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Base-Induced Transformation of 2-Acyl-3-alkyl-2*H*-azirines to Oxazoles: Involvement of Deprotonation-Initiated Pathways

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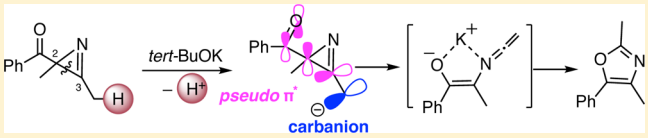
Supporting Information

ABSTRACT: An experimental study of base-induced transformation reaction of 2-acyl-3-alkyl-2*H*-azirines to oxazoles indicated that a deprotonation-initiated mechanism is involved, in addition to nucleophilic addition to the imine functionality. Calculations suggested the participation of a ketenimine (ethenimine) intermediate generated by azirine ring opening of the carbanion intermediate formed by α-deprotonation of 2*H*-azirine. The ketenimine intermediate possessing methyl substituents at C(3) appears to be more stable than the tautomeric nitrile ylide which was proposed to be involved in photoinduced and pyrolysis reactions of 2-acyl-3-alkyl-2*H*-azirines to afford oxazoles. Thus, intermediacy of ketenimine is consistent with both experimental and computational results, at least under strongly basic reaction conditions.



INTRODUCTION

2*H*-Azirines are strained unsaturated heterocyclic compounds possessing a C═N double bond within a three-membered ring. The chemistry of 2*H*-azirines has thrived over the past few decades, and these compounds have been utilized for the construction of various heterocyclic compounds.[1,2] In particular, 2-acyl-3-alkyl-2*H*-azirines (**2a**) are key intermediates in the transformation of isoxazoles (**1a**) to oxazoles (**3a**),[3−5] and they can be directly transformed into oxazoles under photoirradiation (Figure 1a).[3] As shown in Figure 1b, the intermediacy of a nitrile ylide, formed through C−C bond cleavage, in this transformation was proposed on the basis of observation of the infrared (IR) spectra in an argon matrix at 15K.[6] On the other hand, a similar transformation of 2*H*-azirines has been reported to occur under basic conditions (Na_2CO_3 in MeOH).[3b] The mechanism of the latter transformation is shown in Figure 1c, involving nucleophilic addition of methanol to the azirine. However, this kind of transformation has been little studied, in marked contrast to the corresponding photochemical reactions, and the reaction is seldom utilized.[3b,7]

We are interested in the reactivity of 2-acyl-3-alkyl-2*H*-azirines under basic conditions, in view of the similarity of the (pseudo)-π-isolobal properties of 2*H*-azirine and nitrile functionalities (Figure 2 and Figure S1).[8] Although there is limited experimental support, the previously proposed reaction mechanism for the base-induced transformation from **2a** to **3a** seems plausible, being consistent with the high reactivity of azirines toward nucleophiles (e.g., Neber rearrangement).[2a,9] However, the feasibility of deprotonation of 2*H*-azirines to afford ketenimines (ethenimines) (Figure 1d, **8a**) remains unclear, though it is a commonly observed transformation for nitrile compounds.[10] In the present study, we examined whether or not the deprotonation-initiated reaction of 2-acyl-3-alkyl-2*H*-azirines can lead to the formation of oxazoles. DFT calculations were consistent with the formation of ketenimine intermediates after deprotonation of the azirines. These results throw new light on the reactivities of 2-acyl-3-alkyl-2*H*-azirines.

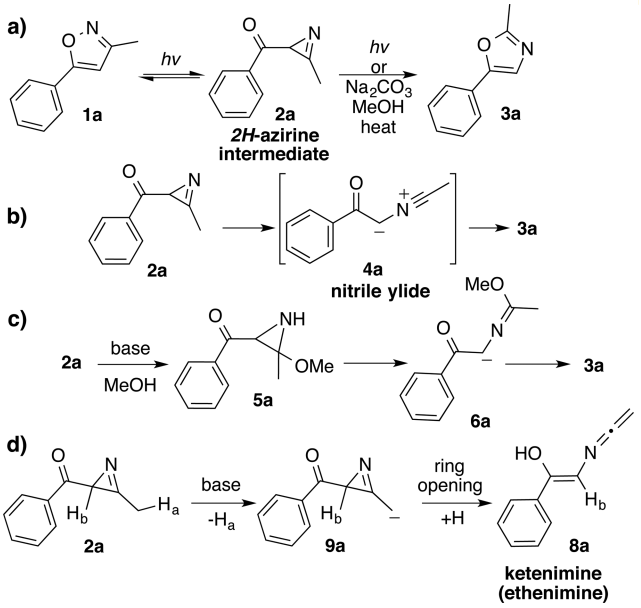


Figure 1. Transformations of azirines. (a) Previously reported transformation from isoxazole **1a** and azirine **2a** to oxazole **3a**. (b) Mechanism of photoirradiation-initiated transformation via the nitrile ylide intermediate. (c) Mechanism of base-initiated transformation from **2a** to **3a** proposed by Singh et al.[1] (d) Plausible deprotonation reaction of **2a** under basic conditions. Two acidic protons (H_a and H_b) are shown.

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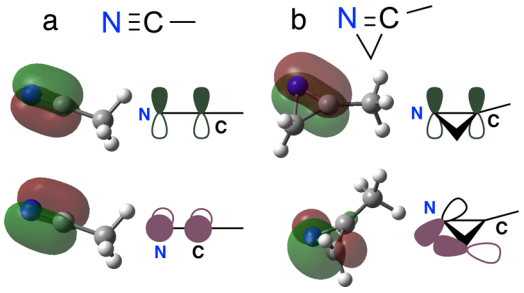


Figure 2. Similarity of the (pseudo)-π-isolobal properties of 2*H*-azirine and nitrile functionalities. Valence bond (VB) models of nitrile (a) and 2*H*-azirine (b). See also Figure S1 to view the similarity of vacant orbitals.

RESULTS AND DISCUSSION

Influence of Bases and Nucleophiles on the Reaction.

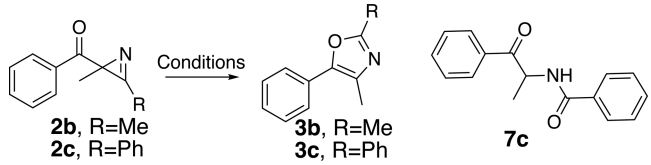
To distinguish between the addition-initiated reaction mechanism (Figure 1c) and the deprotonation-initiated reaction mechanism (Figure 1d), we first examined the influence of nucleophiles on the reaction (Table 1).

Compounds **2b** and **2c** were chosen for the study to avoid possible side reactions caused by deprotonation of another acidic proton(s) (H_b at the α position of the ketone, Figure 1d and Figure S2). It was found that the reaction of **2b** readily occurred at 20 °C in the presence of K_2CO_3 in MeOH, giving the oxazole **3b** in good yield (76%) (Table 1, entry 1) (see also Table S1). A similar reaction proceeded smoothly for **2c** (entry 2). Because the deprotonation mechanism (Figure 1d) is not available for **2c**, these results (entries 1 and 2) suggest that the previously proposed addition mechanism (Figure 1c) may be reasonable. When *tert*-BuOK was employed as a base in a nonpolar solvent, toluene (entry 3), it was found that the reaction of **2b** still proceeded in good yield (85%). In the quenching process, acetic acid was added before aqueous work up to avoid hydrolysis of any unreacted starting materials, which also improved the yield (see footnotes of Table 1 and Table S1). This quenching procedure was also applied to the KH conditions (vide infra). The half-life ($t_{1/2}$) of the reaction with *tert*-BuOK (entry 3), based on the consumption of **2b**, was less than 30 s, even though *tert*-BuOK is poorly nucleophilic. In contrast, the reaction of **2c** with *tert*-BuOK was much slower and afforded **3c** in only 10% yield, together with **2c** (recovery, 19%) and open-chain **7c** (41%), even after 1 h (entry 4). The generation of **7c** is attributable to the nucleophilic addition reaction of *tert*-BuOK[11] to the C=N double bond (Scheme S1). This clear difference in the reactivities of **2b** and **2c** is indicative of the involvement of a different mechanism in the *tert*-BuOK-induced transformation of **2b** to **3b**. Furthermore, in the reaction using KH as a base in THF,[12] **3b** was obtained as a major product (64% yield) from **2b** (entry 5), while only recovered 2*H*-azirine was obtained in the case of **2c** (entry 6). Therefore, these results suggest that the presence of a nucleophile is not necessary for the transformation of **2b** to **3b**, which possesses an acidic H, whereas the nucleophile seems essential for the transformation from **2c** to **3c**. Thus, we propose that an alternative mechanism, probably involving deprotonation, operates in the transformation of **2b**, especially in the presence of non-nucleophilic bases, *tert*-BuOK (entry 3) and KH (entry 5). A less efficient reaction was also observed when **2b** was treated with a sodium base (*tert*-BuONa and NaH, entries 7 and 8) compared to the reactions using a potassium base (*tert*-BuOK and KH, entries 3 and 5).

Isotope labeling experiments suggested that deprotonation of H_a of **2b** occurs in the *tert*-BuOK-initiated reactions with *tert*-BuOK/*tert*-BuOD (Scheme 1a (**1**)) because deuterium was incorporated at the 2-methyl group but not at the 5-methyl group, in the product **3b** (Scheme 1a). In the *tert*-BuOK-initiated reactions, H-D exchange does not occur upon quenching the reaction with AcOD. Furthermore, treatment of the isolated product **3b** with *tert*-BuOK/*tert*-BuOD did not afford deuterated **3b**. The H-D exchange behaviors of **2b** and **3b** in the presence of K_2CO_3/MeOD were similar to those in *tert*-BuOK/*tert*-BuOD. Multiple deuteration of the 2-methyl protons of **3b** was also observed in K_2CO_3/MeOD (Scheme 1a, **2**), which may suggest a deprotonation−protonation equilibrium during the reaction.

These experimental results inspired us to consider an alternative deprotonation-initiated mechanism, as shown in Scheme 1b. After deprotonation to afford anion **9b**,[13] cleavage of the C−C bond of the azirine ring could occur through a Grob-type fragmentation (**9b** → **8b-K**), in a similar manner

Table 1. Study of Reaction Conditions for the Transformation from Azirine 2b−c to Oxazole 3b−c[a,b]



entry	substrate	base	solvent	time	oxazole 3[c]	recovered 2[c]
1[d]	**2b**	K_2CO_3	MeOH	30 min	76% (82%)[e]	
2[d]	**2c**	K_2CO_3	MeOH	30 min	67% (71%)[e]	
3	**2b**	*tert*-BuOK	toluene	1 min	85% (89%)[e]	
4[f]	**2c**	*tert*-BuOK	toluene	1 h	10% (17%)[e]	19% (22%)[e]
5	**2b**	KH	THF	30 min	64% (72%)[e]	
6	**2c**	KH	THF	1 h		77% (80%)[e]
7	**2b**	*tert*-BuONa	toluene	1 min	− (7%)[e]	69% (76%)[e]
8	**2b**	NaH	THF	2 h	25% (42%)[e]	− (22%)[e]

[a]All reactions were performed in 0.3 mmol scale in 3.0 mL of solvent at 20 °C. [b]Quenching: acetic acid before aqueous work up. [c]Isolated yields. [d]Quenching: filtration through a pad of Celite with MeOH. [e]Yields determined by ^{1}H NMR with 1,2-dichloroethane as internal standard are shown in parentheses. [f]**7c** was isolated in 41% yield.

