Organic LETTERS

Letter

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Synthesis of 2-Ethenylcyclopropyl Aryl Ketones via Intramolecular S_N2-like Displacement of an Ester

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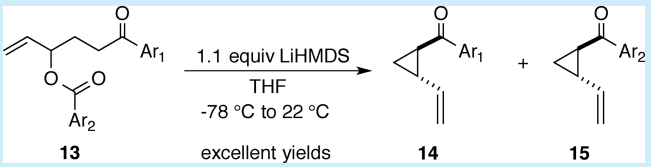
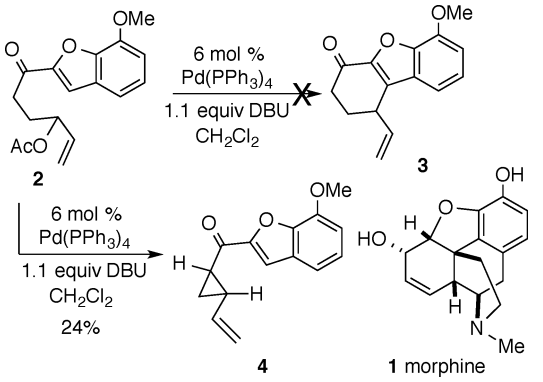
Supporting Information

ABSTRACT: The efficient synthesis of *trans*-2-ethenylcyclopropyl aryl ketones via an intramolecular S_N2-like displacement of an allylic ester is reported. A novel 1,5-acyl shift process is also observed that contributes to the product mixture. Theoretical calculations provide a rationale for the observed product ratio.



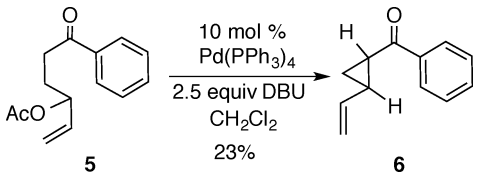
For a projected total synthesis of members of the morphine alkaloid family, we envisioned the palladium-promoted cyclization of the allylic acetate **2** on to the benzofuran unit at the 3-position to give the tricycle **3**, which contains three of the five rings present in morphine **1**. However, treatment of the allylic acetate **2** with a palladium(0) catalyst and the base DBU did not produce any of the tricycle **3** but rather the unexpected 2-ethenylcyclopropyl aryl ketone **4** in 24% yield as nearly a single stereoisomer (Scheme 1). In order to prove the structure and

Scheme 1. Synthesis of *trans*-2-Vinylcyclopropyl Ketones



stereochemistry of the product, we carried out the analogous reaction with the phenyl analogue **5** which under similar treatment afforded the trans-2-ethenylcyclopropyl phenyl ketone **6** in 23% yield (Scheme 2). Comparison of the proton NMR data of this compound with those for the known trans isomer[1] allowed us to confidently assign the structure. In addition we performed a NOESY analysis which also confirmed the trans structure.[2]

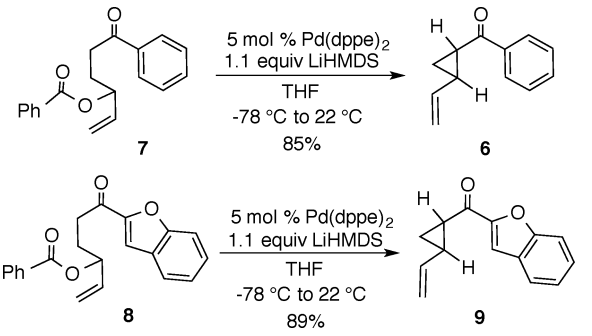
Scheme 2. Synthesis of Ketone 6



Since cyclopropanes and specifically cyclopropyl ketones are important components of natural products[3] and intermediates for synthesis,[4] we decided to examine the generality and scope of this process, with the hope of finding conditions to make it much higher yielding.

