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Efficient Nazarov Cyclization/Wagner–Meerwein Rearrangement Terminated by a Cu^{II}-Promoted Oxidation: Synthesis of 4-Alkylidene Cyclopentenones

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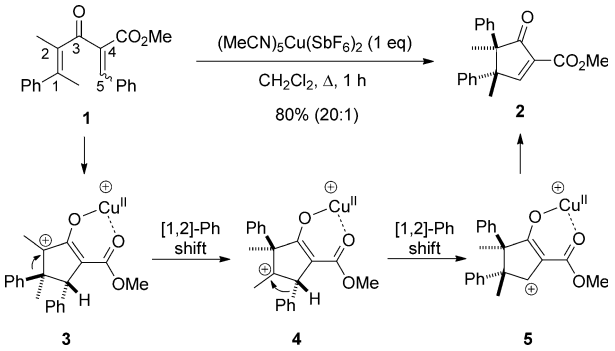
Abstract: The discovery and elucidation of a new Nazarov cyclization/Wagner–Meerwein rearrangement/oxidation sequence is described that constitutes an efficient strategy for the synthesis of 4-alkylidene cyclopentenones. DFT computations and EPR experiments were conducted to gain further mechanistic insight into the reaction pathways.

Keywords: copper · cyclization · density functional calculations · homogeneous catalysis · oxidation · rearrangement

Introduction

Functionalized cyclopentenone derivatives are useful building blocks for the preparation of biologically active molecules. The Nazarov cyclization and its variations are becoming a highly versatile set of strategies for the efficient, stereoselective synthesis of these compounds.[1] Specifically, the recent development of several methods involving capture of the oxyallyl cation intermediate by either a nucleophile[2] or through Wagner–Meerwein rearrangement[3,4] has broadened the array of cyclopentenone compounds that can be prepared by using the Nazarov cyclization.

In recent studies, we have synthesized 2,4,5-trisubstituted cyclopentenones with adjacent quaternary carbon centers in high chemo- and stereospecificity by using the Nazarov cyclization/Wagner–Meerwein rearrangement.[3c–d] For example, cyclopentenone **2** was obtained in 80% yield from **1** after 4π-electrocyclization followed by two consecutive [1,2]-phenyl shifts (Scheme 1). The cyclization of mixtures of *E* and *Z* isomers of alkylidene β-ketoesters is stereoconvergent: *E*/*Z* isomerization occurs readily, and only the *Z* isomer cyclizes.[5] We demonstrated that the chemoselectivity of the [1,2]-suprafacial migration was dependent upon not only migratory aptitude, but also on the steric profile of both the migrating group of the substrate and the promoter.[3b–d] Furthermore, we found that migratory aptitudes could be assessed with a high level of accuracy using DFT calculations.[3d]



Scheme 1. Copper(II)-mediated cyclization of 1,4-dien-3-one **1**.

Herein, we report the discovery and elucidation of a one-pot Nazarov cyclization/Wagner–Meerwein rearrangement/oxidation sequence that provides access to 4-alkylidene cyclopentenones.

Results and Discussion

We have shown that Nazarov cyclization substrates bearing electron-donating groups (EDG) at C5 (e.g., **1** in Scheme 1) undergo cyclization/rearrangement sequences with high efficiency and selectivity. However, Nazarov cyclization of substrates bearing electron-withdrawing groups (EWG) at C5 have never proceeded as smoothly as their electron-rich counterparts.[5] Therefore, extending the cyclization/rearrangement sequence to a substrate like **6** (C5 = 4-nitrophenyl; see Scheme 2) was expected to be a challenge. An assessment of the cyclization/rearrangement reaction pathways available to substrate **6** was conducted using DFT calculations, with Cu^{2+} as promoter.[6–8] In our previous experimental and computational work on related cyclizations, we

