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Heterocycles based on the chemistry of alkylidenecyclopropanes and (aza)-cyclopropenes*

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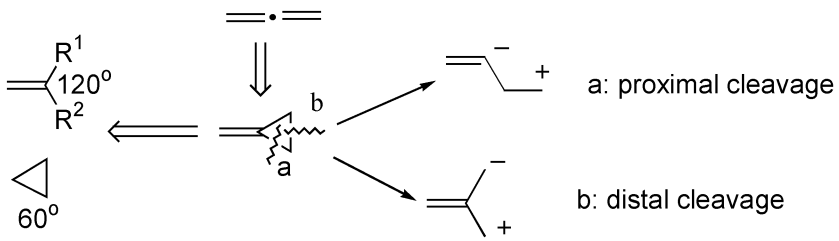
Abstract: Alkylidenecyclopropyl, cyclopropenyl, or azacyclocyclopropenyl ketones or carboxylates have been demonstrated to be versatile starting materials for the synthesis of oxygen- and/or nitrogen-containing heterocycles. The reactivities and regioselectivities may be nicely controlled by subtle choice of the catalysts and reaction condition parameters.

Keywords: heterocycles; ring-opening cyclization; alkylidenecyclopropanes; cyclopropenes; catalysis.

Due to the demonstrated synthetic power of allenes [1], we started to show interest in the reactivity of alkylidenecyclopropanes and cyclopropenes [2], which may be considered as analogs of allenes. Due to the strain of the three-membered ring in alkylidenecyclopropanes, their reactivity should be quite high. In principle, there should be two possible cleavages of the C–C single bonds of the three-membered ring: proximal and distal cleavages (Scheme 1). In addition, the C=C double bond may also be involved in triggering the ring-opening reaction. For example, oxidative addition of the C–C single bond to a low-valent metallic species and hydro- or carbometallation-induced C–C bond cleavage have been demonstrated by many chemists [3,4].



Scheme 1

In 2002, we started to study the reaction initiated by halometallation of the C=C bonds of alkylidenecyclopropanes with a carbonyl group connected to the three-membered ring. After some screening, it was observed that the $PdCl_2(MeCN)_2$-catalyzed sequence of ring-opening and cyclization

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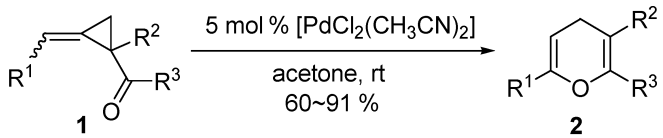
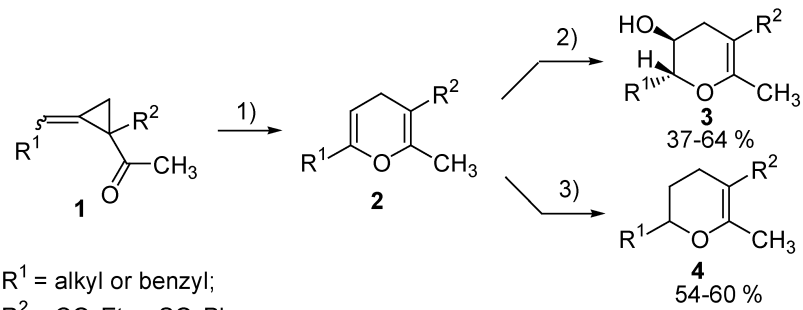
of 2-alkylidenecyclopropanyl ketones **1** in acetone at room temperature afforded 4*H*-pyran derivatives **2** (Scheme 2) [5].



R^1 = alkyl or benzyl;
R^2 = H, COMe, CO_2Et, or SO_2Ph;
R^3 = Me or Ph

Scheme 2

With R^2 being an electron-withdrawing group, the relatively more electron-rich C=C bond in such products may be hydroborated followed by oxidation or hydrogenated to afford hydroxy-substituted 4*H*-pyrans **3** and 2,3-dihydro-4*H*-pyrans **4**, respectively (Scheme 3) [6].

