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Nickel-Catalyzed Rearrangement of 1-Acyl-2-vinylcyclopropanes. A Mild Synthesis of Substituted Dihydrofurans

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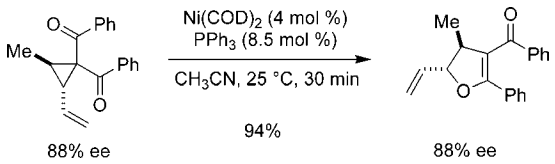
ABSTRACT



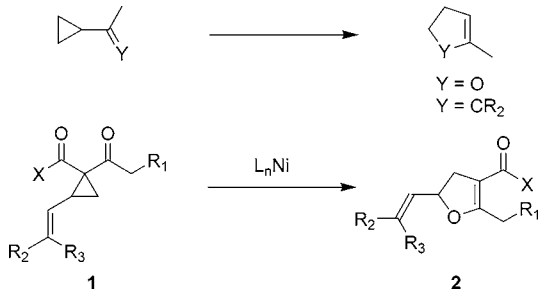
Mild Ni(0)-catalyzed rearrangements of 1-acyl-2-vinylcyclopropanes have been developed. The room-temperature isomerizations afford dihydrofuran products in yields regularly greater than 90%. A highly substituted, stereochemically defined cyclopropane was employed in the rearrangement to evaluate the reaction mechanism. Product analysis indicates that the overall reaction proceeds with retention of configuration at the vinyl-bearing stereogenic center.

Increasingly sophisticated technologies are available for the stereoselective synthesis of functionalized cyclopropanes.[1] Simplified routes to such structures suggest that cyclopropyl ketones might serve as readily accessed precursors to dihydrofurans via [1,3]-transposition. The utility of such a reaction rests in part on the ability of the rearrangement product to undergo subsequent oxidative or reductive manipulation, leading to useful aromatic or saturated five-membered oxygenated heterocycles.

The generalized rearrangement expressed in Scheme 1 (Y = O) is a recognized entry into dihydrofurans,[2] but its development has received less attention than that of the all-carbon variant (Y = CR_2).[3]

In this paper, we describe a strategy for performing mild rearrangements of 1-acyl-2-vinyl cyclopropanes to the derived dihydrofurans (**1** → **2**); the approach relies on the documented propensity of low-valent metal complexes to initiate productive π-allyl complex formation with suitably activated vinyl cyclopropanes.[4]

Scheme 1. Rearrangement of Vinyl- and Acylcyclopropanes to Cyclopentenes and Dihydrofurans



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(2) (a) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778−4782. (b) Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998**, *63*, 2641−2645. (c) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717−2719. (d) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645−9660.

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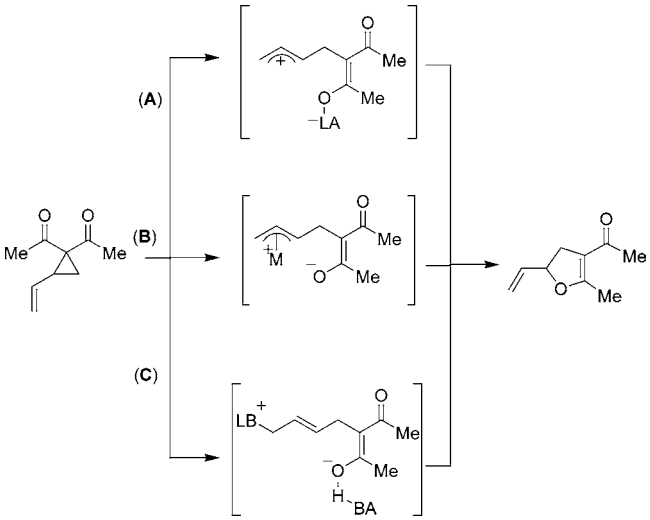
The rearrangement of vinyl cyclopropyl ketone **1a** (X = Me; $R_1 = R_2 = R_3 = H$) to dihydrofuran **2a** may be catalyzed under forcing conditions (≥100 °C) with Cu(I) or Rh(I).[5,6] The success of these preliminary studies and our continuing interest in heterocycle synthesis from three-membered rings[7] led us to consider methods that would effect this transformation under mild conditions. Initially, we chose to examine several mechanistically distinct approaches (Scheme 2).