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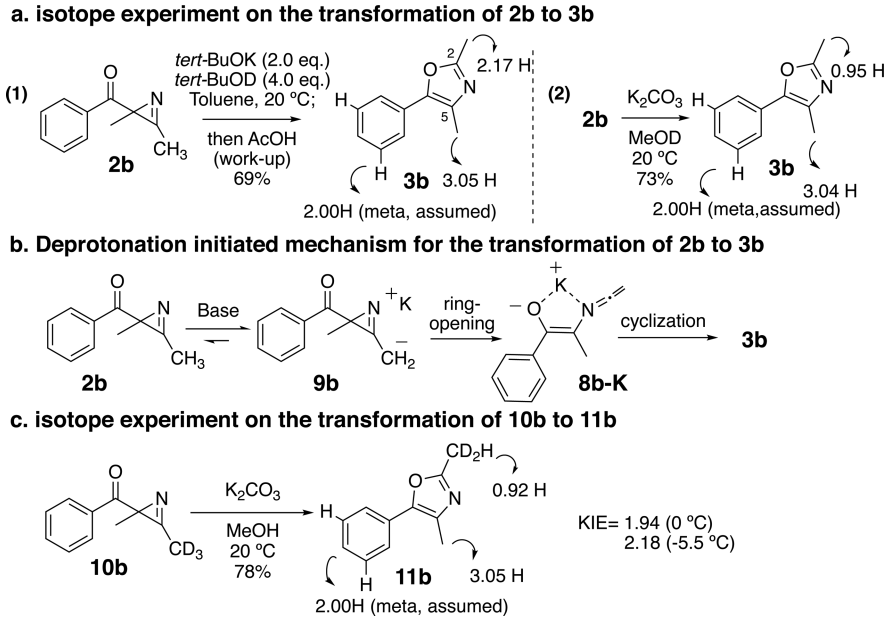
Scheme 1. Isotope Labeling Study of Base-Induced Transformation from 2b to 3b



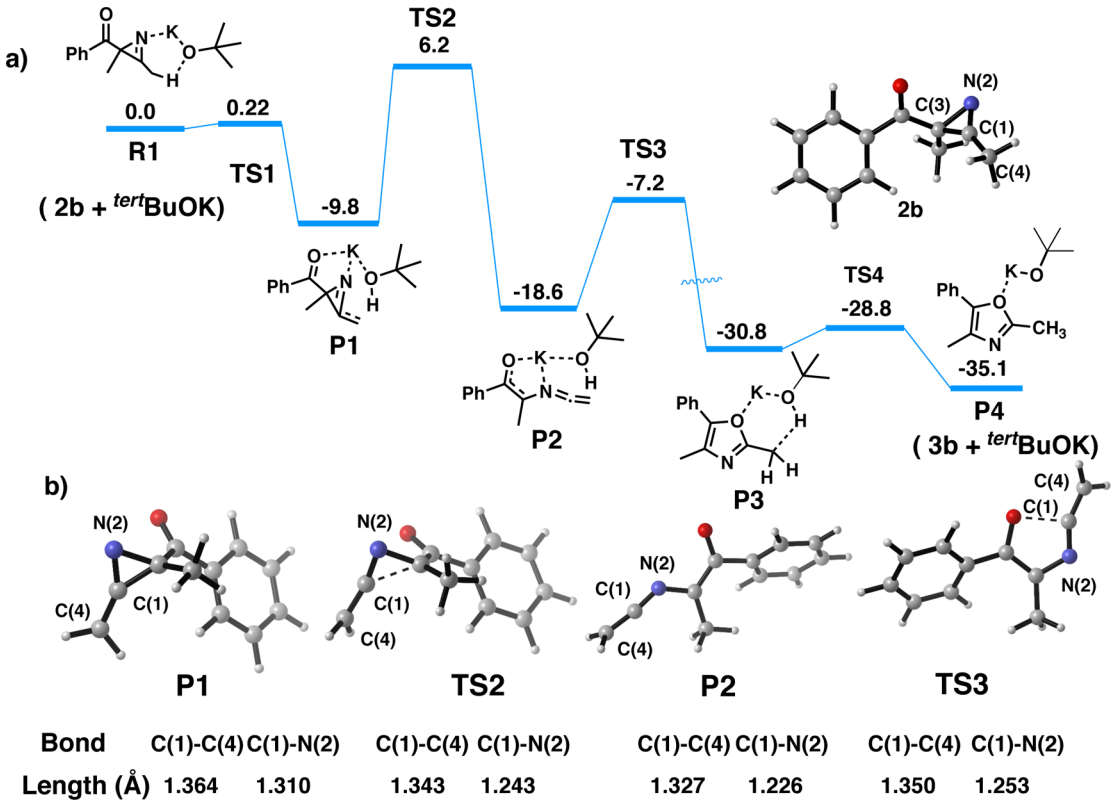


Figure 3. Energy diagram of the deprotonation-initiated pathway. (a) Free energy profile [ΔG in kcal·mol^{-1} at 298 K, M06-2X-D3/def2-TZVPP/CPCM//M06-2X/6-31+G(d,p)/CPCM] for the *tert*-BuOK-induced transformation of **2b** in toluene. (b) Geometry of the reactant (**P1**), transition state (**TS2**), and product (**P2**) for the ring-opening step and transition state (**TS3**) for the cyclization step; *tert*-BuOH and K^+ are removed for clarity.

to heterolytic cleavage of donor–acceptor cyclopropanes.[14] The cleavage can be explained by the high strain in the azirine ring[8,9] and the electron-withdrawing nature of the neighboring carbonyl group.[15] Cyclization of the resulting ketenimine intermediate (**8b**) would occur to give **3b** after protonation. When **10b** (D-labeled **2b**) was treated with K_2CO_3 in the MeOH solution, the reaction also afforded the deuterium-to-proton-exchanged H-labeled product **11b** (Scheme 1c). We measured the kinetic isotope effect (KIE) in MeOH solution and found that the KIEs of **2b** and **10b** in K_2CO_3/MeOH are 1.94 at 0 °C and 2.18 at −5.5 °C, based on the concentration changes of **2b** and **10b**. These KIEs are much larger than a steric KIE or a secondary KIE caused by the difference of bending frequency, and therefore, these results are consistent

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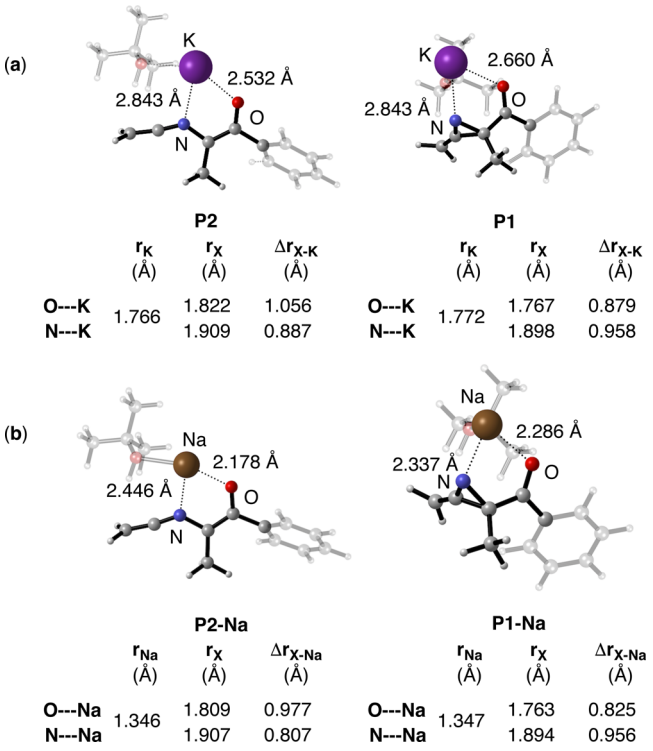
with the idea that the deprotonation reaction of **2b** can occur under the K_2CO_3/MeOH conditions. Therefore, both the addition-initiated mechanism (Figure 1c) and the deprotonation-initiated mechanism (Figure 1d) probably take part in the transformation of **2b** to **3b** in K_2CO_3/MeOH.

Computational Studies. To further explore the reaction mechanism, we embarked on a computational study of the reaction pathway from **2b** to **3b**,[16] using the reaction of **2b** with *tert*-BuOK (Table 1, entry 3) as a model. As shown in Figure 3a, the ring-opening reaction of **2b** occurs stepwise, and **2b** was found to be deprotonated without a significant activation barrier to give deprotonated **9b** (**R1** → **TS1** → **P1**).

The CH_2 group containing the C(4) atom in the resulting carbanion **9b** is planar, with a shorter C(4)−C(1) distance (1.364 Å, Figure 3b, **P1**) than the corresponding covalent radius (1.524 Å).[17] The Mayer bond orders[18] of the C(4)−C(1) bond and C(1)−N(2) bond are 1.39 and 1.38, respectively, suggesting delocalization of negative charge and therefore stabilization of **9b**. This is also in agreement with the results of nature population analysis (NPA),[19] which indicated that negative charge is distributed on both the C(4) and N(2) atoms in **P1** (C(4), −0.764; N(2), −0.634)). Computational study also confirmed the formation of ketenimine intermediate **8b** from deprotonated **9b** (**P1** → **TS2** → **P2**). This ring-opening step is the most energy-demanding step (16.0 kcal/mol) in the putative transformation. The C(1)−C(4) bond and C(1)−N(2) bonds both become shorter, and the reaction gives a slightly NCC angle-bent ketenimine (∠NCC = 172.9°). This angle and the bond length in the resulting ketenimine moiety are similar to reported values.[10] The ketenimines are good electrophiles,[10] and the intramolecular cyclization reaction proceeds with an energy barrier of 11.4 kcal/mol (**P2** → **TS3** → **P3**) to give the oxazolyl anion (**P3**), which is converted into oxazole after protonation (**P3** → **TS4** → **P4**).

