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Iminyl radical-triggered relay annulation for the construction of bridged aza-tetracycles bearing four contiguous stereogenic centers†

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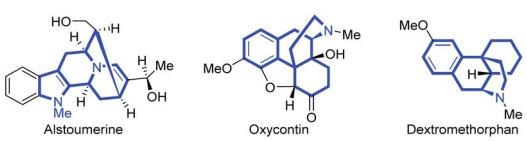
Bridged tetracyclic nitrogen scaffolds are found in numerous biologically active molecules and medicinally relevant structures. Traditional methods usually require tedious reaction steps, and/or the use of structurally specific starting materials. We report an unprecedented, iminyl radical-triggered relay annulation from oxime-derived peresters and azadienes, which shows good substrate scope and functional group compatibility, and can deliver various bridged aza-tetracyclic compounds with complex molecular topology and four contiguous stereogenic centers (dr > 19 : 1) in a single operation. This transformation represents the first example of trifunctionalization of iminyl radicals through simultaneous formation of one C–N and two C–C bonds. DFT calculation studies were conducted to obtain an in-depth insight into the reaction pathways, which revealed that the reactions involved an interesting 1,6-hydrogen atom transfer process.

Introduction

Bridged aza-tetracyclic skeletons represent a structurally complex and important class of polycyclic frameworks, and such skeletons are found in numerous alkaloids and biologically active natural products,[1] such as alstoumerine,[2a] as well as commercial pharmaceuticals such as oxycontin[2b] and dextromethorphan (Scheme 1).[2c] Besides, the interesting structures have also led their use as useful intermediates for the construction of a series of valuable molecules.[3] Owing to the intriguing structures, diverse biological activities and synthetic potentials associated with bridged aza-tetracycles, tremendous attention has been paid to their efficient syntheses. Traditional methods usually require tedious reaction steps, and/or the use of structurally specific starting materials that are often difficult to access.[4,5] As such, the construction of bridged aza-tetracyclic scaffolds using readily available starting materials in a one-step manner would be a highly attractive way.

Radical relay annulation is emerging as a useful synthetic tool enabling access to polycyclic frameworks in one step, such as bicyclic, tricyclic, and sometimes tetracyclic structures.[6] Nevertheless, the synthetic potential of such a strategy towards the formation of bridged aza-tetracyclic skeletons has been significantly underdeveloped. Thus, new protocols remain in high demand for generating more structurally new bridged aza-tetracycles with an aim to increase their molecular diversity and complexity. This work describes an unprecedented radical relay annulation from oxime-derived peresters and azadienes, which delivers various bridged aza-tetracyclic compounds with complex molecular topology and four contiguous stereogenic centers (dr > 19 : 1). Moreover, DFT calculation studies revealed that the reactions involved an interesting 1,6-hydrogen atom transfer process. Significantly, this transformation, to the best of our knowledge, represents the first example of trifunctionalization of iminyl radicals through simultaneous formation of one C–N and two C–C bonds.

Iminyl radicals, one of the most important classes of nitrogen-centered radicals, have attracted much attention from synthetic chemists. A series of transformations based on iminyl radicals have been successfully realized,[7] such as C-halogenation,[8] -phosphorylation,[9] -sulfonylation,[10] -azidation,[11] -alkenylation,[12] and -alkynylation (Scheme 2a).[13] Moreover, iminyl radical-based



Scheme 1 Biologically active compounds bearing bridged aza-tetracyclic moieties.