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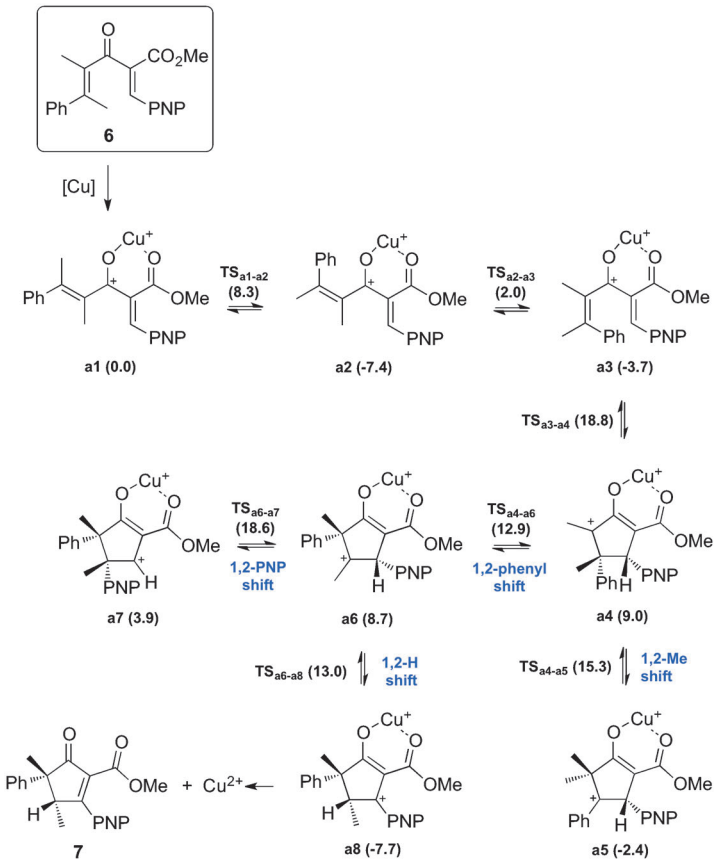


Scheme 2. Computed intermediates for the Cu^{2+}-mediated cyclization of 1,4-dien-3-one **6** (UB3LYP/6-31G**//PCM correction, kcal mol^{-1}). PNP = 4-nitrophenyl.

found that the barrier heights corresponding to the diastereomutation of the C1–C2 double bond ranged from 12 to 25 kcal mol^{-1}, and we found that substrates with stronger electron-donating groups at C5 isomerized more slowly.[3d] This trend was attributed to an increase in the C1–C2 bond order as a function of the greater electron-releasing ability of the substituent at C5. If this hypothesis is correct, the barrier for diastereomutation at C1–C2 should decrease if C5 = 4-nitrophenyl. This supposition is corroborated by DFT computations, which predict a free energy of activation of 8.3 kcal mol^{-1} for the formation of **a2** from **a1** (Scheme 2). Then, complex **a2** is expected to isomerize into the Nazarov-ready conformer **a3** though the low-lying transition state **TS$_{a2-a3}$**. As in our previous studies, the barrier for 4π-electrocyclization leading to **a4** should be about 19 kcal mol^{-1}, and the cyclization should be endergonic. Not surprisingly, since the phenyl group has a higher migratory aptitude than a methyl group, the rearrangement of **a4** to **a6** is expected. From **a6**, the PNP shift to **a7** was found to require a higher free energy of activation than the H-shift to **a8**. Overall, **a8** should be favored both kinetically and thermodynamically. Dissociation of Cu^{2+} from this intermediate should then lead to **7**. This projected outcome is interesting when compared with the experimental result in Scheme 1.

However, when the cyclization/rearrangement of **6** was performed, an unexpected result was obtained. By subjecting **6** to the usual reaction conditions (one equivalent of $[(MeCN)_5Cu(SbF_6)_2]$ in dichloromethane heated at reflux in an open vessel), a complete inversion of the C1–C2 bond was observed, but no cyclization occurred. When compound **6′** was subjected to the same promoter, in 1,2-dichloroethane instead of dichloromethane, cyclization provided 4-methylidene cyclopentenone **8** (87%). This reaction behavior was consistent with the DFT calculations, in that the C1–C2 bond isomerized and the 4-nitrophenyl group did not migrate, but compound **6** also exhibits new reactivity leading to a different type of product (**8** rather than **7**), through some kind of oxidative process [Eq. (1)].

When we conducted further studies to test whether the oxidation pathway could be generalized, we found that cyclopentenones with exocyclic double bonds could be obtained in good yields from several other substrates with electron-withdrawing aromatic substituents (62–92% yield; Table 1). The isomerization of the C1–C2 olefin of **9** was also observed by ^{1}H NMR spectroscopy during its conversion to **10** (Table 1, entry 1). Interestingly, substrates **13** and **15** were transformed into products **14** and **16** exclusively (Table 1, entries 3 and 4). The stereochemistry of compound **14** was assigned by NOE analysis. The result obtained with substrate **17** was initially surprising (Table 1, Entry 5). We did not observe a second [1,2]-phenyl shift, as might be expected based on the result shown in Scheme 1. The result may be understood by comparing intermediates **4** and **4′** (Scheme 3). The C5 to C1 phenyl shift is probably hindered by the C2 phenyl in **4′**, whereas in **4**, the C2 phenyl is not in a position to impede the second [1,2]-phenyl shift. Lastly, when substrate **19** was heated at reflux with one equivalent of [*t*BuBox-Cu(SbF$_6$)$_2$] in an open vessel, the oxidation product cyclopentenone **20** was obtained (Table 1, entry 6). In this case, the use of $[(MeCN)_5Cu(SbF_6)_2]$ as promoter led to the exclusive formation of the classical Nazarov cycloadduct.