We first studied the effect of the leaving group and found that benzoates functioned very well. Changing the ligand from triphenylphosphine to dppe also helped the reaction. Finally changing the base to lithium hexamethyldisilazide (LiHMDS) had a very significant effect on the yield of the process. Thus, the allylic benzoates **7** and **8** afforded the corresponding products **6** and **9** under these conditions in quite high yields, 85% and 89% respectively (Scheme 3). We wanted to test the amount of the palladium catalyst needed for this process and therefore lowered the catalyst loading. In all cases, the reaction still occurred. It was somewhat of a surprise to find that even with no catalyst, in new flasks that had never seen a metal, the desired products were obtained in good yields; thus, the phenyl ketone **7** gave **6** in 84% yield and **8** gave **9** in 80% yield (Scheme 4). Therefore, the

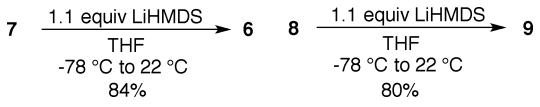
Scheme 3. Variation of Leaving Group, Ligand, and Base



Received: August 29, 2016

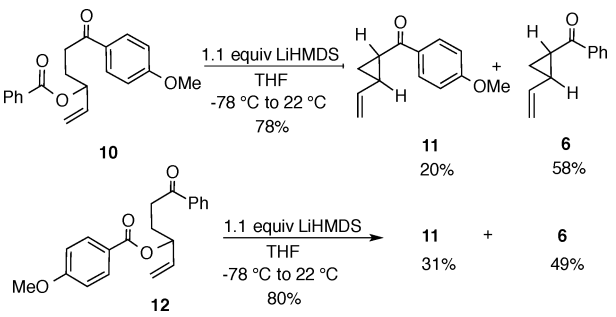
DOI: 10.1021/acs.orglett.6b02588
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Palladium-Free Conditions



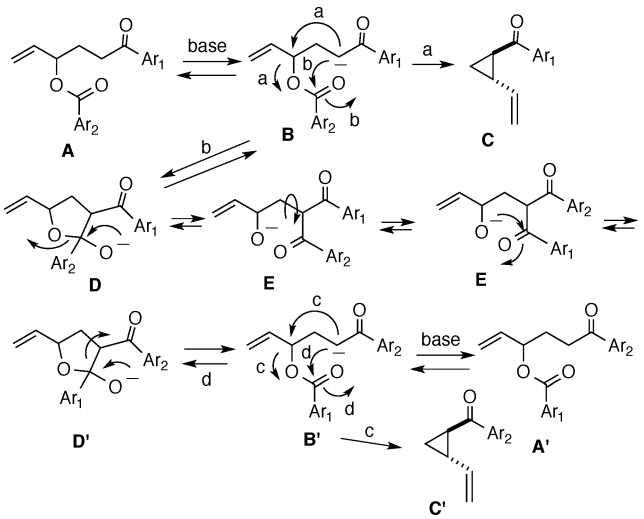
reaction must proceed by a simple S_N2-like displacement of the allylic ester by the enolate of the ketone. It is somewhat curious that no cyclopentanone products are obtained nor are there any 4,5-dihydrofuran products. When the benzoyloxy 4-methoxyphenyl ketone **10** was treated under these conditions, the expected product **11** was formed but in only 20% yield. The major product was the phenyl ketone **6**, formed in 58% yield (Scheme 5). Thus, a rearrangement was occurring to exchange

Scheme 5. Rearrangement and Cyclization



the acyl groups. We showed that the opposite starting material, namely the 4-methoxybenzoyl phenyl ketone **12**, also gave a similar ratio of the two products **11** (31%) and **6** (49%). Thus, the two acyl groups are exchanging via a common intermediate. We propose the mechanism shown in Scheme 6 for this novel

Scheme 6. Mechanism of Rearrangement



rearrangement. Formation of the ketone enolate **B** from the aroyloxy ketone **A** and ejection of the ester leaving group would give **C** (path a). But this enolate **B** could also attack the carbonyl of the ester (path b) to give the alkoxide **D**. Ejection of the alkoxide from **D** would give the symmetrical 1,3-dicarbonyl compound **E**. Attack of the alkoxide on the opposite ester would give **D′** which would proceed via **B′** to give **C′** (path c), the other observed product. And the pathway could also be entered by beginning with the opposite aroyloxy ketone **A′** leading via path d to the same symmetrical intermediate **E** to lead to both observed products.