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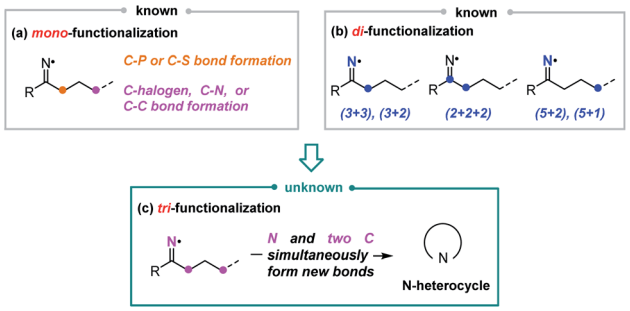
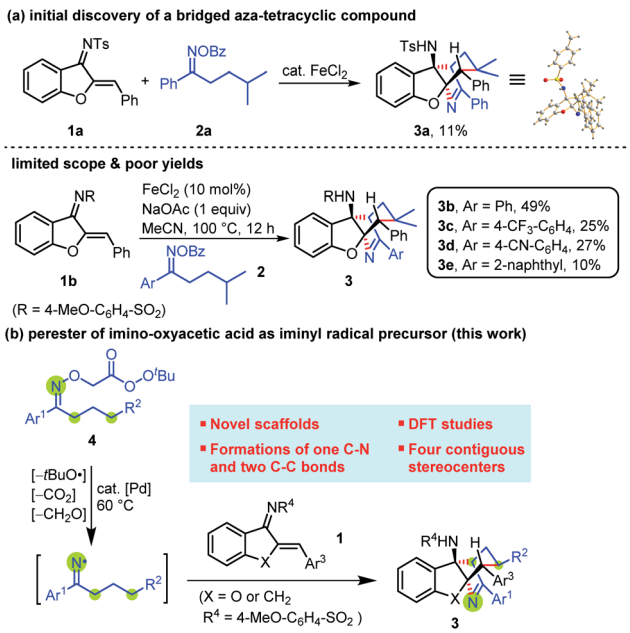


Scheme 2 Functionalization of iminyl radicals.

intermolecular annulations, including $(3+n)$, $(2+2+2)$, and $(5+n)$ annulations, have also been disclosed, by which various N-heterocycles were generated (Scheme 2b).[14] In these reactions, iminyl radicals either provided one atom (mono-functionalization) or two atoms (di-functionalization) to generate new chemical bonds. In terms of the functionalization of iminyl radicals, to the best of our knowledge, only mono- and di-functionalization fashions were revealed, which might limit their synthetic applications to some extent. In order to increase the atom utilization and enrich the structural diversity and complexity of organic molecules, we envisioned to challenge the tri-functionalization of iminyl radicals, in which multiple new chemical bonds (*e.g.*, three new chemical bonds) would be generated in one step (Scheme 2c).

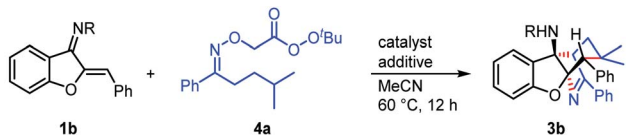
Our group[14l,m] has great interest in the iminyl radical-triggered relay annulation involving 1,5-hydrogen atom transfer[15,16] for the synthesis of N-heterocycles. During the survey of iminyl radical-induced (5 + *n*) annulation, we obtained a bridged aza-tetracyclic compound (**3a**) from the reaction of aurone-derived azadienes (**1a**) with isopentyl(phenyl) ketone-derived oxime (**2a**) (Scheme 3a). The structure of **3a** was unambiguously confirmed by single-crystal X-ray diffraction.[17] In this reaction, one C–N and two C–C bonds were newly formed accompanying the generation of two new bridged rings. This reaction not only involves the trifunctionalization of iminyl radicals, but also generates structurally novel bridged nitrogen skeletons. After numerous experiments,[18] we found that the reaction of azadiene (**1b**) and **2a** afforded a bridged aza-tetracyclic compound **3b** in 49% yield in the presence of $FeCl_2$ (10 mol%) and NaOAc (1 equiv.) at 100 °C in MeCN within 12 h. Unfortunately, the yield cannot be further improved. More regrettably, such reaction conditions were only amenable to limited substrate scope, and the yields were generally below 30% (*e.g.*, **3c**, **3d**, and **3e**). A key problem of this reaction might be the high reaction temperature used which led to rapid decomposition of the oximes.