Unfortunately, subjection of substrate **21** (bearing an isopropyl group at C1) led to a complex mixture with no trace of **22** detected [Eq. (2)]. It is possible that the steric bulk of the isopropyl group prevents oxidation, or that the increased

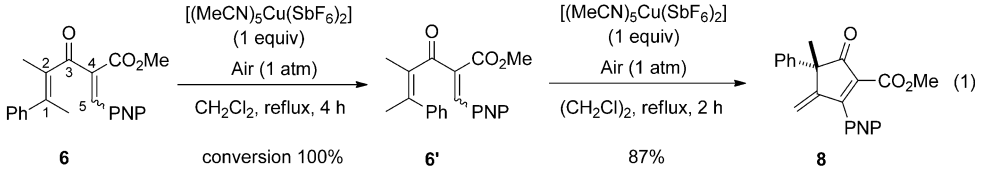
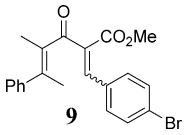
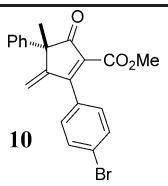
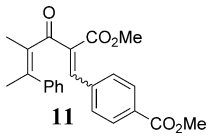
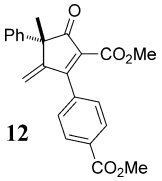
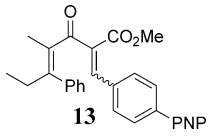
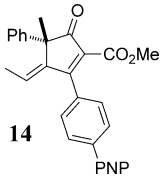
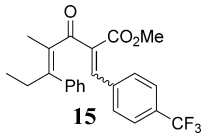
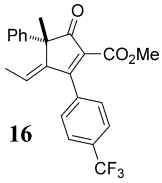
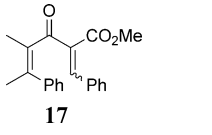
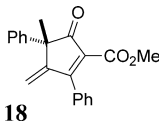
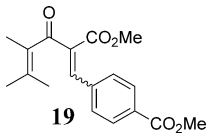
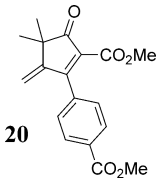
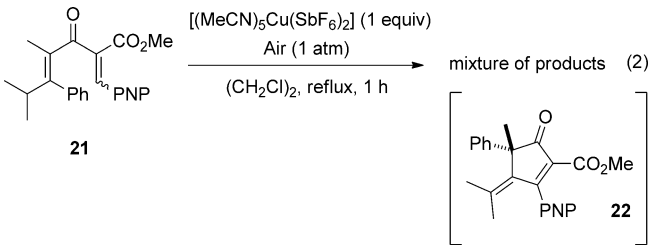


Table 1. Cu^{II}-promoted Nazarov cyclization/Wagner–Meerwein rearrangement/oxidation sequence.

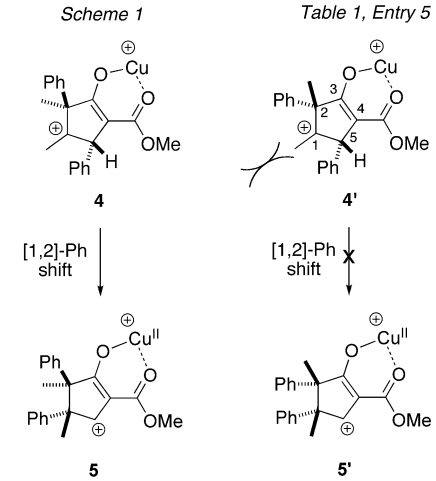
Entry	Substrate	T [°C]	t [h]	Product	Yield [%]
1	 **9**	85	4	 **10**	69[a]
2	 **11**	85	2	 **12**	92[a]
3	 **13**	85	3	 **14**	79[a]
4	 **15**	85	2	 **16**	80[a]
5	 **17**	85	4	 **18**	85[a]
6	 **19**	85	4	 **20**	62[b]

[a] Reaction conditions: substrate in $(CH_2Cl)_2$ (0.03 M) in the presence of one equivalent of $[(MeCN)_5Cu(SbF_6)_2]$ at the indicated temperature in an open vessel. [b] Reaction conditions: substrate in $(CH_2Cl)_2$ (0.03 M) in the presence of one equivalent of [*t*BuBox-$Cu(SbF_6)_2$] at the indicated temperature in an open vessel. PNP = 4-nitrophenyl.