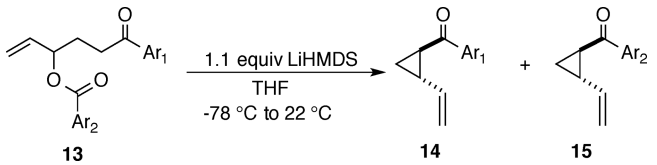
We have carried out a number of cyclization studies with various aroyloxy aryl ketones, and the results are shown in Table 1. Obviously the symmetrical compound **13a** (entry 1) gives only the sole product **14a**. The benzofuryl ketone **13b** (entry 2) gives only the unrearranged ketone product **14b** when starting with **13b** but gives a 73:11 mixture of the ketone **15b**, the rearranged product, and the phenyl ketone **14b**, the unrearranged product, when starting with the isomeric ester **13l** (corresponding to **A′**). The 7-methoxybenzofuryl ketone **13c** (entry 3) gave only the unrearranged ketone **14c**. The furyl ketone **13d** (entry 4) also greatly favors, by 70% to 13%, the unrearranged ketone product **14d** as does the 2-trifluoromethylphenyl ketone **13i** (entry 9) which gives a 70% to 5% ratio of **14i** to **15i**. The 4-trifluoromethylphenyl ketone **13g** (entry 7) gave a 60:20 ratio of unrearranged/rearranged products **14g**:**15g**, but this ratio changes to 49% (unrearranged) to 43% (rearranged) when starting with the isomeric ester **13n** (entry 14). The 3-trifluoromethylphenyl ketone **13h** (entry 8) also preferred the unrearranged ketone but by a smaller ratio (60% to 23%). Finally as mentioned earlier the 4-methoxyphenyl ketone **13j** gave a 20% to 58% mixture of the rearranged ketone **15j** to the unrearranged ketone **14j** and a somewhat similar ratio (31% to 49%) of the same two products when starting from the isomeric ester **13m** (entries 9 and 12).

We attempted two other cyclizations of this type, in which we replaced the vinyl group with either a methyl group or a hydrogen atom. Treatment of the secondary benzoate **16a** afforded the cyclopropyl ketone **17a** in 49% yield (Scheme 7) while the primary benzoate **16b** furnished the simple cyclopropyl ketone **17b** in 38% yield. The trans-stereochemistry of **17a** was determined by comparison of its proton NMR data with those reported in the literature.[1a,4c] Several similar substrates with different acyl groups did not afford good yields of cyclization; e.g., the corresponding methyl or *tert*-butyl ketones, the ethyl ester, or the Weinreb amide all failed. The closest analogy in the literature is the work of Yates[5] who showed that 4-aroyloxy cycloalkanones give cyclopropanes via S_N2-like opening of an intermediate lactone. Several syntheses of bi- and polycyclic cyclopropanes with an ester leaving group are also known.[6]