Our recent study on the oxime transformation suggested that the use of high reaction temperature might be partially responsible for the N–O bond cleavage.[14m] In order to make this step occur at lower temperature, peresters **4** derived from the corresponding imino-oxyacetic acids were synthesized, which was inspired by Forrester's seminal work on iminyl radical transformations.[19] He demonstrated that the perester can undergo thermolysis to generate the iminyl radical. Moreover, it has been known that various transition metals can facilitate the homolysis of the weak O–O bond in peroxides.[20] Based on these significant studies, we envisaged that **4** could be converted into the same iminyl radicals at lower temperature in the presence of a suitable transition metal, which would involve the sequential



Scheme 3 Iminyl radical-triggered bridged aza-tetracycle synthesis.

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Additive	Yield[b] (%)
1	None	NaOAc	15
2	$FeCl_2$	NaOAc	41
3	$Fe(acac)_3$	NaOAc	32
4	CuBr	NaOAc	11
5	$CuBr_2$	NaOAc	Trace
6	$PdCl_2$	NaOAc	36
7	$Pd(OAc)_2$	NaOAc	35
8	$Pd_2(dba)_3$	NaOAc	40
9	$Pd(PPh_3)_2Cl_2$	NaOAc	60
10	$Pd(PCy_3)_2Cl_2$	NaOAc	43
11	$Pd(PPh_3)_2Cl_2$	None	10
12	$Pd(PPh_3)_2Cl_2$	PivONa	35
13	$Pd(PPh_3)_2Cl_2$	$PhCO_2Na$	13
14	$Pd(PPh_3)_2Cl_2$	NaOAc	Trace[c]
15	$Pd(PPh_3)_2Cl_2$	NaOAc	67[d]

[a] Reaction conditions: **1b** (0.3 mmol), **4a** (0.2 mmol), catalyst (0 or 10 mol%), additive (0 or 1 equiv.), MeCN (2 mL), 60 °C, 12 h, in a sealed tube, under Ar. [b] Isolated yields; dr > 19 : 1. [c] Reaction was run at 40 °C. [d] NaOAc (0.5 equiv.) was used.

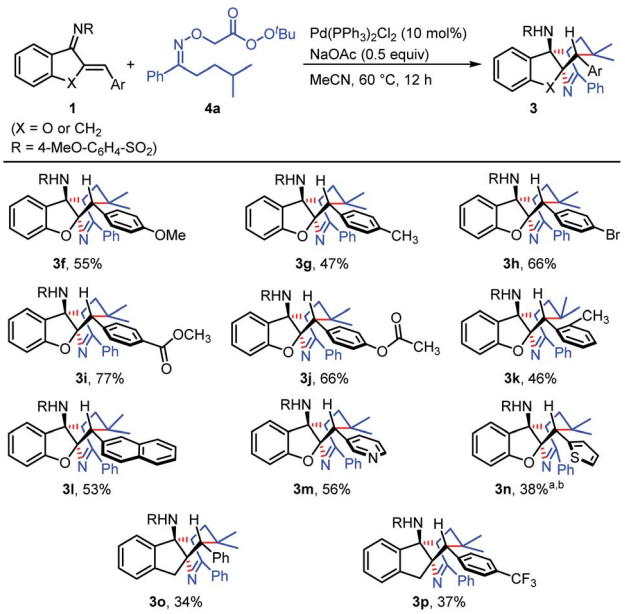
release of a *tert*-butoxy radical, formaldehyde, and carbon dioxide. As such, the desired bridged aza-tetracyclic compounds might also be generated (Scheme 3b). To verify our hypothesis, a plethora of experiments were conducted, and some important results obtained during the process are displayed in Table 1.