2b exhibited greater reactivity in terms of yield and reaction rate when using a potassium base, *tert*-BuOK or KH, compared to the corresponding sodium base, *tert*-BuONa or NaH (Table 1 and also see Table S1). To evaluate the role of potassium ion (K^+) in addition to the difference in basicity, the properties of the corresponding Na-coordinated azirine anion (**P1−Na**) and ketenimine intermediate (**P2−Na**) were calculated (Figure 4). For the X−M interactions (X = O, N and M = K, Na), we calculated the mutual penetration distance ($\Delta r_{X\text{-}M}$) between atoms X and M.[20] The mutual penetration distance is defined as the difference between the summation of the nonbonded radii of two atoms, X (r_X) and M (r_M), and the corresponding bonded distance between atoms X and M ($r_{X\text{-}M}$), i.e., $\Delta r_{X\text{-}M} = r_X + r_M - r_{X\text{-}M}$. The nonbonded radius is defined as the closest distance of a nucleus to the charge density contour of 0.001 au. The larger the mutual penetration distance ($\Delta r_{X\text{-}M}$) is, the more in contact the two atoms are. For potassium ketenimine **P2** in which O and N interact with K^+, the mutual penetration $\Delta r_{X\text{-}K}$ values are 1.056 Å (X = O) and 0.887 Å (X = N), respectively. These values are larger than the corresponding values for Na^+ coordinated species **P2−Na** (0.977 Å for O−Na and 0.808 Å for N−Na). Similar trends are also observed in the product azirine anions **P1**(K^+) and **P1−Na**. Therefore, the K^+ ion can stabilize the azirine anion and ketenimine intermediates to a greater extent than the Na^+ ion, which is related to the efficiency of the reaction of **2b** under *tert*-BuOK and KH conditions.



	P2 r_K (Å)	P2 r_X (Å)	P2 $\Delta r_{X\text{-}K}$ (Å)	P1 r_K (Å)	P1 r_X (Å)	P1 $\Delta r_{X\text{-}K}$ (Å)
O---K	1.766	1.822	1.056	1.772	1.767	0.879
N---K		1.909	0.887		1.898	0.958

	P2-Na r_{Na} (Å)	P2-Na r_X (Å)	P2-Na $\Delta r_{X\text{-}Na}$ (Å)	P1-Na r_{Na} (Å)	P1-Na r_X (Å)	P1-Na $\Delta r_{X\text{-}Na}$ (Å)
O---Na	1.346	1.809	0.977	1.347	1.763	0.825
N---Na		1.907	0.807		1.894	0.956

Figure 4. Roles of metal cations. The mutual penetration distance ($\Delta r_{X\text{-}M}$) of (a) K^+ coordinated intermediates and (b) Na^+ coordinated intermediates.

The deprotonation-initiated mechanism (**D1**→ **D2**→ **D3**→ **D4** → **P**) and addition-initiated mechanism (**A1**→ **A2**→ **A3**→ **A4** → **P**) were also studied in the MeOK-MeOH system (Figure 5). MeOK serves as a base and a nucleophile at the

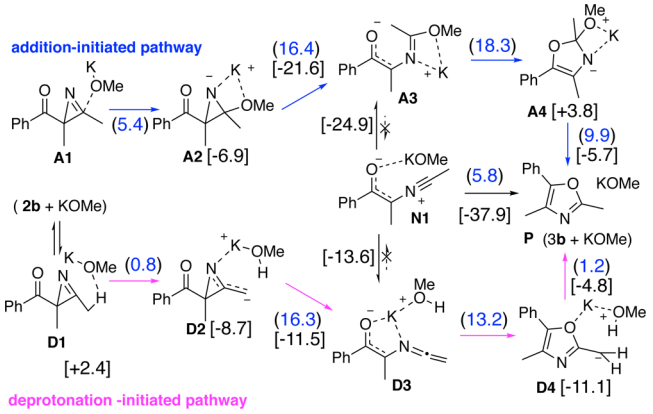


Figure 5. Compatibility of the two reaction pathways. All numbers next to arrows are ΔG in kcal·mol^{-1} at 298 K, calculated at the M06-2X-D3/def2-TZVPP/CPCM//M06-2X/6-31+G(d,p)/CPCM level in methanol. Numbers in blue, relative energies of the corresponding transition state; numbers in black, relative energies of the product compared to those of the corresponding precursors.

same time, which simplifies our experimental system of K_2CO_3/ MeOH. While this simplification may lead to an underestimation of the energy barriers for the addition step (**A1** → **A2**, 5.4 kcal/mol) and deprotonation step (**D1** → **D2**, 0.8 kcal/mol), these model calculations provide invaluable insight into the following ring-opening steps and cyclization steps. The ring-opening steps in both reaction pathways

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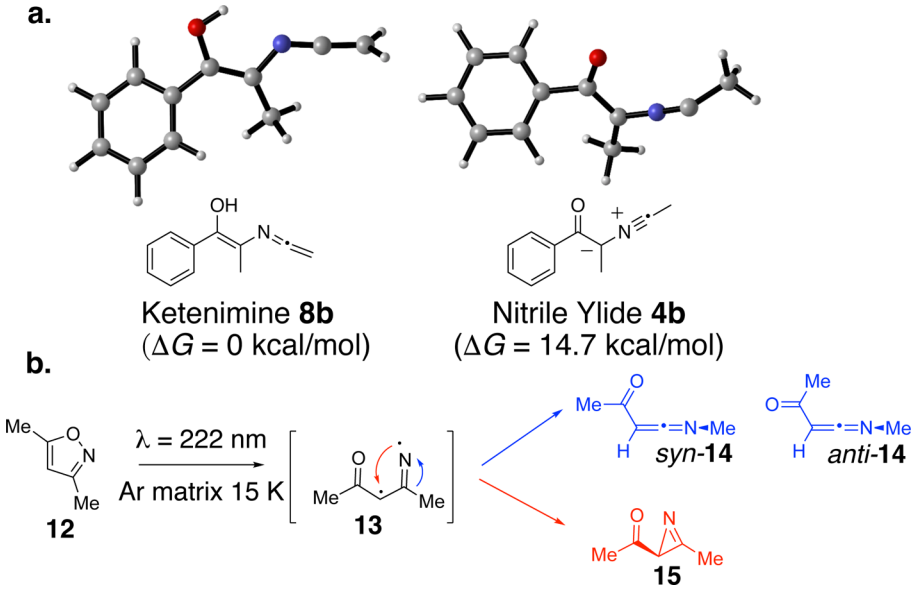


Figure 6. a. Comparisons of ketenimine and nitrile ylide. Calculated relative Gibbs free energy of ketenimine from **8b** and nitrile ylide from **4b** in gas phase; ΔG in kcal·mol^{-1} at 298 K, M06-2X-D3/def2-TZVPP//M06-2X/6-31+G(d,p). (b) Internal ketenimines (**14**) observed in isoxazole−oxazole phototransformation (see ref 6b).

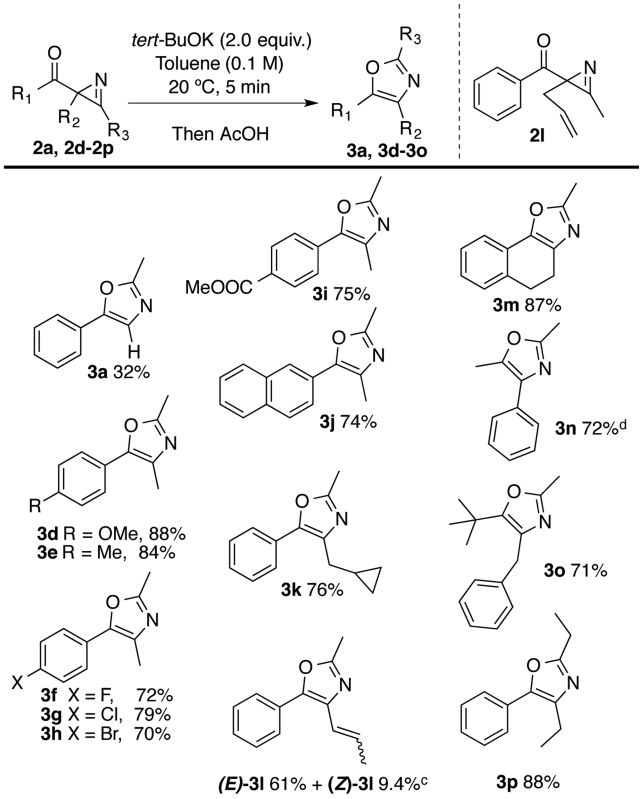
possess similar energy barriers (16.4 kcal/mol for **A2** → **A3**; 16.3 kcal/mol for **D2** → **D3**), affording methyl acetimidate **A3** and ketenimine **D3**, respectively.

Further cyclization of **A3** and **D3** can afford oxazoline **A4** and oxazolyl anion **D4**, respectively, and finally **A4** and **D4** will be transformed into the common oxazole product **P**. Notably, the energy barrier for the transformation from acetimidate **A3** to oxazoline **A4** (18.3 kcal/mol) is more energy-demanding, compared to the preceding step (16.4 kcal/mol, **A2** → **A3**) in the addition-initiated mechanism as well as the ring-opening step (**D2** → **D3**) in the deprotonation-initiated mechanism. However, considering that the transformation from **A2** to **A3** is highly exothermic (−21.6 kcal/mol), both the addition-initiated mechanism and deprotonation-initiated mechanism seem feasible.

The nitrile ylide **N1**, which has been proposed[6,21] and directly observed[6b] to be the intermediate in the photolysis and pyrolysis reactions from 2*H*-azirines to oxazoles, is unstable under these basic conditions (Figure 5), and **N1** can readily collapse into methanol-adduct **A3** and ketenimine **D3**.[22] **N1** can also undergo the cyclization reaction to afford oxazole product **P**.[23] The computational results also indicate that the ketenimine form (**8b**) is thermodynamically more stable than the tautomeric nitrile ylide form (**4b**) (by 14.7 kcal/mol, Figure 6a). Thus, we propose that ketenimines are also likely to be a common intermediate in various transformations of azirines, especially those possessing methyl substituents at C(3). Interestingly, previously reported studies on the photoinduced transformation of isoxazole (Figure 1) suggest the generation of a different kind of internal keteneimine species **14** from a vinyl nitrene intermediate **13** (Figure 6b), together with the formation of 2*H*-azirine **15**.[6b]

Reaction Generality. Finally, we studied the generality of the deprotonation-initiated rearrangement reaction from related azirines to oxazoles (Table 2). With the optimal conditions using *tert*-BuOK as a base in toluene, the azirines with multiple acidic protons (**2a**, **2n**), as well as those bearing different substituents (ester: **3i**; olefin: **3l**), react smoothly under our conditions. For **2a** in which R_2 is an H atom, oxazole **3a** was only obtained in 32% yield. The reaction of **2k** bearing a cyclopropyl group (R_2) also gave oxazole **3k** in a good yield (76%), which excludes the

Table 2. Generality of Base-Induced Isomerization from 2 to 3[a,b,c]



[a]Isolated yield. [b]All reactions were carried out at 0.3 mmol scale. [c]Oxazoles **3l** were obtained from **2l**(R_2= allyl). [d]THF was used as solvent.