In order to understand the energetics of this rearrangement–cyclization manifold, we performed density functional theory (DFT) calculations at the SMD^{THF}/B3LYP-D3/6-31+G(d) level of theory using the Gaussian09 program.[7] The free energy diagram for the reaction of benzofuryl ketone **13b** is shown in Figure 1. Deprotonation of **13b** generates the corresponding enolate **18**, which can undergo the proposed intramolecular S_N2-like reaction to form cyclopropane **14b**. The barrier for this reaction is 14.1 kcal/mol, and the reaction is exergonic by 18.9 kcal/mol. Enolate **18** can also intramolecularly attack the ester carbonyl group via **TS-2** to form a five-membered ring intermediate **19**. Ring opening of **19** generates a high-energy intermediate alkoxide **20**, which can reclose to form another five-membered ring intermediate **21**. The formation of enolate **22** from **21** is calculated to be fast via **TS-3**, but **TS-4** is 3 kcal/mol above **TS-1**; thus, only **14b** is formed from **18**. This is in agreement with the experimental observation that only **14b** is formed. Starting from ketone **13l**, enolate **22** is formed after deprotonation and converts into **15b** via **TS-4** which is only 1.3 kcal/mol above **20**, leading to **14b**. The formation of a small amount of **15b** is predicted. We have also computed the free energy profiles for the reactions of 4-methoxyphenyl ketone **13j**

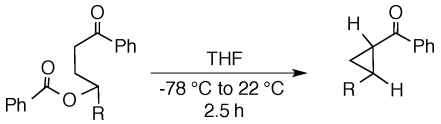
DOI: 10.1021/acs.orglett.6b02588
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Cyclization of Aroyloxy Aryl Ketones



entry	compd	Ar_1	Ar_2	**14** yield (%)	**15** yield (%)	time (h)
1	**a**	Ph	Ph	84	0	1.5
2	**b**	benzofuryl	Ph	80	0	2.5
3	**c**	7-(OMe)benzofuryl	Ph	75	0	5.0
4	**d**	furyl	Ph	70	13	2.0
5	**e**	4-$CH_3C_6H_4$	Ph	49	46	3.0
6	**f**	4-FC_6H_4	Ph	47	43	1.0
7	**g**	4-$CF_3C_6H_4$	Ph	60	20	1.75
8	**h**	3-$CF_3C_6H_4$	Ph	60	23	1.5
9	**i**	2-$CF_3C_6H_4$	Ph	70	5	1.5
10	**j**	4-$MeOC_6H_4$	Ph	20	58	2.5
11	**k**	4-$Me_2NC_6H_4$	Ph	43	42	3.5
12	**l**	Ph	benzofuryl	11	73	3.0
13	**m**	Ph	4-$MeOC_6H_4$	49	31	2.5
14	**n**	Ph	4-$CF_3C_6H_4$	49	43	2.5

Scheme 7. Cyclization of Other Esters



and 4-trifluoromethylphenyl ketone **13g**. The predicted ratios of unrearranged to rearranged product (**C**:**C′**) are comparable to the experimental ratios. The results are summarized in Table 2.

For 4-methoxyphenyl ketone **13j**, the corresponding **TS-1** is 0.5 kcal/mol higher in energy than that of **TS-4**. This corresponds to a 1:2 ratio of **C** to **C′** (Table 2, entry 3). The intermediate alkoxide is lower in energy than both TSs. Starting from the isomeric ester **13j**, the ratio of **C** to **C′** is predicted to be 2:1 (Table 2, entry 4). For 4-trifluoromethylphenyl ketone **13g**,

Table 2. Predicted and Experimental Product Ratios

entry	Ar_1	Ar_2	pred. ratio	exper. ratio
1	benzofuryl	Ph	159:1	>20:1
2	Ph	benzofuryl	1:9	1:7
3	4-$MeOC_6H_4$	Ph	1:2	1:3
4	Ph	4-$MeOC_6H_4$	2:1	2:1
5	4-$CF_3C_6H_4$	Ph	5:1	3:1
6	Ph	4-$CF_3C_6H_4$	2:1	1:1