Results and discussion

Initially, aurone-derived azadiene (**1b**) and an oxime-derived perester (**4a**) were chosen as model substrates to optimize the reaction conditions toward the formation of the target product (**3b**).[18] We set the reaction temperature at 60 °C for the screening of transition metals. A control experiment showed that the product was obtained in 15% yield in the absence of a transition metal (entry 1). Since iron and copper salts are usually used to promote the O–O bond homolysis of peroxides, a series of iron and copper salts were studied (entries 2–5). The results showed that $FeCl_2$ and $Fe(acac)_3$ can promote the transformation (entries 2 and 3), while CuBr and $CuBr_2$ inhibited the reaction (entries 4 and 5). Gratifyingly, it was found that palladium salts were beneficial for the reaction (entries 6–10), and $Pd(PPh_3)_2Cl_2$ (ref. 21) exhibited the best reactivity, using which a 60% yield was obtained (entry 9). It is noteworthy that NaOAc was important for this transformation, because a very low yield was observed without such an additive (entry 11). By replacing NaOAc with PivONa or $PhCO_2Na$, the reaction took place albeit 35 and 13% yields were obtained, respectively (entries 12 and 13). In addition, decreasing the reaction temperature from 60 to 40 °C was detrimental to the transformation (entry 14). Finally, reducing the amount of NaOAc from 1 to 0.5 equiv. afforded a 67% yield of **3b** (entry 15).

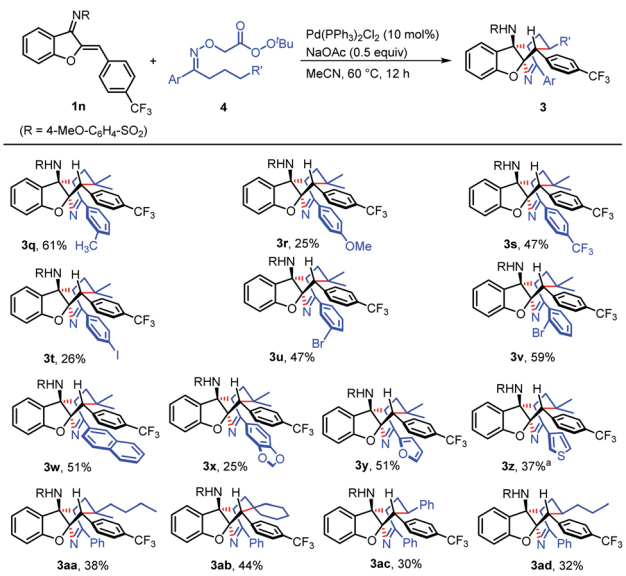
With the optimal reaction conditions in hand, we subsequently evaluated the substrate scope with respect to the azadienes using **4a** as another substrate (Scheme 4). Azadienes bearing methoxy (**3f**) and methyl (**3g**) groups at the para position of the aryl ring showed moderate reactivity, delivering the target products in 55 and 47% yields, respectively. In addition, azadienes with electron-withdrawing groups on the aromatic ring, such as bromo (**3h**) and ester (**3i** and **3j**) groups, reacted with **4a** to give rise to the products in moderate to good yields. The reaction gave 46% yield in the case of an azadiene with an *ortho*-methyl substitution on the aryl ring (**3k**). Note that, this protocol was applicable to some heterocycle-containing azadienes, including pyridine (**3m**) and thiophene (**3n**), which displayed moderate reactivity in the transformations. Furthermore, 1-indanone-derived azadienes were also found to be potential substrates to participate in the synthesis of the bridged tetracyclic N-heterocycles, which produced the target products in synthetically useful yields (**3o** and **3p**). Note that, in all cases, the target products were formed with excellent diastereoselectivity (>19 : 1).

This approach can be applied to a variety of oxime-derived peresters containing diverse functionalities (Scheme 5). The peresters bearing methyl (**3q**), methoxy (**3r**), trifluoromethyl (**3s**), iodo (**3t**), bromo (**3u** and **3v**), and naphthyl (**3w**) groups took part in the reactions to generate the corresponding bridged aza-tetracyclic compounds in synthetically useful yields.



Scheme 4 Substrate scope of aurone-derived azadienes. Reaction conditions: **1** (0.3 mmol), **4a** (0.2 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol%), NaOAc (0.5 equiv.), MeCN (2 mL), 60 °C, 12 h, in a sealed tube, under Ar; dr > 19 : 1. [a] $Pd(PPh_3)_2Cl_2$ (20 mol%) was used. [b] Reaction was run at 80 °C.