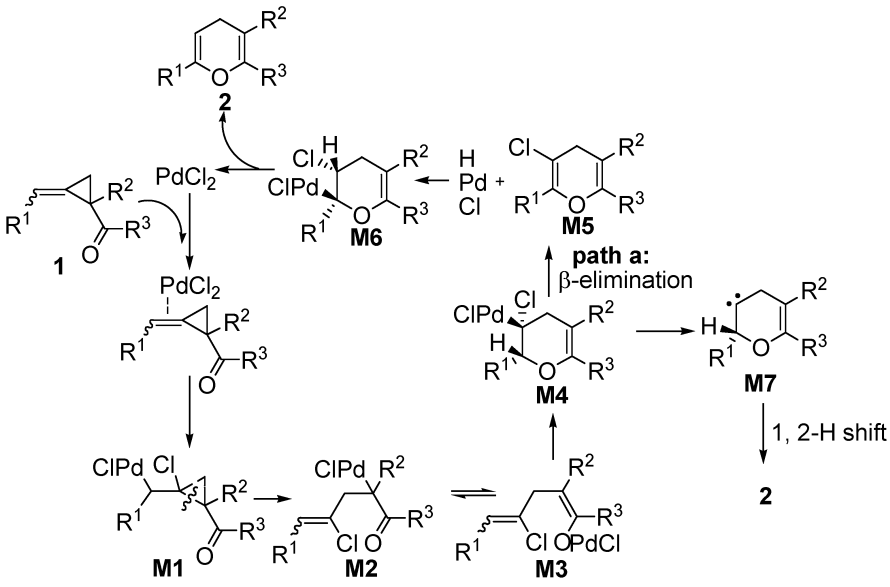


R^1 = alkyl or benzyl;
R^2 = CO_2Et or SO_2Ph

1) 5 mol % $PdCl_2(CH_3CN)_2$, acetone, rt, 15 min, or CH_2Cl_2, rt, 5 min;
2) a) $BH_3{\cdot}SMe_2$, THF, 0-25 °C, 1 h; b) NaOH-H_2O_2, 0-25 °C, 6 h
3) 10 mol % Pd/C, MeOH, H_2 (10 atm), 50 °C

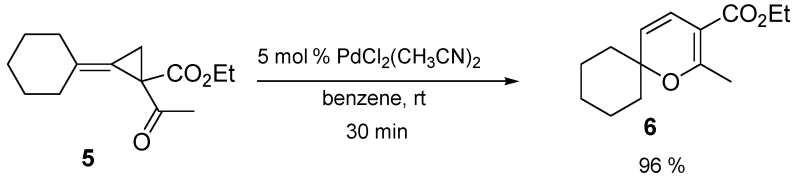
Scheme 3

According to mechanistic studies, it was believed that the reaction may be triggered by the regioselective chloropalladation forming intermediate **M1**, which was followed by the cleavage of the relatively electron-deficient proximal C–C single bond to afford intermediate **M2**. Subsequent isomerization may produce palladium enolate intermediate **M3**. Insertion of the C=C bond bearing the chlorine atom into the O–Pd bond in **M3** would produce six-membered intermediate **M4**, which upon β-dehydropalladation would afford 3-chloro-4*H*-pyran **M5**. The insertion reaction of the newly formed C=C bond with the in situ generated HPdCl species with a reversed regioselectivity would afford the 1-metallated intermediate **M6**, which may easily undergo β-dehalopalladation to form the final products 4*H*-pyran **2** with the regeneration of the catalyst $PdCl_2$. Of course, the α-dehalopalladation [7] of **M4** forming a carbene intermediate **M7** may also afford **2** by a regioselective 1,2-H shift (Scheme 4). Oxypalladation of the **1**-$PdCl_2$ coordination complex may also be a possible pathway to rationalize this conversion.



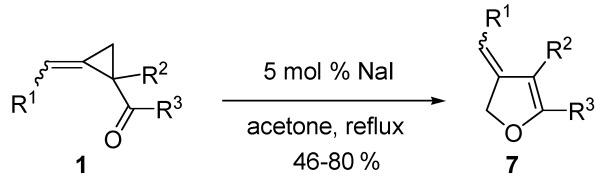
Scheme 4

In all these reactions, the formation of 2*H*-pyrans was not observed. However, for a substrate with a fully substituted C=C bond, for example, **5**, its $PdCl_2(MeCN)_2$-catalyzed reaction in benzene afforded 2*H*-pyran **6** in 96 % yield (Scheme 5) [6].