Scheme 2. Strategies for 1-Acyl-2-vinylcyclopropane Rearrangement (See Text)



Under Lewis acid catalysis (A), chelation to the geminal acyl groups would act to weaken the cyclopropane bond leading to ring opening.[8] In the limiting case, this would result in an allyl cation/enolate zwitterion that could undergo internal quenching to give product. Our second option (B) was to use transition metals capable of triggering π-allyl chemistry. In this scenario, association of the alkene followed by π-allyl formation by ring opening of the cyclopropane would result in an (allyl)metal species with a pendant enolate.[4a,d] A third option (C) was use of a Lewis base in conjunction with a Brønsted acid. Under these conditions the Brønsted acid would activate the pendant carbonyl in the same manner as a Lewis acid, then attack of the Lewis base would open the cyclopropane in a "pull−push" fashion.[9]

In the event, all three strategies proved adequate for isomerization to dihydrofuran. Lewis acid catalysis was observed with several metal salts; $Cu(OTf)_2$ facilitated complete conversion of cyclopropane **1a** to dihydrofuran **2a** at ambient temperature with a catalyst loading of 10 mol % (4 h).[10] Pd(0) and Ni(0) catalysts were also effective, with the latter typically providing >95% conversion in less than 1 h, while Pd(0) catalysts required several hours to reach completion. The combination of BINOL/PPh_3 provided **2a** but showed incomplete conversion even over extended reaction times (74% conversion, THF, 25 °C, 17 h). Of the methods examined, the use of Ni(0) was most efficient in terms of catalyst loading and reaction time and was selected for further exploration.

The application of the L_nNi system to a group of diverse vinyl cyclopropyl ketones resulted in an efficient rearrangement protocol (Table 1). Cyclopropanes made from derivatives of alkyl acetoacetates (entries 1−3) underwent smooth isomerization at ambient temperature. The reactions were complete in 10 min and required only 2 mol % of $Ni(COD)_2$. 2,2'-Bipyridyl proved the most effective ligand for these substrates. Low conversion was observed in the absence of a ligand. As reported previously,[6] the substrate containing the geminal ester moiety (entry 4) does not isomerize to **2** even with a higher catalyst loading and longer reaction time.

Substitution at the keto-arm was successful as well (entries 5−8), with substrates containing alkene, aryl, cyano, and acetal functional groups undergoing efficient rearrangement. We were able to reduce catalyst loading to 1 mol % $Ni(COD)_2$ by changing the supporting ligand from 2,2'-bipyridyl to triphenylphosphine. This extended the reaction time to 1 h; however, dihydrofurans **2e**−**h** were all isolated in >95% yield. We observed incomplete conversion using $(Ph_3P)_2Ni(COD)$ for substrates 1−3. The two metal−ligand systems could be interchanged based on the exact (to date undefined) requirements of the substrate.

Structural changes to the alkene were also tolerated. Disubstitution of the vinyl group was tolerated employing 2 mol % $(Ph_3P)_2Ni(COD)$ (entry 9). While trisubstitution of the olefin was initially unsuccessful using the $(Ph_3P)_2Ni(COD)$ catalyst system, switching to 2,2'-bipyridyl as the ligand led to higher yields. It was necessary to increase the catalyst loading to 5 mol % and the reaction time to 4.5 h (entry 10); however, this protocol successfully afforded dihydrofuran **2j** in 80% yield.

Attempted asymmetric catalysis of this rearrangement using scalemic catalysts in no case led to product enantioenrichment. The retention of chirality through an inversion−inversion mechanism is the normal reaction mode for stabilized anions[11,12] and we hypothesized that this mechanism was operative.

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(9) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094−12095.

(10) Other promoters tested, THF, 25 °C (GC yield, time): $TiCl_4(THF)_2$ (21%, 4 h), $SnCl_2$ (<3%, 4 h), $AlCl_3$ (<3%, 4 h), $ZnCl_2$ (<3%, 4 h), $MgCl_2$ (<3%, 4 h), $Sn(OTf)_2$ (55%, 4 h), $Mg(OTf)_2$ (<3%, 4 h), $Zn(OTf)_2$ (<3%, 4 h), $La(OTf)_3$ (24%, 4 h), TiF_4 (<3%, 4 h), $ZrCl_4$ (48%, 4 h), DMAP/BINOL (<3%, 17 h), $P(OPh)_3$/BINOL (<3%, 17 h), PPh_3 (19%, 18 h), quinuclidine (14%, 18 h).

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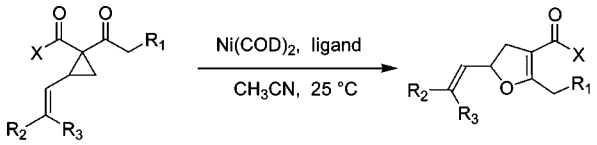
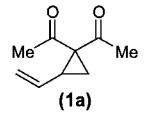
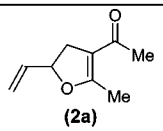
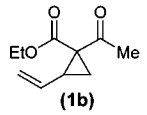
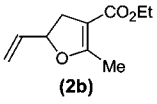
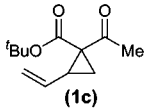
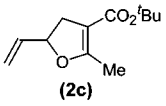
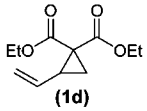
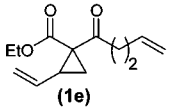
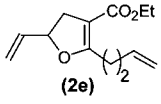
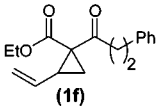
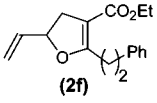
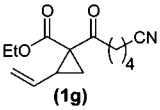
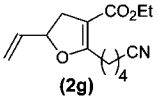
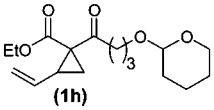
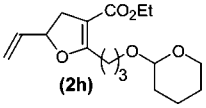
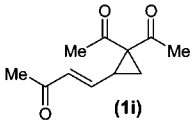
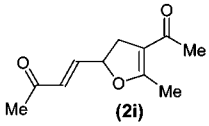
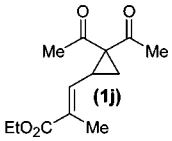
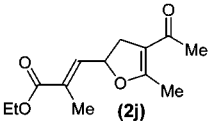
(12) Hayashi, T.; Yamane, M.; Ohno, A. *J. Org. Chem.* **1997**, *62*, 204−207.