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possibility of radical generation.[6] Substrate **2l**, possessing an allyl group, is prone to generate thermodynamically more stable oxazoles (*E*)-**3l** and (*Z*)-**3l**. Substrates **2n** and **2o**, possessing an aliphatic ketone functionality, also underwent a smooth reaction to afford oxazoles **3n** and **3o**, respectively. When the substituent R_3 was changed to an ethyl group (**2p**), the corresponding oxazole (**3p**) was formed in 88% yield.

CONCLUSION

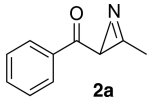
In conclusion, we found effective reaction conditions for base-induced transformation of 2-acyl-3-alkyl-2*H*-azirines **2** to oxazoles **3**, and we obtained evidence of the involvement of multiple reaction pathways in this base-induced isomerization reaction. Computational studies indicated that the deprotonation-initiated mechanism and addition-initiated mechanism are both energetically reasonable and that in the reaction with less nucleophilic bases, including *tert*-BuOK and KH, the deprotonation-initiated mechanism may be the major reaction pathway. The computational results are consistent with the idea that deprotonation of **2** yields ketenimines, which is an unprecedented transformation of 2*H*-azirines. Since ketenimine (**8b**) is thermodynamically favored over nitrile ylide (**4b**), we anticipate that ketenimines would be involved in various transformations of 2*H*-azirines.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under argon atmosphere in oven-dried glassware. Toluene was purified by distillation over sodium and stored with molecular sieves 4A. All other commercially available compounds and solvents were used as received unless otherwise mentioned.

Open column chromatography was carried out using Kanto chemical silica gel (silica gel 60 N (100−210 μm)). Melting points were determined with a Yanaco micromelting point apparatus without correction. ^{1}H (400 MHz)- and ^{13}C (100 MHz)-NMR spectra were recorded on a Bruker Avance 400. Chemical shifts were calibrated with tetramethylsilane and solvent as an internal standard or with the solvent peak, and are shown in ppm (δ) values, and coupling constants are shown in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, dq = double quartet, h = hextet, m = multiplet, brs = broad singlet, and br = broad signal. Temperature in the NMR experiments was calibrated using signals of methanol according to the reported method.[24] Electron spray ionization time-of-flight mass spectra (ESI-TOF MS) were recorded on a Bruker micrOTOF-05 to give high-resolution mass spectra (HRMS). The combustion analyses were carried out in the microanalytical laboratory of this department.

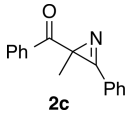
Synthesis of 2*H*-Azirines.



2a

2H-Azirine ***2a***. **2a** was synthesized according to the literature procedure.[6a] Red oil. ^{1}H NMR ($CDCl_3$): δ 8.04 (2H, dd, J = 8.4, 1.2 Hz), 7.06−7.58 (1H, m), 7.52−7.48 (2H, m), 3.47 (1H, s), 2.55 (3H, s). ^{13}C NMR ($CDCl_3$): δ 198.1, 157.1, 137.7, 133.3, 128.7, 128.2, 32.5, 12.7. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{10}H_9NNaO^+$, 182.0576. Found: 182.0584.

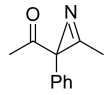
2H-Azirine ***2c***.



2c

2c was synthesized according to the literature procedure.[25] Yellow solid. Mp.: 67−69 °C. ^{1}H NMR ($CDCl_3$): δ 7.89 (2H, d, J = 8.0 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.62−7.58 (2H, m), 7.45−7.41 (1H, m), 7.35−7.32 (2H, m), 1.75 (3H, s). ^{13}C NMR ($CDCl_3$): δ 201.9, 166.0, 137.0, 133.8, 131.6, 130.0, 129.5, 128.4, 128.1, 123.3, 43.3, 19.1. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{16}H_{13}NNaO^+$, 258.0889. Found: 258.0892. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.36; H, 5.79; N, 5.67.

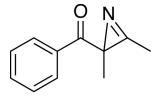
2H-Azirine ***2n***.



2n

2n was synthesized according to the literature procedure.[4c] Colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.36−7.29 (5H, m), 2.59 (3H, s), 2.04 (3H, s). ^{13}C NMR ($CDCl_3$): δ 206.1, 163.1, 136.5, 128.5, 128.2, 127.9, 47.5, 27.9, 12.7. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{11}H_{11}NNaO^+$, 196.0733. Found: 196.0727. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.11; H, 6.49; N, 7.91.

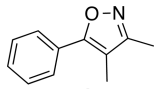
2H-Azirine ***2b***.



2b

To a solution of 2-methyl-1-phenylbutane-1,3-dione (1.75 g, 10.0 mmol) and pyridine (2.5 mL) in ethanol (20.0 mL) was added hydroxylamine hydrochloride (700.0 mg, 10.07 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (40 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford 3-(hydroxyimino)-2-methyl-1-phenylbutan-1-one (white solid, 1.02 g, 5.34 mmol, 53%). Because of the unstable nature of the oxime compound, the oxime compound was immediately used in the next step.

To a solution of the oxime 3-(hydroxyimino)-2-methyl-1-phenylbutan-1-one in 20.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]-octane (DABCO, 1.50 g, 13.4 mmol) at 0 °C followed by the addition of a solution of MsCl (0.67 g, 5.8 mmol) in 10 mL of CH_2Cl_2. The



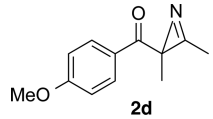
1b

whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford (2,3-dimethyl-2*H*-azirin-2-yl) (phenyl)methanone **2b** (colorless oil, 808.6 mg, 88%, 47% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.62 (2H, dd, J = 2.0, 8.0 Hz), 7.48−7.44 (1H, m), 7.40−7.36 (2H, m), 2.47 (3H, s), 1.55 (3H, s). ^{13}C NMR ($CDCl_3$): δ 202.2, 166.7, 137.3, 131.5, 128.2, 128.2, 42.0, 19.0, 12.9. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{11}H_{11}NNaO^+$, 196.0733. Found: 196.0746. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.13. Found: C, 76.48; H, 6.55; N, 8.13.

Note: the oxime compound was unstable over silica gel and transformed into isoxazole **1b**. The same transformation was observed by elevating the reaction temperature.

2H-Azirine ***2d***.



2d

To a solution of 1-(4-methoxyphenyl)-2-methylbutane-1,3-dione (513.7 mg, 2.491 mmol) and pyridine (1.0 mL) in ethanol (10.0 mL) was added hydroxylamine hydrochloride (175.0 mg, 2.518 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and

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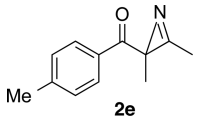
diluted with EtOAc (40 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to 3-(hydroxyimino)-1-(4-methoxyphenyl)-2-methylbutan-1-one (sticky oil, 406.2 mg, 1.838 mmol, 74%).

To a solution of the oxime 3-(hydroxyimino)-1-(4-methoxyphenyl)-2-methylbutan-1-one in 5.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 550.0 mg, 4.903 mmol) at 0 °C followed by the addition of a solution of MsCl (230.0 mg, 2.008 mmol) in 5 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford **2d** (colorless oil, 315.4 mg, 84%, 62% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.74−7.72 (2H, m), 6.87 (2H, d, J = 8.8 Hz), 3.83 (3H, s), 2.46 (3H, s), 1.53 (3H, s). ^{13}C NMR ($CDCl_3$): δ 199.8, 167.4, 162.6, 131.0, 129.5, 113.5, 55.4, 41.6, 19.6, 12.9. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{12}H_{13}NNaO_2^+$, 226.0839. Found: 226.0829.

2H-Azirine ***2e***.



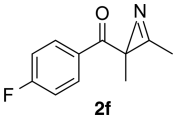
2e

To a solution of 2-methyl-1-(*p*-tolyl)butane-1,3-dione (497.8 mg, 2.618 mmol) and pyridine (1.0 mL) in ethanol (10.0 mL) was added hydroxylamine hydrochloride (200.0 mg 2.878 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (40 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 6:1) to afford 3-(hydroxyimino)-2-methyl-1-(*p*-tolyl)butan-1-one (sticky oil, 238.3 mg, 1.161 mmol, 44%).

To a solution of the oxime 3-(hydroxyimino)-2-methyl-1-(*p*-tolyl)-butan-1-one in 3.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]-octane (DABCO, 350.0 mg, 3.120 mmol) at 0 °C followed by the addition of a solution of MsCl (150.0 mg, 1.309 mmol) in 2 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford **2e** (colorless oil, 187.0 mg, 86%, 38% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.57 (2H, d, J = 8.4 Hz), 7.19 (2H, d, J = 8.0 Hz), 2.47 (3H, s), 2.37 (3H, s), 1.54 (3H, s). ^{13}C NMR ($CDCl_3$): δ 201.6, 166.9, 142.3, 134.5, 128.9, 128.5, 41.8, 21.6, 19.2, 12.9. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{12}H_{13}NNaO^+$, 210.0889. Found: 210.0897. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.06; H, 7.16; N, 7.34.

2H-Azirine ***2f***.



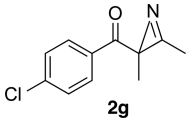
2f

To a solution of 1-(4-fluorophenyl)-2-methylbutane-1,3-dione (362.0 mg, 1.864 mmol) and pyridine (1.0 mL) in ethanol (10.0 mL) was added hydroxylamine hydrochloride (140.0 mg, 2.014 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (40 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford 1-(4-fluorophenyl)-3-(hydroxyimino)-2-methylbutan-1-one (white solid, 190.1 mg, 0.909 mmol, 49%).

To a solution of the oxime 1-(4-fluorophenyl)-3-(hydroxyimino)-2-methylbutan-1-one in 3.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 250.0 g, 2.229 mmol) at 0 °C followed by the addition of a solution of MsCl (110.0 mg, 0.960 mmol) in 2 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford **2f** (colorless oil, 156.4 mg, 90%, 45% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.72−7.69 (2H, m), 7.08−7.04 (2H, m), 2.47 (3H, s), 1.54 (3H, s). ^{13}C NMR ($CDCl_3$): δ 200.3, 167.1, 164.7 (d, $J_{C,F}$=251.7 Hz), 133.2 (d, $J_{C,F}$=3.4 Hz), 131.1 (d, $J_{C,F}$=8.9 Hz), 115.3 (d, $J_{C,F}$=21.7 Hz), 41.9, 19.0, 12.9. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{11}H_{10}FNNaO^+$, 214.0639. Found: 214.0631.

2H-Azirine ***2g***.



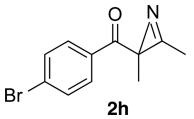
2g

To a solution of 1-(4-chlorophenyl)-2-methylbutane-1,3-dione (496.2 mg, 2.355 mmol) and pyridine (1.0 mL) in ethanol (10.0 mL) was added hydroxylamine hydrochloride (180.0 mg, 2.590 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (40 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford 1-(4-chlorophenyl)-3-(hydroxyimino)-2-methylbutan-1-one (white solid, 394.5 mg, 1.748 mmol, 74%).