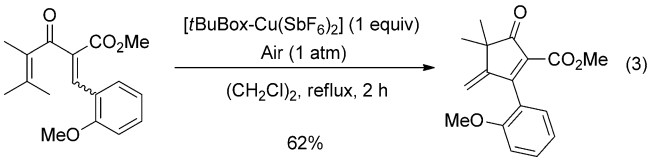
branching allows alternative rearrangement pathways to compete with the oxidation.

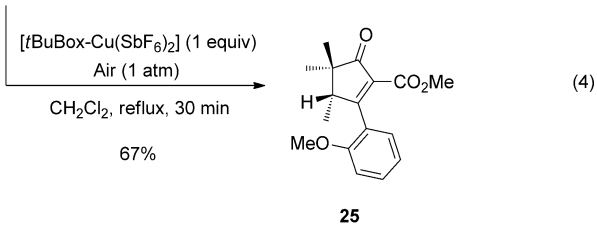
Further experimentation revealed that this reaction pathway is not limited to acyclic substrates bearing an electron-withdrawing group at C5. For example, substrate **23** also furnished the corresponding oxidized product **24** in good yield



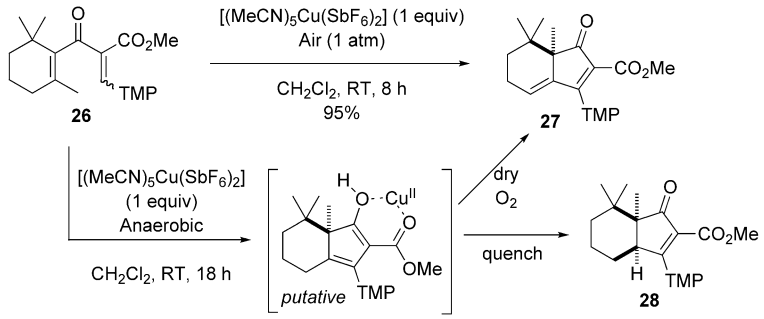
Scheme 3.

[Eq. (3)]. Elevated reaction temperatures were required for this reaction. For example, in dichloromethane heated at reflux, the formation of compound **24** was not observed and compound **25** was obtained as the major product [Eq. (4)].





The cyclization of compound **26**, initially expected to produce a spirocyclic product,[3a–b] also terminated with an oxidation. Ring contraction is probably blocked by the large *gem*-dimethyl group. Cyclization/oxidation was complete in 8 h, providing **27** in 95% yield (Scheme 4). The structure of **27** was confirmed by X-ray crystallography (Figure 1). When the reaction was run under rigorously anaerobic conditions, and an aliquot was removed and quenched after a reaction time of 18 h, compound **28** was the only product detected.[9] However, when dry O_2 (g) was added to this reaction mixture, formation of the oxidized product **27** was observed. This result indicates that oxygen is essential for the conversion of **26** to **27**, and is responsible for the oxidation of a reactive intermediate. The putative intermediate structure is



Scheme 4. Cyclization/rearrangement of **26** under aerobic and anaerobic conditions.

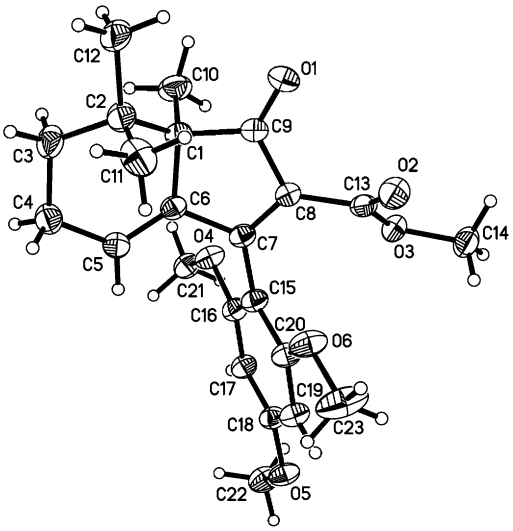


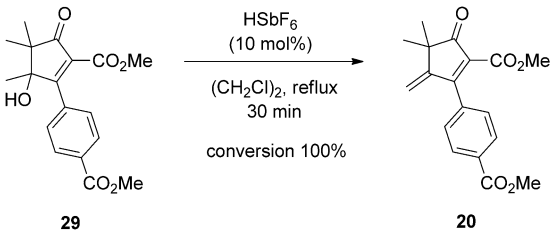
Figure 1. ORTEP drawing of **27**.

shown in Scheme 4 (see below for a detailed discussion of the mechanism).

We have been able to gain some insight into the mechanism of the reaction through further experimentation with substrates **19** and **26**. Interestingly, if the reaction of substrate **19** is stopped after 2 h [Eq. (5)], two products are isolated: 4-methylidenecyclopentenone **20** (36%), and γ-hydroxycyclopentenone **29** (22%).