Table 1. Rearrangement of Acyl Cyclopropanes to Dihydrofurans

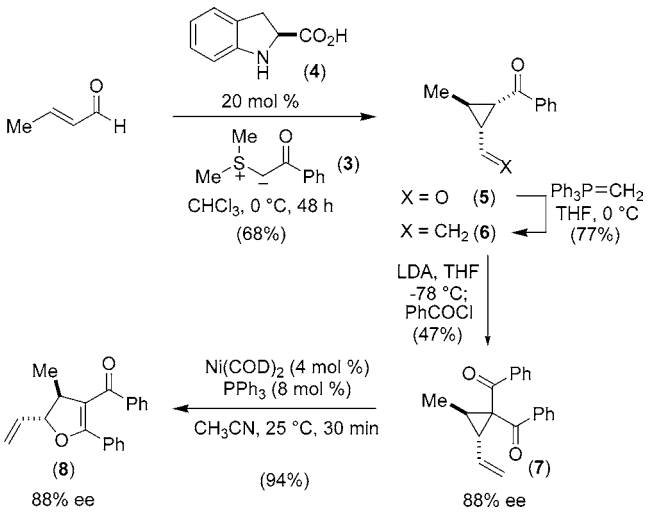


entry	cyclopropane	$Ni(COD)_2$ (mol %)	ligand (mol %)	time (h)	product	% yield
1	 (1a)	2	bipy (2.2)	0.20	 (2a)	97
2	 (1b)	2	bipy (2.2)	0.20	 (2b)	93
3	 (1c)	2	bipy (2.2)	0.20	 (2c)	94
4	 (1d)	10	bipy (11)	1	no reaction	---
5	 (1e)	1	PPh_3 (2.2)	1	 (2e)	99
6	 (1f)	1	PPh_3 (2.2)	1	 (2f)	97
7	 (1g)	1	PPh_3 (2.2)	1	 (2g)	99
8	 (1h)	1	PPh_3 (2.2)	1	 (2h)	97
9	 (1i)	2	PPh_3 (4.2)	0.5	 (2i)	76
10	 (1j)	5	bipy (10.5)	4.5	 (2j)	80

To gain greater insight into the mechanism and to implement the overall reaction strategy in a more complex system, we evaluated the rearrangement of vinyl cyclopropane **7**. This particular cyclopropane includes a vicinal substituent that can be used as a stereochemical marker to evaluate the fate of the neighboring vinyl-bearing stereogenic center.

The use of **7** also provided us the opportunity to implement newly developed enantioselective technology for cyclopropane synthesis that enables downstream Ni-catalyzed rearrangement: reaction of crotonaldehyde with sulfonium ylide **3** catalyzed by indoline-2-carboxylic acid **(*S*)-4** afforded trisubstituted cyclopropane **5** selectively according to the MacMillan protocol (Scheme 3).[1b] Wittig olefination of the cyclopropyl aldehyde led to vinylcyclopropane **6**. Acylation of the derived enolate (LDA, benzoyl chloride) gave the geminal diketone **7** in 47% yield (88% ee). Exposure to 5 mol % of $(Ph_3P)_2Ni(COD)$ afforded dihydrofuran **8** in 94%

Scheme 3. Synthesis of Enantioenriched Vinylcyclopropane and Test for Chirality Transfer



yield (88% ee), as a single diastereomer with the methyl and vinyl substituents disposed *trans* on the five-membered ring. The observed stereochemical outcome is consistent with a double-inversion mechanism.

We have successfully realized ring opening of vinyl cyclopropyl ketones substituted geminally with electron withdrawing groups at ambient temperature under mild reaction conditions to afford dihydrofuran products. This method is noteworthy for low catalyst loadings and short reaction times and is tolerant of both functional and structural changes made to the cyclopropane. Work is underway to extend this method to the formation of other heterocycles, and experimentation to intercept putative intermediates to further probe the reaction mechanism is ongoing.

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Supporting Information Available: Experimental procedures 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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