Significantly, heterocyclic moieties, including benzodioxole (**3x**), furan (**3y**), and thiophene (**3z**) also participated in the transformations. Besides the di-methyl group located at the γ position of the perester, methyl/*n*-butyl (**3aa**) and cyclohexyl (**3ab**) groups were also suitable. Not only tertiary carbon radicals, but also secondary carbon radicals can be formed, which



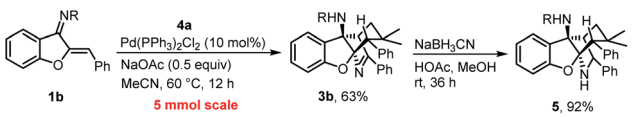
Scheme 5 Substrate scope of oxime-derived peresters. Reaction conditions: **1n** (0.3 mmol), **4** (0.2 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol%), NaOAc (0.5 equiv.), MeCN (2 mL), 60 °C, 12 h, in a sealed tube, under Ar; dr > 19 : 1. [a] Reaction was run at 80 °C.

can participate in the reactions to deliver the target products (**3ac** and **3ad**). In contrast, butyrophenone-derived perester failed to react, probably due to the low stability of the corresponding primary carbon radical.

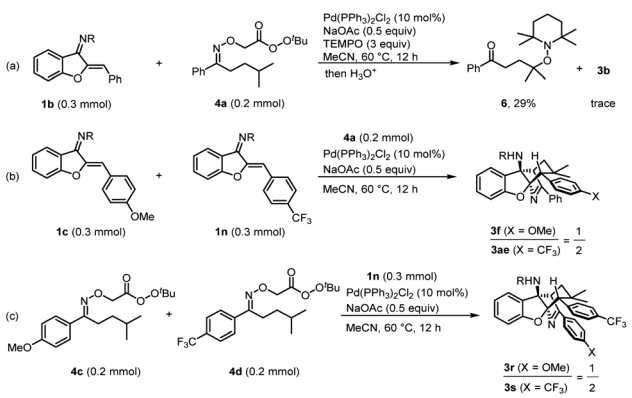
Our method is suitable for gram-scale reactions, which was demonstrated by a 5 mmol scale reaction between **1b** and **4a**. The obtained bridged aza-tetracyclic product **3b** can easily undergo reduction to generate a tetracyclic secondary amine **5** in excellent yield (Scheme 6).

To obtain insight into the reaction mechanism, we performed some experiments (Scheme 7). A reaction between **1b** and **4a** cannot generate the desired product **3b** in the presence of 3 equiv. of TEMPO as a radical scavenger, and significant amounts of radical-trapping product **6** were formed (Scheme 7a). These results suggested that a γ-carbon radical might be formed in the reaction. In addition, intermolecular competitive experiments were carried out. Under otherwise identical conditions, the azadiene bearing a trifluoromethyl group (**1n**) showed better reactivity, probably because it would be inclined to react with a nucleophilic carbon radical (Scheme 7b). Besides, the N–O bond might be more easily cleavable for **4d** containing a trifluoromethyl group, and thus, the reaction of **4d** with **1n** was faster than the reaction between **4c** and **1n** (Scheme 7c).