We found that dehydration of **29** can be triggered by a catalytic amount of $HSbF_6$ (10 mol%), with quantitative production of **20** after 30 min [Eq. (6)]. This suggests that tertiary alcohol intermediates undergo efficient dehydration to the product 4-alkylidene cyclopentenones upon exposure to adventitious Brønsted acid in the reaction mixture.

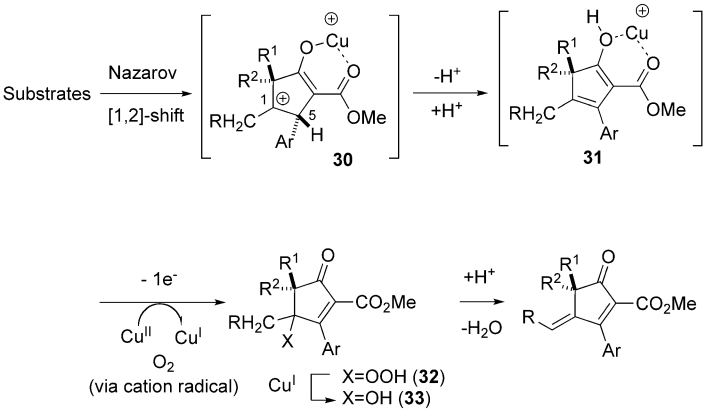
A mechanistic hypothesis that accounts for the oxidation of the various substrates is presented in Scheme 5. The dienone substrates undergo the usual 4π-electrocyclization followed by [1,2]-alkyl or -aryl shift to produce cationic intermediate **30**. Then, loss of the acidic C5 proton occurs to give the extended enol **31**, which suffers oxidation by copper(II) to give an enol cation radical.[10] Interception of the radical by dioxygen produces the unstable hydroperoxide **32**,[11] which is



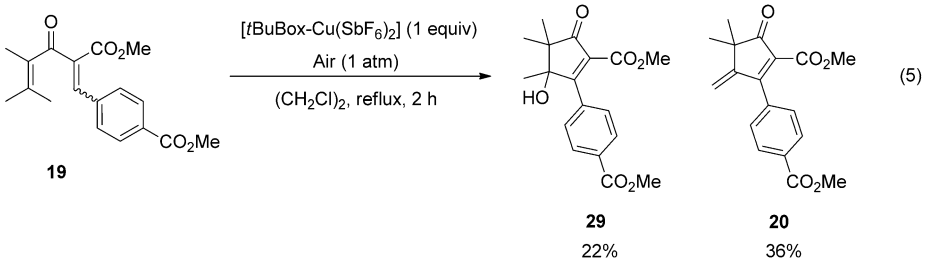
(6)

readily reduced to the alcohol **33** through a Fenton-type fragmentation.[12] Finally, the acid-promoted dehydration generates the 4-alkylidene cyclopentenones; see [Eq. (6)].

To further investigate this proposed mechanism, we conducted electron paramagnetic resonance (EPR) studies. The anaerobic reaction of **26** with the active copper catalyst was performed to determine whether reduction of Cu^{II} (d^9, $S=1/2$, EPR active) to Cu^{I} (d^{10}, $S=0$, EPR silent) occurred



Scheme 5. Cyclization/rearrangement/oxidation sequence.



(5)

during the reaction.[13] Addition of one equivalent of substrate to $[(MeCN)_5Cu(SbF_6)_2]$ in dichloromethane ($t=0$ h sample) led to the immediate formation of an axial Cu^{II} site with $g_{ll}=2.365$, $g\perp=2.076$ ($A_{ll}=144\times10^{-4}\,cm^{-1}$, $A\perp=0\,cm^{-1}$). A

small (≈1.5%) additional isotropic $g=2.003$ Cu^{II} signal is also present, possibly indicating a copper species that is not complexed with the substrate. Importantly, the reduction of the Cu^{II} can be quantified using the integrated area of the Cu^{II} EPR signal, which directly corresponds to the amount of Cu^{II} in solution. Taking the initial $t=0$ h reaction point as purely Cu^{II}, the amount of Cu^{II} remaining as a function of reaction time is found to be 36% of the initial $t=0$ h amount after 24 h (see the Supporting Information, Figure S2) and 5% after 2 days (Figure 2). No additional reduction in signal occurred between 48 and 72 h of reaction time, indicating that the reaction has effectively reached completion. Thus, the EPR results are consistent with a mechanistic hypothesis involving the reduction of Cu^{II} to Cu^{I}. Lastly, the exposure of the reduced sample to air leads to partial re-oxidation of the Cu^{I} to Cu^{II} (see the Supporting Information, Figure S3). No substrate radical could clearly be identified in these measurements, possibly because the spectrum is complicated by the broad copper signals in the $g=2$ region. It is also possible that the radical is rapidly consumed in a side reaction process that occurs in the absence of oxygen.