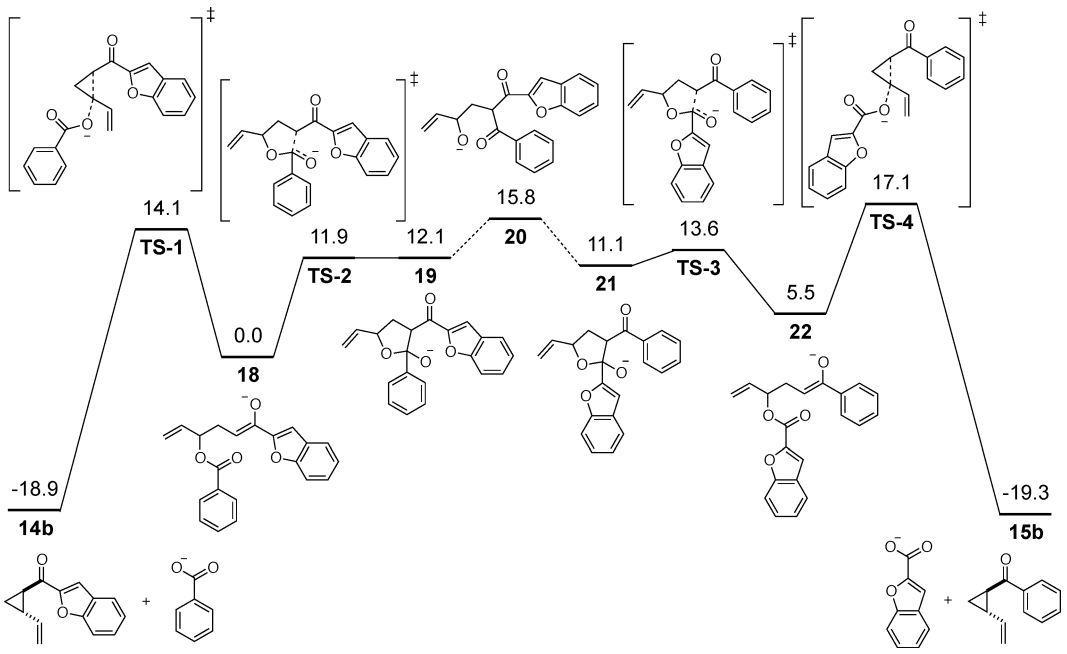


Figure 1. Free energy profile for the reaction of benzofuryl ketone **13b**. Energies are in kcal/mol.

DOI: 10.1021/acs.orglett.6b02588
Org. Lett. XXXX, XXX, XXX−XXX

the corresponding alkoxide intermediate is slightly higher in energy than either **TS-1** or **TS-4**. Therefore, the unrearranged product **C** is predicted to be predominant (Table 2, entries 5 and 6).

In general the various pathways in Scheme 6 can all occur, and there is a rather delicate balance between which products are favored. As indicated in Table 2, computations and experiment are in very good agreement. Were **18** and **22** (Figure 1) in rapid equilibrium (Curtin−Hammett conditions), the ratio of products would only depend on the relative energies of **TS-1** and **TS-4**. Because **20** may be above either **TS-1** or **TS-4**, as it is in Figure 1, the product ratio is not that expected with Curtin−Hammett conditions and sometimes is influenced by the reactant identity.

In summary, we have developed an efficient synthesis of *trans*-2-ethenylcyclopropyl aryl ketones through an intramolecular S_N2-like displacement of allylic esters. A novel 1,5-acyl shift process is observed that contributes to the product mixture. Theoretical calculations show that the S_N2-like reactions and 1,5-acyl shifts may have similar barriers, and whether or not Curtin−Hammett conditions prevail depends upon the relative energies of these processes. B3LYP/6-31+G(d)/SMD calculations reproduce experimental results and provide insights into the origins of the observed product ratios.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02588.

Experimental procedures and spectral characterization of all new compounds along with proton and carbon NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. Craig Merlic, UCLA, for helpful discussions. We are grateful to the National Science Foundation for financial support of this research (CHE-1361104).

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(2) The NOESY experiment was performed on compound **6** and showed a correlation between the proton α to the carbonyl and the methine vinyl proton, thereby confirming that they were cis.

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DOI: 10.1021/acs.orglett.6b02588
Org. Lett. XXXX, XXX, XXX−XXX