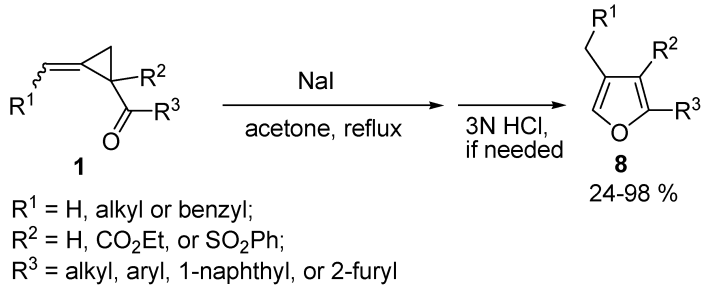
Scheme 5

Further studies indicated that in the presence of 5 mol % NaI in refluxing acetone, the distal C–C bond of the three-membered ring may be cleaved highly selectively to afford 3-alkylidene-2,3-dihydrofurans **7** obviously along a different reaction pathway (Scheme 6) [6].



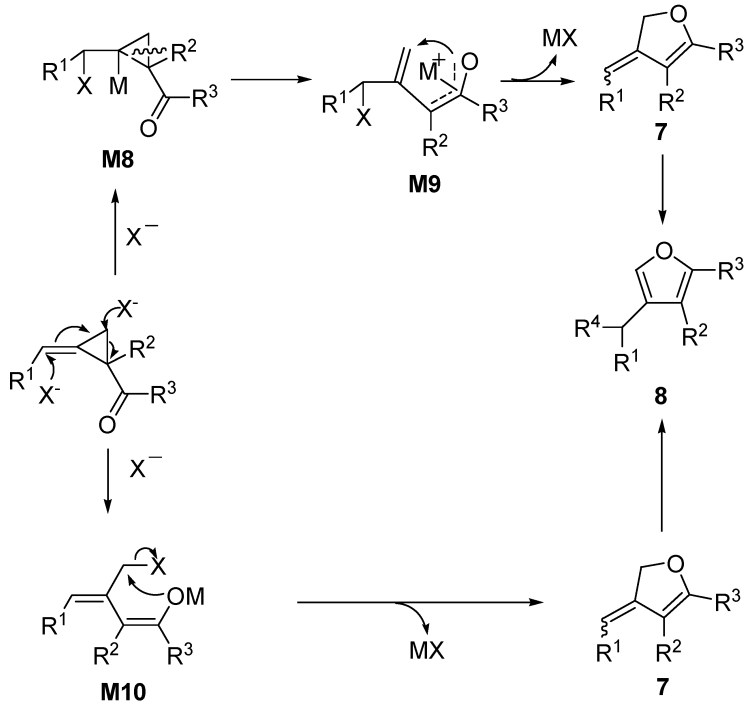
Scheme 6

With 1 equiv of NaI, prolonged reaction time, or treatment of the crude reaction products with 3N HCl, 2,3,4-trisubstituted furans **8** may be formed by the aromatization of 3-alkylidene-2,3-dihydrofurans **7** (Scheme 7) [6].



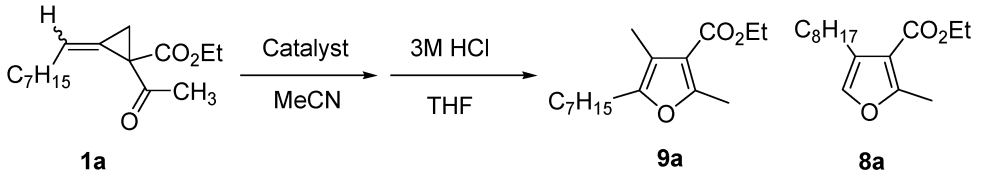
Scheme 7

The formation of the products may be explained by the attack of I^- at the terminal position of the C=C bond or the non-substituted carbon atom of the three-membered ring to afford a metal enolate intermediate **M9** or **M10** bearing an allylic halide moiety, which may undergo intramolecular nucleophilic substitution to afford 3-alkylidene-2,3-dihydrofurans **7**. Upon isomerization of the exo-cyclic double bond, 2,3,4-trisubstituted furans **8** would be formed (Scheme 8).