To a solution of the oxime 1-(4-chlorophenyl)-3-(hydroxyimino)-2-methylbutan-1-one in 3.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 500.0 mg, 4.45 mmol) at 0 °C followed by the addition of a solution of MsCl (220.0 mg, 1.92 mmol) in 3 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 6:1) to afford **2g** (light yellow oil, 300.4 mg, 82%, 61% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.58 (2H, d, J = 8.8 Hz), 7.35 (2H, d, J = 8.8 Hz), 2.45 (3H, s), 1.58 (3H, s). ^{13}C NMR ($CDCl_3$): δ 200.8, 166.9, 138.0, 135.4, 129.9, 128.5, 42.1, 18.8, 12.8. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{11}H_{10}ClNNaO^+$, 230.0343, Found: 230.0335. Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.49; H, 4.99; N, 6.58.

2H-Azirine ***2h***.



2h

To a solution of 1-(4-bromophenyl)-2-methylbutane-1,3-dione (539.9 mg, 2.116 mmol) and pyridine (1.0 mL) in ethanol (10.0 mL) was added hydroxylamine hydrochloride (160.0 mg, 2.30 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (40 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by recrystallization from isopropanol to afford 1-(4-bromophenyl)-3-(hydroxyimino)-2-methylbutan-1-one (white solid, 355.3 mg, 1.315 mmol, 62%).

To a solution of the oxime 1-(4-bromophenyl)-3-(hydroxyimino)-2-methylbutan-1-one in 5.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 400.0 mg, 3.566 mmol) at 0 °C followed by the addition of a solution of MsCl (160.0 mg, 1.397 mmol) in 2.5 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 6:1) to afford **2h** (colorless oil, 272.4 mg, 82%, 51% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.56−7.51 (4H, m), 2.48 (3H, s), 1.55 (3H, s). ^{13}C NMR ($CDCl_3$): δ 201.0, 166.9, 135.9, 131.5, 123.0, 126.5, 42.1, 18.8, 12.9. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{11}H_{10}BrNNaO^+$, 273.9838. Found: 273.9841.

DOI: 10.1021/acs.joc.7b00904
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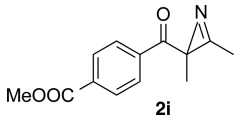
2H-Azirine ***2i***.



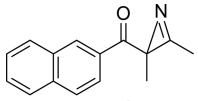
2i

To a solution of methyl 4-(2-methyl-3-oxobutanoyl) benzoate (303.7 mg, 1.296 mmol) and pyridine (1.0 mL) in ethanol (5.0 mL) was added hydroxylamine hydrochloride (100.0 mg, 1.439 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (20 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 3:2) to methyl 4-(3-(hydroxyimino)-2-methylbutanoyl)benzoate (white solid, 138.2 mg, 0.554 mmol, 43%).

To a solution of the oxime methyl 4-(3-(hydroxyimino)-2-methylbutanoyl)benzoate in 2.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 160.0 mg, 1.426 mmol) at 0 °C followed by the addition of a solution of MsCl (70.0 mg, 0.611 mmol) in 2.0 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 7:3) to afford **2i** (colorless oil, 121.2 mg, 94%, 40% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 8.03 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.8 Hz), 3.92 (3H, s), 2.45 (3H, s), 1.53 (3H, s). ^{13}C NMR ($CDCl_3$): δ 202.1, 166.4, 166.3, 141.4, 132.3, 129.4, 127.9, 52.4, 42.4, 18.4, 12.9. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{13}H_{13}NNaO_3^+$, 254.0788. Found: 254.0797. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.51; H, 5.73; N, 5.91.

2H-Azirine ***2j***.



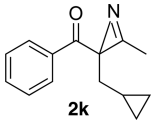
2j

To a solution 1-(naphthalen-2-yl)butane-1,3-dione (592.5 mg, 2.618 mmol) and pyridine (1.0 mL) in ethanol (10.0 mL) was added hydroxylamine hydrochloride (200.0 mg, 2.878 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (40 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford 3-(hydroxyimino)-2-methyl-1-(naphthalen-2-yl)butan-1-one (white solid, 377.7 mg, 1.565 mmol, 60%).

To a solution of the oxime 3-(hydroxyimino)-2-methyl-1-(naphthalen-2-yl)butan-1-one in 5.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 400.0 mg, 3.566 mmol) at 0 °C followed by the addition of a solution of MsCl (180.0 mg, 1.572 mmol) in 2 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford **2j** (yellow oil, 263.4 mg, 75%, 45% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 8.18 (1H, s), 7.91 (1H, d, J = 7.6 Hz), 7.85–7.83 (2H, m), 7.72 (1H, dd, J = 1.6, 8.8 Hz), 7.59–7.51 (2H, m), 2.48 (3H, s), 1.61 (3H, s). ^{13}C NMR ($CDCl_3$): δ 201.9, 167.0, 134.7, 134.5, 132.3, 129.4, 129.3, 128.1, 128.0, 127.7, 126.7, 124.6, 42.1, 19.2, 12.9. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{15}H_{13}NNaO^+$, 246.0889. Found: 246.0890.

2H-Azirine ***2k***.



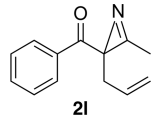
2k

To a solution of 2-(cyclopropylmethyl)-1-phenylbutane-1,3-dione (727.7 mg, 3.365 mmol) and pyridine (1.0 mL) in ethanol (15.0 mL) was added hydroxylamine hydrochloride (240.0 mg, 3.453 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (20 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 6:1) to afford 2-(cyclopropylmethyl)-3-(hydroxyimino)-1-phenylbutan-1-one (colorless oil, 427.2 mg, 1.847 mmol, 55%).

To a solution of the oxime 2-(cyclopropylmethyl)-3-(hydroxyimino)-1-phenylbutan-1-one in 2.5 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 520 mg, 4.635 mmol) at 0 °C followed by the addition of a solution of MsCl (230.0 mg, 2.008 mmol) in 2.5 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford **2k** (colorless oil, 299.0 mg, 76%, 42% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.65 (2H, dd, J = 1.6, 8.4 Hz), 7.48–7.45 (1H, m), 7.40–7.36 (2H, m), 2.52 (3H, s), 2.05 (1H, dd, J = 7.6, 15.2 Hz), 1.96 (1H, dd, J = 6.8, 15.2 Hz) 0.59–0.55 (1H, m), 0.55–0.52 (2H, m), 0.26–0.22 (2H, m). ^{13}C NMR ($CDCl_3$): δ 202.1, 166.4, 137.4, 131.6, 128.2, 128.2, 46.2, 36.4, 14.0, 7.7, 4.8, 4.6. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{14}H_{15}NNaO^+$, 236.1046. Found: 236.1035.

2H-Azirine ***2l***.



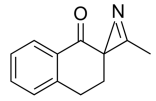
2l

To a solution of 2-allyl-1-phenylbutane-1,3-dione (458.9 mg, 2.269 mmol) and pyridine (1.0 mL) in ethanol (10.0 mL) was added hydroxylamine hydrochloride (160.0 mg, 2.302 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (40 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 7:3) to 2-(1-(hydroxyimino)ethyl)-1-phenylpent-4-en-1-one (colorless oil, 262.0 mg, 1.206 mmol, 53%).

To a solution of the oxime 2-(1-(hydroxyimino)ethyl)-1-phenylpent-4-en-1-one in 3.0 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 340.0 mg, 3.031 mmol) at 0 °C followed by the addition of a solution of MsCl (150.0 mg, 1.310 mmol) in 3.0 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 2:1) to afford **2l** (light yellow oil, 210.8 mg, 88%, 47% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.63–7.61 (2H, m), 7.47–7.43 (1H, m), 7.40–7.36 (2H, m), 5.74–5.64 (1H, m), 5.09–5.04 (2H, m), 2.89–2.83 (1H, m), 2.745–2.683 (1H, m), 2.46 (3H, s). ^{13}C NMR ($CDCl_3$): δ 201.4, 166.4, 137.2, 133.4, 131.6, 128.2, 128.2, 118.0, 45.2, 36.3, 13.7. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{13}H_{13}NNaO^+$, 222.0889. Found: 222.0877.

Azirine ***2m***.



2m

To a solution of 2-acetyl-3,4-dihydronaphthalen-1(2*H*)-one (501.7 mg, 2.665 mmol) and pyridine (1.0 mL) in ethanol (10.0 mL) was added hydroxylamine hydrochloride (190.0 mg, 2.734 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (20 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 7:3) to afford 2-(1-(hydroxyimino)ethyl)-3,4-dihydronaphthalen-1(2*H*)-one (colorless oil, 373.6 mg, 1.838 mmol, 69%).

To a solution of the oxime 2-(1-(hydroxyimino)ethyl)-3,4-dihydronaphthalen-1(2*H*)-one in 5 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 520 mg, 4.636 mmol) at 0 °C

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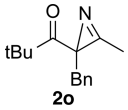
followed by the addition of a solution of MsCl (230.0 mg, 2.008 mmol) in 5 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford **2m** (colorless oil, 259.2 mg, 76%, 52% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 8.00 (1H, dd, J = 7.6, 0.8 Hz), 7.53−7.49 (1H, m), 7.36−7.30 (1H, m), 3.28−3.03 (2H, m), 2.52 (3H, s), 2.20−2.07 (2H, m). ^{13}C NMR ($CDCl_3$): δ 197.1, 162.3, 143.8, 133.8, 133.6, 128.6, 127.2, 126.8, 41.3, 30.2, 28.6, 12.3. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{12}H_{11}NNaO^+$, 208.0733. Found: 208.0717. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.69; H, 6.28; N, 7.20.

Azirine ***2o***.



2o

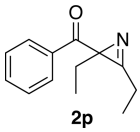
To a solution of 3-benzyl-5,5-dimethylhexane-2,4-dione (250.2 mg, 1.077 mmol) and pyridine (0.5 mL) in ethanol (1.0 mL) was added hydroxylamine hydrochloride (80.0 mg, 1.151 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (20 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford 4-benzyl-5-(hydroxyimino)-2,2-dimethylhexan-3-one (colorless oil, 139.0 mg, 0.606 mmol, 53%).

To a solution of the oxime 4-benzyl-5-(hydroxyimino)-2,2-dimethylhexan-3-one in 2 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 75.0 mg, 0.668 mmol) at 0 °C followed by the addition of a solution of MsCl (76.5 mg, 0.668 mmol) in 2 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated to give mesylated oxime as a colorless oil.

The crude mesylated oxime was dissolved in 2.0 mL of CH_2Cl_2 and added to 0.5 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The whole was stirred at room temperature for 2 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 8:1) to afford **2o** (colorless oil, 95.7 mg, 0.417 mmol, 39% for 3 steps).