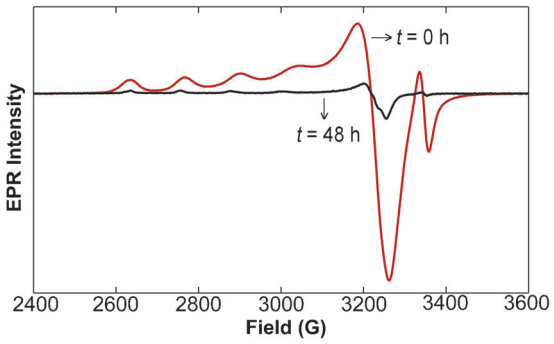
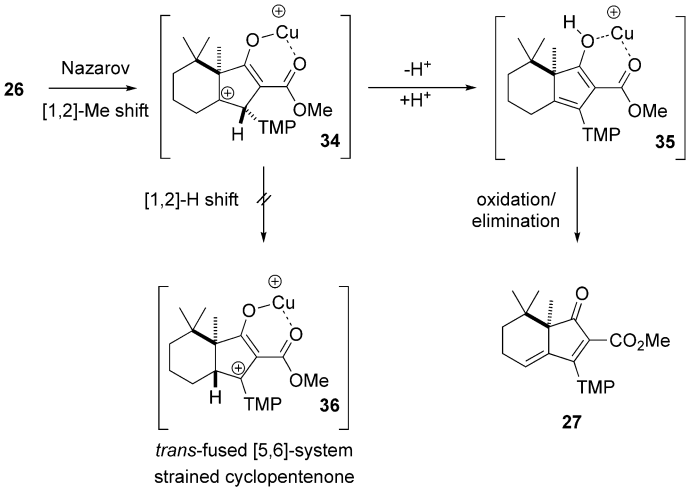


Figure 2. Electron paramagnetic resonance spectra of the reaction of **26** with copper(II) at different reaction time intervals: $t=0$ h and $t=48$ h.

In previous work with related substrates,[3] we found that stereochemical outcomes were consistent with a suprafacial [1,2]-hydride shift (from C5 to C1). In these studies, the mechanism presented in Scheme 3 is proposed instead, to account for the facile oxidation. In contrast to our earlier studies, cation **30** (Ar = EWG) will possess a more acidic C5 proton, and the C5 to C1 hydride shift would produce a less stable C5 cation. Thus, proton elimination might be expected to compete with [1,2]-hydride shift for these substrates. However, we cannot rule out C5–C1 hydride shift, with subsequent formation of enol species **31**.

Since oxidation and/or epimerization at C1 has not been observed during our earlier Nazarov cyclization/Wagner–Meerwein rearrangement studies,[3] the outcome of the cyclization rearrangement of substrates **23** and **26** (which contain electron-rich aryl groups) was surprising. We suggest that the formation of enols of type **31** is especially favorable in these systems, and that these enol species are highly susceptible to oxidation. For substrate **23**, elevated temperatures may facilitate enol formation ([Eq. (3)] vs. [Eq. (4)]). In compound **26**, the projected C5–C1 hydride shift would generate a highly strained [5,6]-*trans* fused-ring system (Scheme 6). In this case, it is plausible that elimination of the C5 proton is more favorable than a hydride shift, which would produce enol **35** and subsequently, oxidation to give **27**.



Scheme 6. Rationale for the unexpected oxidation of compound **26**.

Conclusion

We have reported an efficient protocol for the synthesis of 4-alkylidene cyclopentenones by using a copper(II) complex as promoter. The substrate isomerization, cyclization, and chemoselectivity of the subsequent migration were accurately anticipated by using DFT. The mechanistic hypothesis proposed for the final oxidation is consistent with EPR data. Further experimentation focused on understanding and characterizing the unique reactivity of the copper(II) complex is ongoing.

Experimental Section

General procedure for the cyclization: The copper complex [L-Cu-$(SbF_6)_2$] (1 equiv) was added to a stirred solution of α-alkylidene β-keto esters in CH_2Cl_2 or $(CH_2Cl)_2$ (0.03 M) under air. The reaction mixture was stirred at room temperature or heated at reflux until completion of the reaction and then quenched with aqueous NH_4OH and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. After removal of the solvents under reduced pressure, the crude product was purified by flash column chromatography by using different gradients of pentane and ethyl acetate to obtain the pure desired products.