Scheme 8

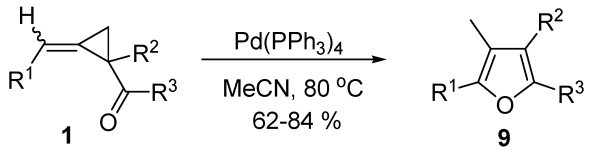
However, a catalyst with a combination of $Pd_2(dba)_3{\cdot}CHCl_3$ and a phosphine ligand may promote the formation of the new tetrasubstituted furan **9**a, along with the trisubstituted furan **8a** from **1a** in MeCN after subsequent treatment with 3N HCl. The formation of **8a** may be caused by the nucleophilic attack of the phosphine added in the way as NaI did. After screening, it was observed that $Pd(PPh_3)_4$ is the best catalyst, with which the reaction of **1a** afforded **9a** highly selectively with a ratio of **9a/8a** as high as 50:1 (Scheme 9) [6].



1a **9a** **8a**

Scheme 9

This new type of $Pd(PPh_3)_4$-catalyzed sequence of ring-opening and cyclization is quite general affording differently tetrasubstituted furans **9** in 62–84 % yield (Scheme 10) [6].

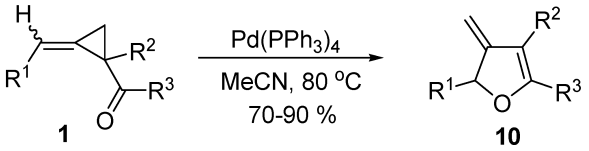


1 **9**

R^1 = alkyl;
R^2 = COMe, CO_2Et, or SO_2Ph;
R^3 = Me or Ph

Scheme 10

However, the reaction may also be stopped at the stage of 3-methylene-2,3-dihydrofurans **10**, revealing the intermediacy of this type of new transformation (Scheme 11) [6].

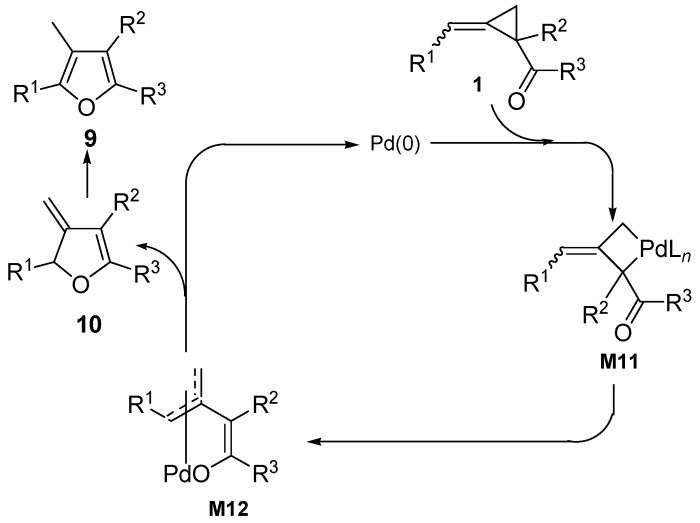


1 **10**

R^1 = alkyl;
R^2 = CO_2Et or SO_2Ph;
R^3 = Me or Ph

Scheme 11

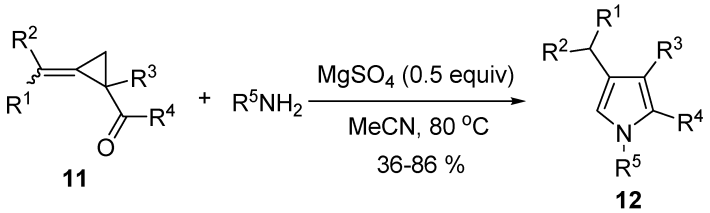
The formation of tetrasubstituted furans **9** can be rationalized via the oxidative addition of distal C–C single bond in **1** onto Pd(0) to form intermediate **M11**, which may isomerize to yield π-allylic palladium enolate intermediate **M12**. Subsequent regioselective reductive elimination or intramolecular nucleophilic allylation affords 3-methylene-2,3-dihydrofurans **10**, which would further isomerize to yield tetrasubstituted furans **9**. A minor pathway with the reaction occurring at the non-substituted ter-



Scheme 12

minal in **M12** would also form 1,2,3-trisubstituted furans via the intermediacy of 3-alkylidene-2,3-dihydrofurans (Scheme 12) [6].