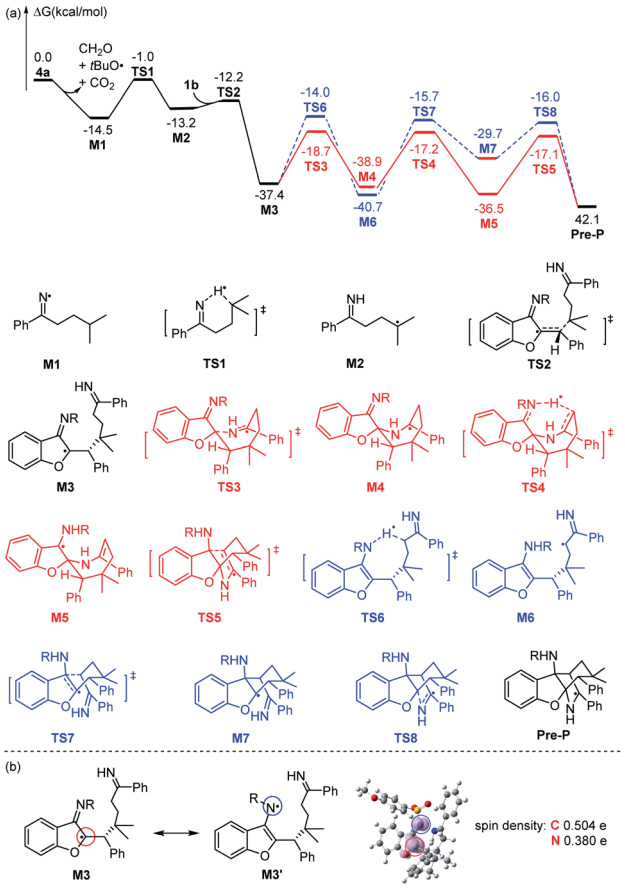
To further understand the mechanism of this interesting reaction from the oxime-derived peresters and azadienes, density functional theory (DFT) calculation has been performed at the M06-2X/Def2-SVP level of theory (Scheme 8).[22] Iminyl radical **M1** could be obtained from the homolytic cleavage of the peroxy bond of **4a** in the presence of a palladium salt,[23] which is exergonic by 14.5 kcal mol^{-1} with the release of carbon dioxide, formaldehyde, and a *tert*-butoxy radical. Then, 1,5-hydrogen



Scheme 6 Gram-scale reaction and reduction of **3b**. R = 4-MeO–C_6H_4–SO_2.



Scheme 7 Mechanistic studies: (a) a radical-trapping experiment. (b) and (c) Intermolecular competitive reactions. R = 4-MeO–C_6H_4–SO_2.



Scheme 8 (a) The free energy barrier for the transformation. (b) The resonance structure and the spin density population for the **M3**. R = 4-MeO–C_6H_4–SO_2.

atom transfer occurs *via* transition state **TS1** to deliver a tertiary alkyl radical **M2** with an energy barrier of 13.5. kcal mol^{-1}. The generated radical **M2** could be caught by azadiene **1b** *via* transition state **TS2** with a free energy barrier of only 1.0 kcal mol^{-1}. The formation of **M3** is exergonic by 25.2 kcal mol^{-1}. This species is a stable intermediate that might be caused by the spin distribution. As shown in Scheme 8b, two possible resonance structures for the intermediate **M3** could be drawn, which reveals either a carbon radical character (**M3**) or amino radical character (**M3′**). The further spin density calculation proved this point. The spin densities of carbon and nitrogen atoms are 0.504 and 0.380, respectively. Based on this idea, two possible pathways starting from either of these radical atoms have been proposed and considered by DFT calculations. From carbon radical resonance **M3**, an intramolecular radical addition into the imine moiety takes place *via* transition state **TS3** with a free energy barrier of 18.7 kcal mol^{-1}. The generated benzylic radical **M4** undergoes 1,6-hydorgen transfer *via* transition state **TS4** with a free energy barrier of 21.7 kcal mol^{-1} to afford carbon radical **M5**. Followed by another intramolecular radical addition to the C=C double bond *via* transition state **TS5**, the precursor of product **Pre-P** could be obtained, which can undergo oxidation to yield the final product **3b**. The free energy

barrier for the radical addition step is detected to be 19.4 kcal mol^{-1}. From the alternative amino radical resonance **M3′**, 1,7-hydrogen atom transfer would occur *via* transition state **TS6** to generate **M6** with a quite higher free energy barrier of 23.4 kcal mol^{-1}. After that, the relay intramolecular radical additions *via* transition states **TS7** and **TS8** would also provide the common precursor of product **Pre-P**. The computed free energy barriers for these two steps are 25.0 kcal mol^{-1} and 13.7 kcal mol^{-1}, respectively. The calculated results clearly show that the second pathway would be unfavorable.