Compound 8: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.37$ (d, $J=8.4$ Hz, 2H), 7.59 (d, $J=8.4$ Hz, 2H), 7.38–7.26 (m, 5H), 5.57 (s, 1H), 5.47 (s, 1H), 3.71 (s, 3H), 1.74 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.0$, 167.9, 154.1, 148.6, 140.0, 138.4, 131.4, 129.3, 128.8, 127.5, 126.4, 123.6, 119.5, 54.9, 52.4, 22.9; IR (neat): $\tilde{\nu}=2947$, 1713, 1574, 1520, 1493,

1435, 1346, 1261, 1204 cm^{-1}; HRMS (EI+): m/z calcd for $C_{21}H_{18}NO_5$: 364.1185 [$M+H^+$]; found: 364.1189.

Compound 10: Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.63$ (d, $J=8.4$ Hz, 2H), 7.37–7.26 (m, 7H), 5.56 (s, 1H), 5.52 (s, 1H), 3.72 (s, 3H), 1.71 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.5$, 168.5, 163.5, 154.2, 140.4, 131.7, 130.9, 130.5, 129.9, 128.7, 127.3, 126.5, 124.5, 119.0, 54.8, 52.3, 22.8 ppm; IR (neat): $\tilde{\nu}=2928$, 1734, 1721, 1601, 1489, 1435, 1362, 1269, 1231, 1207, 1010 cm^{-1}; HRMS (EI+): m/z calcd for $C_{21}H_{18}O_3Br$: 397.0439 [$M+H^+$]; found: 397.0438.

Compound 12: Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.16$ (d, $J=8.4$ Hz, 2H), 7.48 (d, $J=8.4$ Hz, 2H), 7.40–7.28 (m, 5H), 5.53 (s, 2H), 3.96 (s, 3H), 3.68 (s, 3H), 1.73 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.4$, 168.9, 166.4, 163.3, 154.2, 140.3, 136.3, 131.4, 131.1, 129.6, 128.7, 128.3, 127.3, 126.5, 119.2, 54.8, 52.4, 52.2, 22.8 ppm; IR (neat): $\tilde{\nu}=2951$, 1720, 1589, 1435, 1362, 1277, 1230, 1107 cm^{-1}; HRMS (EI+): m/z calcd for $C_{23}H_{20}O_5$: 376.1311 [$M+H^+$]; found: 376.1317.

Compound 14: Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.36$ (d, $J=8.8$ Hz, 2H), 7.55 (d, $J=8.7$ Hz, 2H), 7.37–7.25 (m, 5H), 5.89 (q, $J=7.5$ Hz, 1H), 3.66 (s, 3H), 1.80 (s, 3H), 1.61 ppm (d, $J=7.5$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.5$, 171.3, 163.1, 148.3, 147.4, 139.5, 138.9, 134.9, 129.1, 128.8, 128.5, 127.3, 126.2, 123.5, 54.2, 52.2, 21.3, 15.9 ppm; IR (neat): $\tilde{\nu}=2947$, 1735, 1713, 1574, 1520, 1493, 1435, 1346, 1261, 1204, 1177 cm^{-1}; HRMS (EI+): m/z calcd for $C_{22}H_{20}NO_5$: 378.1341 [$M+H^+$]; found: 378.1345.

Compound 16: Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.76$ (d, $J=8.0$ Hz, 2H), 7.49 (d, $J=7.8$ Hz, 2H), 7.37–7.31 (m, 5H), 5.92 (q, $J=7.5$ Hz, 1H), 3.66 (s, 3H), 1.80 (s, 3H), 1.60 ppm (d, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.8$, 171.9, 163.3, 147.5, 139.2, 136.4, 134.5, 128.8, 128.5, 127.2, 126.3, 125.2, 54.1, 52.1, 21.3, 15.8 ppm; IR (neat): $\tilde{\nu}=2958$, 2924, 1705, 1589, 1570, 1435, 1319, 1261, 1203, 1165, 1122, 1065 cm^{-1}; HRMS (EI+): m/z calcd for $C_{23}H_{19}F_3O_3$: 400.1286 [$M+H^+$]; found: 400.1290.

Compound 18: Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.50$–7.26 (m, 10H), 5.61 (s, 1H), 5.51 (s, 1H), 3.69 (s, 3H), 1.72 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.7$, 169.6, 163.7, 154.4, 140.6, 131.7, 130.9, 130.0, 128.6, 128.4, 128.3, 127.2, 126.5, 119.0, 54.7, 52.1, 22.8 ppm; IR (neat): $\tilde{\nu}=3059$, 2974, 1736, 1713, 1605, 1574, 1492, 1435, 1362, 1273, 1230, 1203, 1176 cm^{-1}; HRMS (EI+): m/z calcd for $C_{21}H_{19}O_3$: 319.1334 [$M+H^+$]; found: 319.1335.