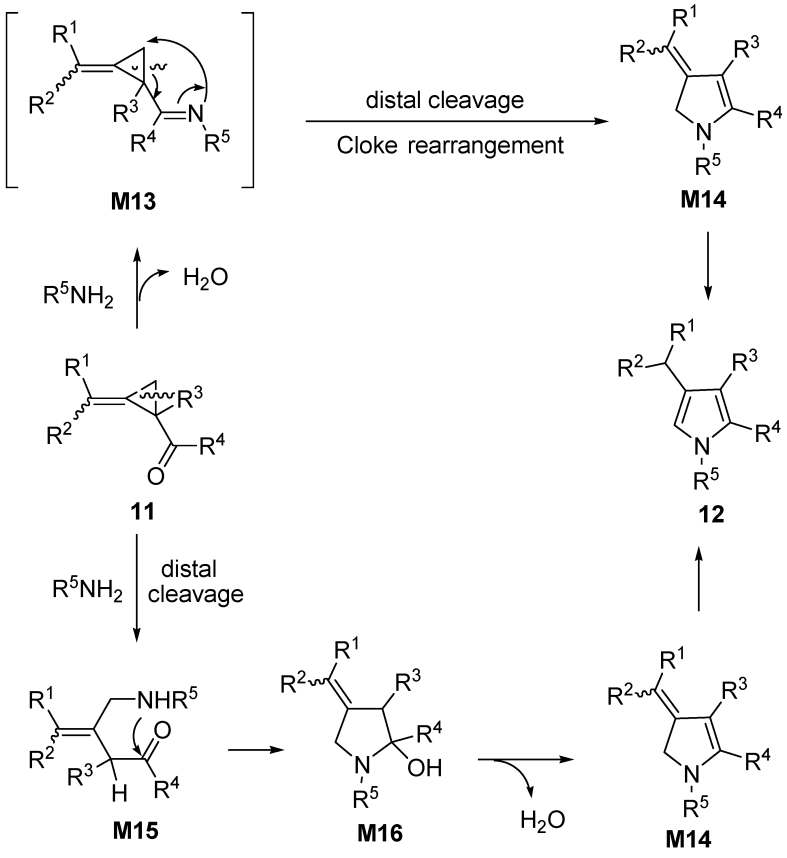
Based on the results of the NaI-triggered ring-opening cyclization sequence, we then started to screen a variety of different nucleophiles, which may open the three-membered ring by nucleophilic attack. After some study, amines were found to be effective reagents, which reacted with 2-alkylidenecyclopropyl ketones **11** to afford 2,3,4-trisubstituted pyrroles **12** (Scheme 13) [7]. The addition of 0.5 equiv of $MgSO_4$ improved the yield of this reaction by removing the in situ formed water.



R^1 = H, alkyl, or benzyl;
R^2 = H or Et;
R^3 = H, COMe, CO_2Et, or SO_2Ph;
R^4 = Me, CF_3, or Ph;
R^5 = alkyl or benzyl

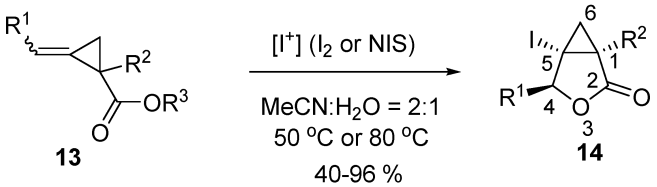
Scheme 13

Mechanistically speaking, 2,3,4-trisubstituted pyrroles may be formed from the condensation of the carbonyl group in **11** with amines to form 2-alkylidenecyclopropyl ketimines **M13**, which may undergo Cloke rearrangement to afford 3-alkylidene-2,3-dihydropyrroles **M14**. Of course, this type of intermediate products may also be formed via the nucleophilic attack of the amine at the non-substituted carbon atom in the three-membered ring of **11**, intramolecular nucleophilic attack of the nitrogen at the carbonyl group, and elimination of H_2O (Scheme 14) [7].