^{1}H NMR ($CDCl_3$): δ 7.28−7.24 (2H, m), 7.22−7.17 (1H, m), 7.13−7.11 (2H, m), 3.49 (1H, d, J = 14.4 Hz), 2.98 (1H, d, J = 14.8 Hz), 2.19 (3H, s), 1.07 (9H, s). ^{13}C NMR ($CDCl_3$): δ 212.5, 167.0, 137.8, 129.9, 128.3, 126.3, 46.3, 43.4, 38.9, 26.6, 13.8. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{15}H_{19}NNaO^+$, 252.1359. Found: 252.1357.

Azirine ***2p***.



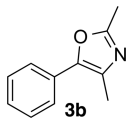
2p

To a solution of 2-ethyl-1-phenylpentane-1,3-dione (1.4613 g, 7.154 mmol) and pyridine (3.0 mL) in ethanol (30.0 mL) was added hydroxylamine hydrochloride (550.0 mg, 7.913 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc (60 mL). The whole was washed with 2 M aqueous HCl, water, and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford 2-ethyl-3-(hydroxyimino)-1-phenylpentan-1-one (colorless oil, 585.7 mg, 2.671 mmol, 37%).

To a solution of the oxime afford 2-ethyl-3-(hydroxyimino)-1-phenylpentan-1-one in (239.1 mg, 1.090 mmol) in 5 mL of CH_2Cl_2 was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 500 mg, 4.450 mmol) at 0 °C followed by the addition of TsCl (250.0 mg, 1.311 mmol) in 2.5 mL of CH_2Cl_2. The whole was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 6:1) to afford **2p** (colorless oil, 141.8 mg, 70%, 24% for 2 steps).

^{1}H NMR ($CDCl_3$): δ 7.68−7.66 (2H, m), 7.50−7.46 (1H, m), 7.43−7.38 (2H, m), 2.86−2.74 (2H, m), 2.26−2.16 (1H, m), 2.01−1.92 (1H, m), 1.26 (3H, t, J = 7.2 Hz), 0.87 (3H, t, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 201.9, 170.4, 137.4, 131.5, 128.3, 128.2, 47.8, 24.7, 21.7, 10.1, 8.7. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{13}H_{15}NNaO^+$, 224.1046. Found: 224.1049.

Transformation of 2*H*-Azirines to Oxazoles with *tert*-BuOK/Toluene.

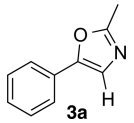


3b

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2b** (52.0 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 2:1) to afford oxazole **3b** (white solid, 44.4 mg, 85%).

Mp.: 42−44 °C. ^{1}H NMR ($CDCl_3$): δ 7.57 (2H, dd, J = 2.0, 8.0 Hz), 7.44−7.40 (2H, m), 7.31−7.29 (1H, m), 2.48 (3H, s), 2.38 (3H, s). ^{13}C NMR ($CDCl_3$): δ 159.4, 145.1, 131.6, 129.3, 128.7, 127.3, 125.1, 13.9, 13.2. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{11}H_{11}NNaO^+$, 196.0733. Found: 196.0744. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.13. Found: C, 76.11; H, 6.39; N, 8.17.

Oxazole ***3a***.

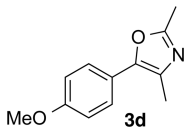


3a

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2a** (47.8 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford oxazole **3a** (yellow solid, 15.5 mg, 32%).

Mp.: 51−53 °C. ^{1}H NMR ($CDCl_3$): δ 7.62−7.59 (2H, m), 7.43−7.38 (2H, m), 7.33−7.30 (1H, m), 7.21 (1H, s), 2.53 (3H, s). ^{13}C NMR ($CDCl_3$): δ 161.0, 151.1, 128.9, 128.2, 128.1, 123.9, 121.9, 14.1. HRMS (ESI-TOF, $[M + H]^+$): Calcd for $C_{10}H_{10}NO^+$, 160.0757. Found: 160.0779.

Oxazole ***3d***.



3d

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2d** (61.0 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 1:1) to afford oxazole **3d** (colorless oil, 53.6 mg, 88%).

^{1}H NMR ($CDCl_3$): δ 7.49 (2H, d, J = 8.8 Hz), 6.95 (2H, d, J = 8.8 Hz), 3.84 (3H, s), 2.46 (3H, s), 2.33 (3H, s). ^{13}C NMR ($CDCl_3$):

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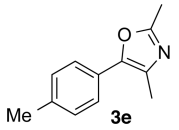
δ 158.9, 158.8, 145.1, 130.0, 126.6, 122.2, 114.2, 55.3, 13.9, 13.0. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{12}H_{13}NNaO_2^+$, 226.0839. Found: 226.0822.

Oxazole ***3e***.

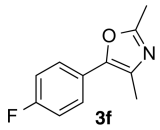


3e

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2e** (56.2 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford oxazole **3e** (light yellow oil, 47.5 mg, 84%).

^{1}H NMR ($CDCl_3$): δ 7.46 (2H, d, *J* = 8.4 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 2.47 (3H, s), 2.38 (3H, s), 2.36 (3H, s). ^{13}C NMR ($CDCl_3$): δ 159.1, 145.3, 137.2, 130.9, 129.4, 126.3, 125.1, 21.3, 13.9, 13.2. HRMS (ESI-TOF, [M + H]$^+$): Calcd for $C_{12}H_{14}NO^+$, 188.1070. Found: 188.1071. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.63; H, 7.17; N, 7.29.

Oxazole ***3f***.

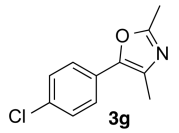


3f

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2f** (57.4 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford oxazole **3a** (yellow oil, 41.2 mg, 72%).

^{1}H NMR ($CDCl_3$): δ 7.54−7.51 (2H, m), 7.13−7.09 (2H, m), 2.46 (3H, s), 2.34 (3H, s). ^{13}C NMR ($CDCl_3$): δ 161.9 (d, $J_{C,F}$=246.0 Hz), 159.3, 144.4, 131.2, 126.9 (d, $J_{C,F}$=9.0 Hz), 125.6 (d, $J_{C,F}$=3.5 Hz), 115.8 (d, $J_{C,F}$=21.7 Hz), 13.9, 13.1. HRMS (ESI-TOF, [M + H]$^+$): Calcd for $C_{11}H_{11}FNO^+$, 192.0819. Found: 192.0822.

Oxazole ***3g***.

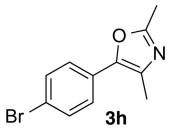


3g

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2g** (62.5 mg, 0.301 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford oxazole **3g** (yellow solid, 49.2 mg, 79%).

Mp.: 41−42 °C. ^{1}H NMR ($CDCl_3$): δ 7.48 (2H, d, *J* = 8.8 Hz), 7.37 (2H, d, *J* = 8.8 Hz), 2.46 (3H, s), 2.35 (3H, s). ^{13}C NMR ($CDCl_3$): δ 159.6, 144.2, 133.0, 132.1, 128.9, 127.8, 126.2, 13.9, 13.3. HRMS (ESI-TOF, [M + H]$^+$): Calcd for $C_{11}H_{11}ClNO^+$, 208.0524. Found: 208.0518. Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.52; H, 5.00; N, 6.65.

Oxazole ***3h***.

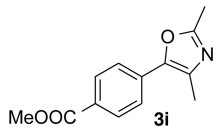


3h

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2h** (75.6 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford oxazole **3h** (light yellow solid, 52.6 mg, 70%).

Mp.: 47−50 °C. ^{1}H NMR ($CDCl_3$): δ 7.53 (2H, d, *J* = 8.8 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 2.46 (3H, s), 2.35 (3H, s). ^{13}C NMR ($CDCl_3$): δ 159.6, 144.2, 132.2, 131.9, 128.2, 126.5, 121.1, 13.9, 13.3. HRMS (ESI-TOF, [M + H]$^+$): Calcd for $C_{11}H_{11}BrNO^+$, 252.0019. Found: 252.0008. Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41, H, 4.00, N, 5.56; Found: C, 52.48, H, 4.32, N, 5.20.

Oxazole ***3i***.

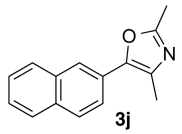


3i

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2i** (69.4 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 1:1) to afford oxazole **3i** (white solid, 52.1 mg, 75%).

Mp.: 76−77 °C. ^{1}H NMR ($CDCl_3$): δ 8.08 (2H, d, *J* = 8.8 Hz), 7.63 (2H, d, *J* = 8.8 Hz), 3.93 (3H, s), 2.49 (3H, s), 2.42 (3H, s). ^{13}C NMR ($CDCl_3$): δ 166.7, 160.2, 144.3, 134.0, 133.4, 130.1 128.5, 124.5, 52.2, 14.0, 13.6. HRMS (ESI-TOF, [M + H]$^+$): Calcd for $C_{13}H_{14}NO_3^+$, 232.0968. Found: 232.0969. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.42; H, 6.03; N, 5.72.

Oxazole ***3j***.

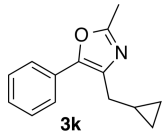


3j

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2j** (67.1 mg, 0.301 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford oxazole **3j** (white solid, 49.8 mg, 74%).

Mp.: 74−77 °C. ^{1}H NMR ($CDCl_3$): δ 8.03 (1H, s), 7.92−7.84 (3H, m), 7.74 (1H, dd, *J* = 2.0, 8.4 Hz), 7.55−7.48 (2H, m), 2.55 (3H, s), 2.50 (3H, s). ^{13}C NMR ($CDCl_3$): δ 159.5, 145.3, 133.4, 132.4, 132.1, 128.5, 128.1, 127.7, 126.7, 126.6, 126.2, 123.8, 123.1, 14.0, 13.5. HRMS (ESI-TOF, [M + H]$^+$): Calcd for $C_{15}H_{14}NO^+$, 224.1070. Found: 224.1054.

Oxazole ***3k***.



3k

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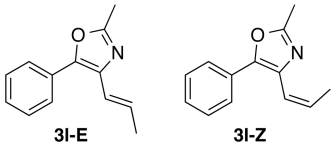
A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2k** (64.0 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford oxazole **3k** (colorless oil, 48.8 mg, 76%).

^{1}H NMR ($CDCl_3$): δ 7.57 (2H, dd, J = 1.2, 8.4 Hz), 7.42−7.39 (2H, m), 7.31−7.29 (1H, m), 2.68 (2H, d, J = 6.4 Hz), 2.49 (3H, s), 1.16−1.09 (1H, m), 0.53−0.50 (2H, m), 0.26−0.22 (2H, m). ^{13}C NMR ($CDCl_3$): δ 159.6, 145.2, 135.4, 129.2, 128.7, 127.5, 125.4, 31.2, 14.0, 10.1, 4.3. HRMS (ESI-TOF, $[M + H]^+$): Calcd for $C_{14}H_{16}NO^+$, 214.1226. Found: 214.1231.