Compound 20: Pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.13$ (d, $J=8.0$ Hz, 2H), 7.41 (d, $J=8.1$ Hz, 2H), 5.54 (s, 1H), 5.34 (s, 1H), 3.95 (s, 3H), 3.69 (s, 3H), 1.30 ppm (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 204.2, 167.4, 166.4, 154.8, 136.5, 131.2, 131.0, 129.5, 128.3, 116.2, 52.4, 52.2, 46.7, 23.9 ppm, one carbon missed due to overlapping; IR (neat): $\tilde{\nu}=2955$, 2928, 1717, 1620, 1589, 1435, 1408, 1362, 1277, 1234, 1192, 1150, 1107, 1007 cm^{-1}; HRMS (EI+): m/z calcd for $C_{18}H_{18}O_5$: 314.1154 [$M+H^+$]; found: 314.1447.

Compound 24: Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.42$ (dt, $J=8.3$, 1.7 Hz, 1H), 7.20 (dd, $J=7.5$, 1.7 Hz, 1H), 7.04 (t, $J=7.5$ Hz, 1H), 6.96 (d, $J=8.4$ Hz), 5.47 (s, 1H), 5.36 (s, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 1.28 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=204.7$, 166.1, 164.0, 156.3, 155.0, 131.0, 130.7, 129.5, 121.1, 120.1, 115.1, 110.9, 55.3, 51.7, 46.4, 23.9 ppm; IR (neat): $\tilde{\nu}=2947$, 2928, 1720, 1615, 1573, 1440, 1356, 1280, 1230, 1203, 1126 cm^{-1}; HRMS (ES+): m/z calcd for $C_{17}H_{19}O_4$: 287.1283 [$M+H^+$]; found: 287.1289.

Compound 25: Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.39$ (ddd, $J=8.4$, 7.5, 1.7 Hz, 1H), 7.19 (dd, $J=7.6$, 1.7 Hz, 1H), 7.01 (dt, $J=7.5$, 1.0 Hz, 1H), 6.94 (d, $J=8.4$ Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.19 (q, $J=7.4$ Hz, 1H), 1.24 (s, 3H), 1.10 (s, 3H), 0.96 ppm (d, $J=7.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=208.0$, 177.4, 164.4, 156.3, 131.2, 131.0, 128.4, 123.4, 120.5, 111.0, 55.3, 51.7, 48.8, 47.7, 25.9, 20.6, 14.1 ppm; IR (neat): $\tilde{\nu}=2947$, 2924, 1740, 1697, 1612, 1510, 1462, 1346, 1288, 1258, 1230, 1203, 1126, 1022, 995 cm^{-1}; HRMS (EI+): m/z calcd for $C_{17}H_{20}O_4$: 288.1368 [$M+H^+$]; found: 288.1361.

Compound 27: Yellow wax. ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.16$ (s, 1H), 6.15 (s, 1H), 5.70 (t, $J=3.8$ Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.67 (s, 6H), 2.29–2.25 (m, 1H), 2.20–2.15 (m, 1H), 1.86–1.80 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.26–1.20 (m, 1H), 0.78 ppm (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=205.5$, 167.6, 164.1, 162.5, 158.1, 158.0, 144.4, 128.6, 126.5, 103.9, 91.1, 90.8, 56.0, 55.8, 55.4, 52.1, 51.4, 34.2, 32.8, 24.7, 24.1, 22.1, 22.0 ppm; IR (neat): $\tilde{\nu}=2943$, 2875, 2841, 1736, 1701, 1609, 1586, 1458, 1515, 1366, 1335, 1227, 1204, 1127 cm^{-1}; HRMS (EI+): m/z calcd for $C_{23}H_{28}O_6$: 400.1886 [$M+H^+$]; found: 400.1892.

Compound 29: Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.10$ (d, $J=8.1$ Hz, 2H), 7.53 (d, $J=8.1$ Hz, 2H), 3.95 (s, 3H), 3.67 (s, 3H), 1.79 (s, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.19 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=204.6$, 174.1, 166.4, 163.6, 136.8, 131.2 (2 C), 129.4, 128.1, 81.4, 53.3, 52.4, 52.3, 24.3. 21.8, 20.6 ppm; IR (neat): $\tilde{\nu}=3476$, 2951, 2932, 1721, 1636, 1605, 1435, 1335, 1277, 1231, 1161, 1107, 1014, 995 cm^{-1}; HRMS (EI+): m/z calcd for $C_{18}H_{20}O_6$: 332.1560 [$M+H^+$]; found: 332.1550.

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