Scheme 14

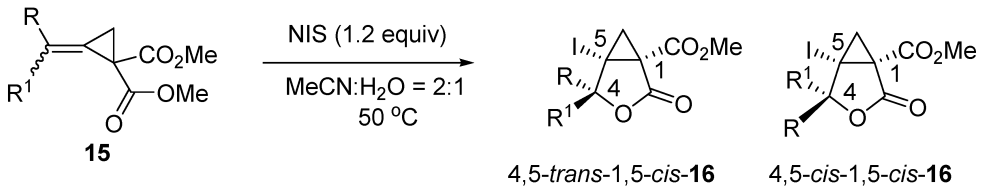
On the other hand, 2-alkylidenecyclopropanecaboxylates **13** may react with I_2 or NIS to induce a halocyclization forming the bicyclic lactones **14** highly diastereoselectively via the electrophilic interaction of the C=C bond with I^+ and the subsequent intramolecular nucleophilic attack of the carbonyl oxygen atom (Scheme 15) [9].



R^1 = alkyl, benzyl, or phenyl;
R^2 = H, Ph, CO_2Me, CO_2Et, or SO_2Ph;
R^3 = alkyl or benzyl

Scheme 15

In products **14**, R^2 and I are *cis*-oriented. Through control experiment of **15**, it was observed that the relative configuration for the chiral centers at 4,5-position in **16** depends on the relative steric effect of R and R^1 with the bulkier group being *trans* to the iodine atom (Scheme 16) [9].



R = Et, R^1 = TMS (**15a**)
E/*Z* = 13:1

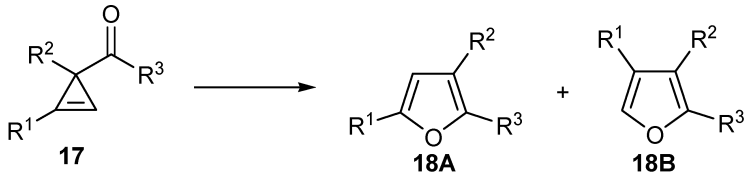
yield of **16a**: 46 %, 4,5-*trans*:*cis* = 19:1

R = Me, R^1 = Et (**15b**)
E/*Z* = 2:1

yield of **16b**: 86 %, 4,5-*trans*:*cis* = 2:1

Scheme 16

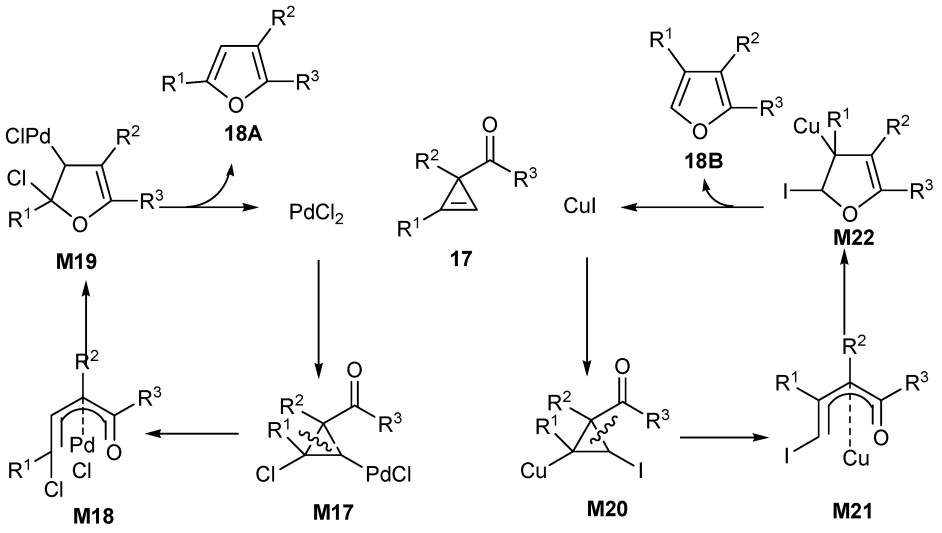
Based on the chemistry we observed with 2-alkylidenecyclopropyl ketones or 2-alkylidenecyclopropane carboxylates, we started to look into the chemistry of their close analogs cyclopropenyl ketones or cyclopropenecarboxylates. After some screening it was observed that $PdCl_2(MeCN)_2$ may catalyze the ring-opening cyclization sequence of cyclopropenyl ketones **17** in $CHCl_3$ under reflux to afford 2,3,5-trisubstituted furans **18A** while CuI transformed the same starting compounds into 2,3,4-trisubstituted furans **18B** (Scheme 17) [10]. The selectivity is general and practical. The formation of different products may be determined by the different regioselectivity of the initiating halometallation of the C=C bonds forming intermediates **M17** and **M20**, respectively, which induced the cleavage of different C–C single bond in the three-membered ring (Scheme 18) [10]. The regioselectivity of the halometallation may be caused by the relative steric hindrance of M and X.