Oxazole ***3l***.



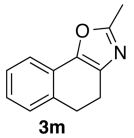
3l-E **3l-Z**

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2l** (59.8 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 6:1) to afford oxazole (***E***)-**3l** (colorless oil, 36.3 mg, 61%) and (***Z***)-**3l** (yellow oil, 5.6 mg, 9.4%).

Oxazole ***(E)-3l***. ^{1}H NMR ($CDCl_3$): δ 7.1 (2H, dd, J = 1.2, 8.4 Hz), 7.43−7.39 (2H, m), 7.33−7.28 (1H, m), 6.37 (1H, dd, J = 2.0, 15.7), 5.92−5.84 (1H, m), 2.52 (3H, s), 2.02 (3H, dd, J = 2.0, 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 159.4, 146.3, 133.2, 130.5, 129.1, 128.6, 127.7, 125.9, 119.0, 15.3, 14.1. HRMS (ESI-TOF, $[M + H]^+$): Calcd for $C_{13}H_{14}NO^+$, 200.1070. Found: 200.1065. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.06; H, 6.76; N, 6.65.

Oxazole ***(Z)-3l***. ^{1}H NMR ($CDCl_3$): δ 7.59 (2H, dd, J = 1.2, 7.6 Hz), 7.44−7.40 (2H, m), 7.33−7.28 (1H, m), 6.56−6.54 (2H, m), 2.49 (3H, m), 1.91 (3H, d, J = 5.2 Hz). ^{13}C NMR ($CDCl_3$): δ 160.1, 144.3, 133.8, 129.3, 129.1, 128.8, 127.8, 125.9, 120.0, 18.6, 14.0. HRMS (ESI-TOF, $[M + H]^+$): Calcd for $C_{13}H_{14}NO^+$, 200.1070. Found: 200.1089.

Oxazole ***3m***.

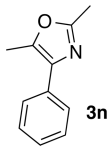


3m

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2m** (55.6 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 7:3) to afford oxazole **3m** (colorless oil, 48.6 mg, 87%).

^{1}H NMR ($CDCl_3$): δ 7.32 (1H, d, J = 7.2 Hz), 7.22−7.10 (3H, m), 3.04 (2H, t, J = 8.0 Hz), 2.82 (2H, t, J = 8.0 Hz), 2.51 (3H, s). ^{13}C NMR ($CDCl_3$): δ 160.8, 146.0, 135.4, 134.1, 128.1, 127.0, 126.8, 126.4, 119.1, 29.0, 21.5, 14.2. HRMS (ESI-TOF, $[M + H]^+$): Calcd for $C_{12}H_{12}NO^+$, 186.0913. Found: 186.0898. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.54; H, 6.33; N, 7.19.

Oxazole ***3n***.

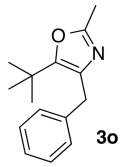


3n

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of THF was kept at 20 °C with an external water bath. A solution of **2n** (52.0 mg, 0.300 mmol) in 1.5 mL of THF was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 6:1) to afford oxazole **3n** (yellow oil, 36.5 mg, 72%).

^{1}H NMR ($CDCl_3$): δ 7.63 (2H, dd, J = 8.0, 1.2 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.19 (1H, d, J = 7.2 Hz), 2.49 (3H, s), 2.46 (3H, s). ^{13}C NMR ($CDCl_3$): δ 159.1, 145.4, 134.3, 132.5, 128.6, 127.1, 126.5, 13.8, 11.8. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{11}H_{11}NNaO^+$, 196.0733. Found: 196.0732. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.29; H, 6.44; N, 7.97.

Oxazole ***3o***.

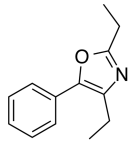


3o

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2o** (68.8 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford oxazole **3o** (colorless oil, 48.6 mg, 71%).

^{1}H NMR ($CDCl_3$): δ 7.31−7.18 (5H, m), 3.95 (2H, s), 2.39 (3H, s), 1.34 (9H, s). ^{13}C NMR ($CDCl_3$): δ 158.3, 153.8, 140.1, 130.7, 128.4, 128.3, 126.0, 32.9, 32.4, 29.6, 13.9. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{15}H_{19}NNaO^+$, 252.1359. Found: 252.1354.

Oxazole ***3p***.



3p

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2o** (60.4 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 5 min and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 6:1) to afford oxazole **3o** (colorless oil, 52.9 mg, 88%).

^{1}H NMR ($CDCl_3$): δ 7.57 (2H, dd, J = 1.2, 7.2 Hz), 7.44−7.40 (2H, m), 7.32−7.29 (1H, m), 2.82 (2H, q, J = 7.6 Hz), 2.76 (2H, q, J = 7.6 Hz), 1.38 (3H, t, J = 7.6 Hz), 1.31 (3H, t, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 164.0, 144.3, 137.3, 129.4, 128.7, 127.4, 125.3, 21.8, 20.4, 13.3, 11.4. HRMS (ESI-TOF, $[M + H]^+$): Calcd for $C_{13}H_{16}NO^+$, 202.1226. Found: 202.1237.

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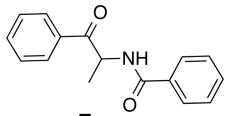
Amide ***7c***.



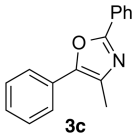
7c

A suspension of *tert*-BuOK (67.3 mg, 0.600 mmol) in 1.5 mL of toluene was kept at 20 °C with an external water bath. A solution of **2c** (70.6 mg, 0.300 mmol) in 1.5 mL of toluene was added dropwise at 20 °C. The solution was stirred at 20 °C for 1 h and quenched with 0.3 mL of acetic acid. The reaction mixture was diluted with EtOAc (10 mL) and washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The solvent was evaporated, and the residue was purified with column chromatography (hexane/EtOAc = 4:1) to afford amide **7c** (light yellow solid, 31.0 mg, 41%).

Mp.: 101−103 °C. ^{1}H NMR ($CDCl_3$): δ 8.05 (2H, d, J = 8.0 Hz), 7.86 (2H, dd, J = 1.2, 8.0 Hz), 7.66−7.61 (1H, m), 7.55−7.44 (5H, m), 7.47−7.335 (1H, br), 5.77 (1H, quint, J = 6.8 Hz), 1.55 (3H, d, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 199.3, 166.7, 134.2, 134.1, 133.8, 131.7, 129.0, 128.8, 128.6, 127.1, 50.6, 20.0. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{16}H_{15}NNaO_2^+$, 276.0995. Found: 276.1006.

General Procedure for the Transformation to Oxazoles with K_2CO_3/MeOH. To a solution of **2b** (52.0 mg, 0.300 mmol) in 3.0 mL of methanol was added K_2CO_3 (165.8 mg, 1.200 mmol) at 20 °C. The solution was stirred at 20 °C for 1 h and diluted with EtOAc (10 mL). K_2CO_3 was removed by filtration through a pad of Celite, and the solution was concentrated by evaporation. The residue was purified with column chromatography to afford oxazole **3b** (white solid, 39.5 mg, 76%).

Oxazole ***3c***.



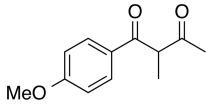
3c

To a solution of **2c** (70.6 mg, 0.300 mmol) in 3.0 mL of methanol was added K_2CO_3 (165.8 mg, 1.200 mmol) at 20 °C. The solution was stirred at 20 °C for 1 h and diluted with EtOAc (10 mL). K_2CO_3 was removed by filtration, and the solution was concentrated by evaporation. The residue was purified with column chromatography (hexane/ethyl acetate = 4:1) to afford oxazole **3c** (white solid, 47.3 mg, 67%).

Mp.: 79−81 °C. ^{1}H NMR ($CDCl_3$): δ 8.11−8.09 (2H, m), 7.71−7.69 (2H, m), 7.50−7.44 (5H, m), 7.34 (1H, t, J = 7.6 Hz), 2.52 (3H, s). ^{13}C NMR ($CDCl_3$): δ 159.4, 145.5, 133.4, 130.2, 129.2, 128.8, 128.8, 127.6, 127.5, 126.2, 125.4, 13.6. HRMS (ESI-TOF, $[M + H]^+$): Calcd for $C_{16}H_{14}NO^+$, 236.1070, Found: 236.1073.

General Procedure for Transformation to Oxazoles with KH/THF. To a suspension of KH (64.2 mg of 37.5 wt % mixture of KH suspended in parrafin, 0.600 mmol of KH) in 1.5 mL of THF was added a solution of **2b** (52.0 mg, 0.300 mmol) in 1.5 mL of THF dropwise at 20 °C. The whole was stirred for 30 min and then cooled to 0 °C. The reaction was quenched with a solution of acetic acid (0.3 mL) in THF (3 mL) and diluted with EtOAc (20 mL). The reaction mixture was washed with water, saturated aqueous $NaHCO_3$ solution and brine. The solvent was evaporated, and the residue was purified with column chromatography to afford oxazole **3b** (off-white solid, 35.7 mg, 69%).

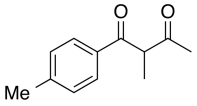
General Procedure for the Synthesis of 1,3-Diketones.



A solution of 1-(4-methoxyphenyl)butane-1,3-dione (2.89 g, 15.0 mmol), MeI (2.20 g, 15.4 mmol), and K_2CO_3 (2.25 g, 16.3 mmol) in acetone (50 mL) was stirred at room temperature for 1 h and then refluxed for 4 h. The reaction solution was cooled to room temperature and diluted with $CHCl_3$ (70 mL). The reaction mixture was filtered, and the solution was concentrated. The resiude was dissolved in $CHCl_3$ and washed sequentially with water, 2 M hydrochloric acid, saturated aqueous $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated to afford 1-(4-methoxyphenyl)-2-methylbutane-1,3-dione as a light yellow oil (92%, 2.84 g).

^{1}H NMR ($CDCl_3$): δ 7.96 (2H, d, J = 9.2 Hz), 6.94 (2H, d, J = 9.2 Hz), 4.11 (1H, q, J = 6.8 Hz), 3.87 (3H, s), 2.13 (3H, s), 1.43 (3H, d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 205.4, 195.7, 164.0, 131.1, 129.0, 114.1, 56.7, 55.6, 27.7, 13.7. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{12}H_{14}NaO_3^+$, 229.0835. Found: 229.0835.

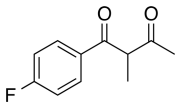
2-Methyl-1-(*p*-tolyl)butane-1,3-dione.



A solution of 1-(*p*-tolyl)butane-1,3-dione (2.64 g, 15.0 mmol), MeI (2.20 g, 15.4 mmol), and K_2CO_3 (2.25 g, 16.3 mmol) in acetone (50 mL) was stirred at room temperature for 1 h and then refluxed for 4 h. The reaction solution was cooled to room temperature and diluted with $CHCl_3$ (70 mL). The reaction mixture was filtered, and the solution was concentrated. The resiude was dissolved in $CHCl_3$ and washed sequentially with water, 2 M hydrochloric acid, saturated aqueous $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated to afford the desired 1,3-dione as a yellow oil (90%, 2.57 g).

