield (entry 3). With dihydropyran as the π-nucleophile, phenol **24b** was obtained in 26% yield (entry 4). The conformation and steric impact of the pyranyl ring are implicated in the decreased reaction efficiency. To examine that premise, the ACP **25b**, containing an ethoxy vinyl subtituent, was prepared. **25b**, having less destabilizing steric and conformational influences, should perform more effectively. Indeed, **25b** smoothly afforded phenol **26b** in 51% yield (entry 5).

Finally, to understand the regioselectivity of the reaction of ACPs derived from 1,3-disubstituted allenes, we prepared **21h** from 3-methyl-1-(4-methoxyphenyl)allene **3h**. Under the standard reaction conditions, **21h** afforded the expected phenol **22h** in 58% yield (eq 2).



(2)

In conclusion, we have disclosed a Lewis acid catalyzed, formal homo-Nazarov-type cyclization of alkylidene-1,1-ketoesters to form functionalized arenes and heteroarenes in up to 98% yield. Of the two possible regioisomeric outcomes, the major product arises from intramolecular π-attack on the most energetically favorable allylic cationic intermediate, unless steric constraints prevent such an attack. The choice of the alkylidene substituent also affects reaction outcomes. The reaction is amenable to alkenyl, aryl, and heteroaryl intramolecular π-nucleophiles. Application of the methodology in both natural product and materials synthesis is underway, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.F. gratefully acknowledges financial support from the National Science Foundation (CAREER Award CHE-1056687) and Georgia Tech for a Blanchard Assistant Professor Fellowship. J.A.-G. thanks the National Science Foundation for a graduate research fellowship (DGE-1148903) and Georgia Tech for a Presidential Fellowship. E.T. acknowledges Georgia Tech and the National Science Foundation for a summer REU (NSF REU 1156657).

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