R^1 = alkyl or phenyl;
R^2 = COMe, CO_2Et, or SO_2Ph;
R^3 = Me or Ph

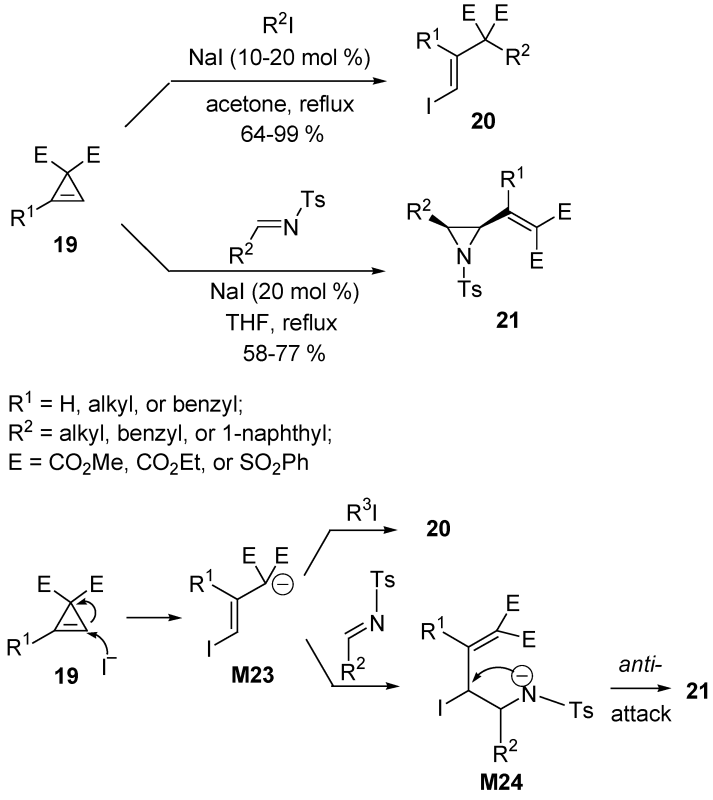
Conditions A: $[PdCl_2(CH_3CN)_2]$ (5 mol %), $CHCl_3$, reflux;
Conditions B: [CuI] (5 mol %), MeCN, reflux.

Scheme 17



Scheme 18

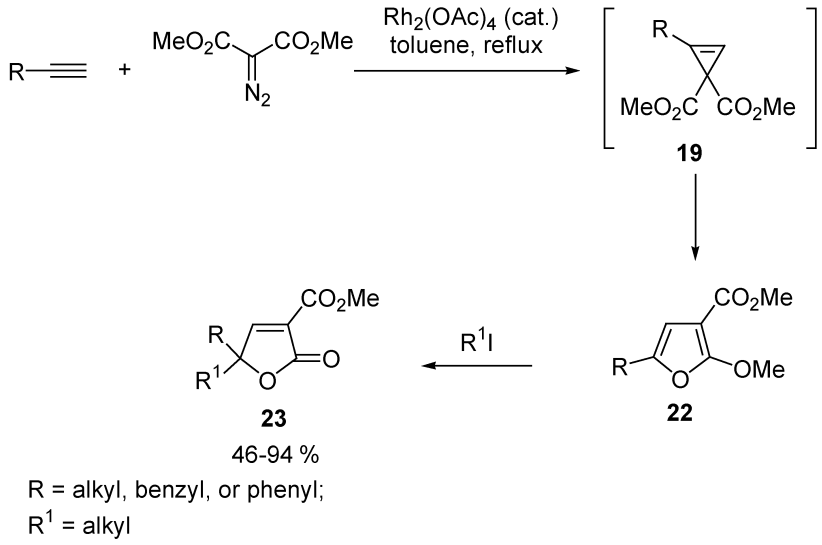
However, by using 3,3-bis(alkoxycarbonyl)cyclopropenes **19**, NaI may also open the three-membered ring, forming intermediate **M23**, which is followed by the reaction with alkyl iodide to form (*E*)-2-iodoalkenylmalonates **20** (Scheme 19) [11]. Furthermore, it is interesting to observe that when an