^{1}H NMR ($CDCl_3$): δ 7.87 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.4 Hz), 4.45 (1H, q, J = 6.8 Hz), 2.41 (3H, s), 2.13 (3H, s), 1.44 (3H, d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 205.2, 196.9, 144.7, 133.5, 129.6, 128.8, 56.82, 27.8, 21.7, 13.6. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{12}H_{14}NaO_2^+$, 213.0886. Found: 213.0890.

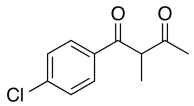
1-(4-Fluorophenyl)-2-methylbutane-1,3-dione.



A solution of 1-(4-fluorophenyl) butane-1,3-dione (1.80 g, 9.99 mmol), MeI (1.50 g, 10.6 mmol), and K_2CO_3 (1.60 g, 11.6 mmol) in acetone (30 mL) was stirred at room temperature for 1 h and then refluxed for 4 h. The reaction solution was cooled to room temperature and diluted with $CHCl_3$ (70 mL). The reaction mixture was filtered, and the solution was concentrated. The residue was dissolved in $CHCl_3$ and washed sequentially with water, 2 M hydrochloric acid, saturated aqueous $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate = 9:1) to afford the desired 1,3-dione as a yellow oil (73%, 1.42 g).

^{1}H NMR ($CDCl_3$): δ 8.06−8.06 (2H, m), 7.20−7.16 (2H, m), 4.47 (1H, q, J = 6.8 Hz), 2.18 (3H, s), 1.49 (3H, d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 205.0, 195.6, 166.1 (d, J = 254.6 Hz), 132.4 (d, J = 2.9 Hz), 131.5 (d, J = 9.4 Hz), 116.1 (d, J = 21.8 Hz), 57.0, 27.7, 13.6. HRMS (ESI-TOF, $[M + Na]^+$): Calcd for $C_{11}H_{11}FNaO_2^+$, 217.0635. Found: 217.0626.

1-(4-Chlorophenyl)-2-methylbutane-1,3-dione.



A solution of 1-(4-chlorophenyl) butane-1,3-dione (1.97 g, 10.0 mmol), MeI (1.50 g, 10.6 mmol), and K_2CO_3 (1.60 g, 11.6 mmol) in acetone (30 mL) was stirred at room temperature for 1 h and then refluxed for 4 h. The reaction solution was cooled to room temperature and diluted with $CHCl_3$ (70 mL). The reaction mixture was filtered, and the solution was concentrated. The resiude was dissolved in $CHCl_3$ and washed sequentially with water, 2 M hydrochloric acid, saturated aqueous $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate = 9:1) to afford the desired 1,3-dione as a yellow oil (84%, 1.77 g).

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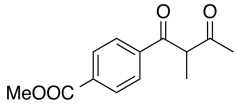
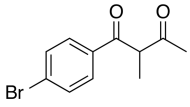
^{1}H NMR ($CDCl_3$): δ 7.91 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.8 Hz), 4.42 (1H, q, J = 6.8 Hz), 2.15 (3H, s), 1.45 (3H, d, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 204.8, 196.0, 140.3, 134.3, 130.1, 129.2, 57.0, 27.7, 13.6. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{11}H_{11}ClNaO_2^+$, 233.0340. Found: 233.0322.



1-(4-Bromophenyl)-2-methylbutane-1,3-dione.

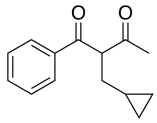


A solution of 1-(4-bromophenyl) butane-1,3-dione (2.41 g, 10.0 mmol), MeI (1.50 g, 10.6 mmol), and K_2CO_3 (1.60 g, 11.6 mmol) in acetone (30 mL) was stirred at room temperature for 1 h and then refluxed for 4 h. The reaction solution was cooled to room temperature and diluted with $CHCl_3$ (70 mL). The reaction mixture was filtered, and the solution was concentrated. The resiude was dissolved in $CHCl_3$ and washed sequentially with water, 2 M hydrochloric acid, saturated aqueous $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated to afford the desired 1,3-dione as a yellow oil (91%, 2.32 g). The contained impurity was purified in further steps.

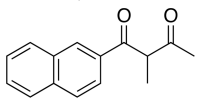
^{1}H NMR ($CDCl_3$): δ 7.83 (2H, d, J = 8.8 Hz), 7.63 (2H, d, J = 8.8 Hz), 4.42 (1H, q, J = 6.8 Hz), 2.15 (3H, s), 1.45 (3H, d, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 204.8, 196.2, 134.7, 132.2, 130.2, 128.1, 57.0, 27.8, 13.5. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{11}H_{11}BrNaO_2^+$, 276.9835. Found: 276.9833.

A solution of methyl 4-(2-methyl-3-oxobutanoyl)benzoate (3.30 g, 15.0 mmol), MeI (2.20 g, 15.2 mmol), and K_2CO_3 (2.25 g, 16.3 mmol) in acetone (50 mL) was stirred at room temperature for 1 h and then refluxed for 4 h. The reaction solution was cooled to room temperature and diluted with $CHCl_3$ (70 mL). The reaction mixture was filtered, and the solution was concentrated. The resiude was dissolved in $CHCl_3$ and washed sequentially with water, 2 M aqueous HCl, saturated aqueous $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified with column chromatography (hexane/ethyl acetate = 6:1) to afford methyl 4-(2-methyl-3-oxobutanoyl)benzoate as an off-white solid (60%, 2.11 g).

Mp.: 37−39 °C ^{1}H NMR ($CDCl_3$): δ 8.16 (2H, d, J = 8.4 Hz), 8.04 (2H, d, J = 8.4 Hz), 4.52 (1H, q, J = 6.8 Hz), 3.98 (3H, s), 2.20 (3H, s) 1.49 (3H, d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 204.7, 196.8, 166.0, 139.1, 134.4, 130.1, 128.6, 57.2, 52.6, 27.9, 13.5. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{13}H_{14}NaO_4^+$, 257.0784. Found: 257.0782.



2-Methyl-1-(naphthalen-2-yl)butane-1,3-dione.



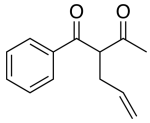
A solution of 1-(naphthalen-2-yl)butane-1,3-dione (2.12 g, 9.99 mmol), MeI (1.50 g, 10.6 mmol), and K_2CO_3 (1.60 g, 11.6 mmol) in acetone (30 mL) was stirred at room temperature for 1 h and then refluxed for 4 h. The reaction solution was cooled to room temperature and diluted with $CHCl_3$ (70 mL). The reaction mixture was filtered, and the solution was concentrated. The residue was dissolved in $CHCl_3$ and washed sequentially with water, 2 M hydrochloric acid, saturated aqueous $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated to afford the desired 1,3-dione as a yellow solid (91%, 2.06 g).

Mp.: 66−68 °C ^{1}H NMR ($CDCl_3$): δ 8.53 (1H, s), 8.07−7.89 (4H, m), 7.68−7.58 (2H, m), 4.68 (1H, q, J = 7.2 Hz), 2.22 (3H, s), 1.55 (3H, d, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 205.2, 197.2, 135.8, 133.3, 132.50, 130.8, 129.8, 129.0, 128.9, 127.8, 127.0, 124.0, 57.0, 27.8, 13.8. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{15}H_{14}NaO_2^+$, 249.0892. Found: 249.0886.

To a solution of 1-phenylbutane-1,3-dione (1.62 g, 10.0 mmol) in DMF (30 mL) was added NaH (500.0 mg, 60% in mineral oil, 12.50 mmol NaH) at 0 °C and stirred for 30 min. A solution of (bromomethyl)cyclopropane (1.69 g, 12.5 mmol) in 10 mL of DMF was added, and the whole was stirred at room temperature for 48 h. The reaction was diluted with 60 mL of ethyl ether and quenched by a saturated aqueous solution of NH_4Cl. The reaction mixture was extracted with diethyl ether, and the organic phase was washed with water and brine. The organic phase was concentrated, and the residue was purified with column chromatography (hexane/ethyl acetate = 2:1) to afford 2-(cyclopropylmethyl)-1-phenylbutane-1,3-dione (colorless oil, 734.9 mg, 34%).

^{1}H NMR ($CDCl_3$): δ 8.02−8.00 (2H, m), 7.62−7.59 (1H, m), 7.51−7.48 (2H, m), 4.59 (1H, q, J = 6.8 Hz), 2.16 (3H, s), 1.97−1.85 (2H, m), 0.71−0.67 (1H, m), 0.45−0.41 (2H, m), 0.11−0.07 (2H, m). ^{13}C NMR ($CDCl_3$): δ 204.3, 196.7, 136.7, 133.7, 128.9, 128.7, 63.7, 34.3, 28.2, 9.4, 5.0, 4.9. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{14}H_{16}NaO_2^+$, 239.1043. Found: 239.1048.

2-Allyl-1-phenylbutane-1,3-dione.



The title compound was synthesized according to the literature procedure.[26]

^{1}H NMR ($CDCl_3$): δ 8.01 (2H, dd, J = 8.0, 0.8 Hz), 7.65−7.61 (1H, m), 7.54−7.49 (2H, m), 5.84−5.73 (1H, m), 5.15−5.04 (2H, m), 4.56 (1H, t, J = 7.2 Hz), 2.83−2.71 (2H, m), 2.17 (3H, m). ^{13}C NMR ($CDCl_3$): δ 203.6, 195.8, 136.4, 134.4, 133.8, 128.9, 128.8, 117.5, 62.8, 33.1, 28.1. HRMS (ESI-TOF, [M + Na]$^+$): Calcd for $C_{13}H_{14}NaO_2^+$, 225.0886. Found: 225.0882.

Computational Studies. DFT calculations were performed with Gaussian 09. Computed structures are illustrated using CYLView.[27] Geometry optimizations and frequencies were calculated with the M06-2X density functional with the 6-31+G(d,p) basis set in conjunction with the CPCM implicit solvation model. Optimized geometries were verified by frequency calculations as minima (zero imaginary frequencies) or transition structures (a single imaginary frequency). Intrinsic reaction coordinate (IRC) computations of the transition structures verified the reactants, intermediates, and products. Single point energy calculations were performed on optimized geometries with the M06-2X-D3/def2-TZVPP level with the CPCM model for the experimental solvent reported. The thermal corrections evaluated from the unscaled vibrational frequencies at the M06-2X/6-31+G(d,p)-CPCM level on the optimized geometries were then added to the M06-2X-D3/def2-TZVPP-CPCM electronic energies to obtain the free energies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00904.

DFT calculation data and spectral data for azirines **2a−p**, oxazoles **3a−p**, and amide **7c** (PDF)

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Notes

The authors declare no competing financial interest.

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