Scheme 19

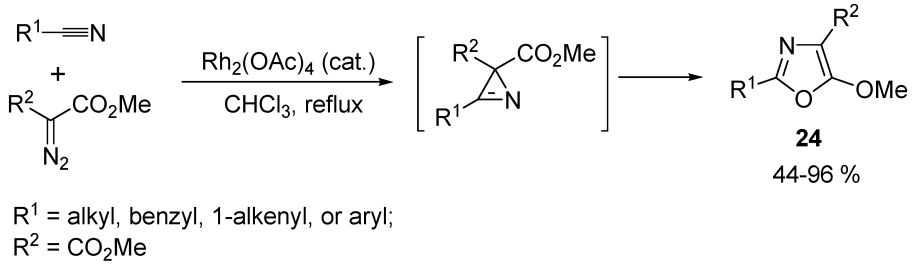
imine was added to capture the anion intermediate **M23**, *cis*-vinylic azridines **21** were formed highly diastereoselectively via anti-intramolecular nucleophilic substitution of the in situ formed intermediate **M24** [12].

The $Rh_2(OAc)_4$-catalyzed cyclopropanation of terminal alkynes easily affords 3,3-bis(methoxycarbonyl)cyclopropenes **19** [13]. However, it may readily undergo ring-opening cyclization to yield 2-methoxy-3-methoxycarbonylfurans **22**. Under the catalysis of NaI, their reaction with RI such as allyl iodide, propargyl ioide, α-iodo ketones, etc. provides γ-substituted 2-(5H)-furanones **23** efficiently (Scheme 20) [14].



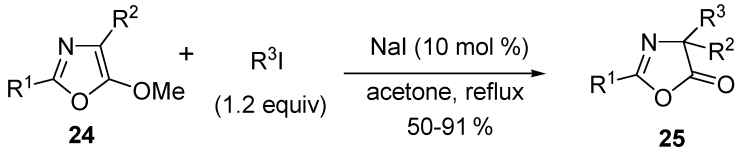
Scheme 20

A similar reaction was also observed with nitriles, which afforded 5-methoxyoxazoles **24** in good yields (Scheme 21) [15].



Scheme 21

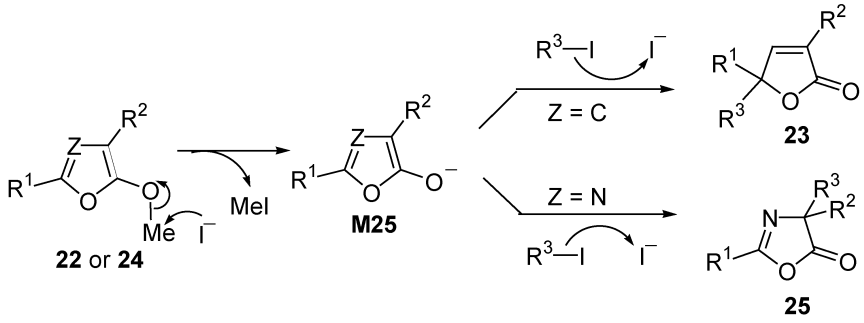
Under the catalysis of 10 mol % of NaI, the reaction of **24** with R^3I, such as allylic iodides, propargylic iodides, and α-iodo ketones, etc., in acetone would afford azalactones **25** with the alkylation occurred at the α-position (Scheme 22) [16].



R^1 = methyl, benzyl, phenyl, or 1-naphthyl;
R^2 = CO_2Me, SO_2Ph;
R^3 = alkyl

Scheme 22

According to mechanistic studies, it was believed that the reaction proceeded via the cleavage of the C–O bond in the methoxy group at the 2-position of **22** or **24** forming anionic intermediate **M25** (Scheme 23). With different nature of the Z atom, alkylation would proceed at either α- or γ-position, highly selectively.



Scheme 23

In conclusion, due to the presence of the C=C bonds and the strained three-membered ring as well as the introduction of the carbonyl group, the reaction of 2-alkylidenecyclopropyl ketones and cyclopropenyl ketones or corresponding carboxylic acid esters provides a variety of different heterocycles with high efficiency. Further studies in this area are being conducted in our laboratory.

ACKNOWLEDGMENTS

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