Conclusions

In conclusion, we have established a new radical relay annulation protocol with oxime-derived peresters and azadienes as readily available substrates. This method shows good substrate scope and functional group tolerance, and generates a series of structurally interesting bridged aza-tetracyclic compounds with complex molecular topology and four contiguous stereogenic centers (dr > 19 : 1). These molecules might be recognized as privileged scaffolds in drug discovery. Our work represents the first example of the trifunctionalization of iminyl radicals by means of simultaneous formation of one C–N and two C–C bonds. The exploitation of more iminyl radical-triggered relay annulation for the efficient construction of N-heterocyclic skeletons is ongoing in our research group.

Data availability

All experimental data, and detailed experimental procedures are available in the ESI.†

Author contributions

K. J. and Y. W. conceived the project and prepared the manuscript. S.-J. L. and Y. L. performed the DFT calculation. Q.-P. L., N. Y., Y.-L. L., Y.-Q. Z., K.-C. H., J. L., T.-Y. Z., and J. L. performed experiments and analyzed the data.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) U. Anthonic, C. Christophersen and P. H. Nielsen, *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Elsevier, New York, 1999, vol. 14, pp. 163–236; (*b*) G. Wang, W. Tang and R. R. Bidigare, Terpenoids as therapeutic drugs and pharmaceuticals agents, in *Natural Products: Drug Discovery and Therapeutic Medicine*, ed. L. Zhang and A. L. Demain, Humana, Totowa, 2005, pp. 197–227.

2 (*a*) N. Keawpradub, P. J. Houghton, E. Eno-Amooquaye and P. J. Burke, *Planta Med.*, 1997, **63**, 97–101; (*b*) J. V. Pergolizzi, R. Taylor, J. A. LeQuang and R. B. Raffa, *J. Pain Res.*, 2018, **11**, 301–311; (*c*) E.-J. Shin, S.-Y. Nah, W.-K. Kim, K. H. Ko, W.-K. Jhoo, Y.-W. Lim, J. Y. Cha, C.-F. Chen and H.-C. Kim, *Br. J. Pharmacol.*, 2005, **144**, 908–918.

3 (*a*) A. B. Smith, B. A. Wexler, C.-Y. Tu and J. P. Konopelski, *J. Am. Chem. Soc.*, 1985, **107**, 1308–1320; (*b*) S. Tanimori, T. Sunami, K. Fukubayashi and M. Kirihata, *Tetrahedron*, 2005, **61**, 2481–2492.

4 For recent reviews, see: (*a*) C. Avendaño and J. C. Menéndez, Bicyclic 6-6 Systems with One Bridgehead (ring junction) Nitrogen Atom: No Extra Heteroatom, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, 2008, vol. 12, pp. 1–75; (*b*) K. Speck and T. Magauer, *Beilstein J. Org. Chem.*, 2013, **9**, 2048–2078.

5 For recent examples, see: (*a*) H.-Y. Lee, S. Lee, B. G. Kim and J. S. Bahn, *Tetrahedron Lett.*, 2004, **45**, 7225–7229; (*b*) Y. S. Tran and O. Kwon, *Org. Lett.*, 2005, **7**, 4289–4291; (*c*) P. B. Finn, B. P. Derstine and S. M. Sieburth, *Angew. Chem., Int. Ed.*, 2016, **55**, 2536–2539; (*d*) M. A. Haque and C. K. Jana, *Chem.–Eur. J.*, 2017, **23**, 13300–13304.

6 For recent reviews, see: (*a*) U. Wille, *Chem. Rev.*, 2013, **113**, 813–853; (*b*) A. Studer and D. P. Curran, *Angew. Chem., Int. Ed.*, 2016, **55**, 58–102; (*c*) J. Xie, H. Jin and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2017, **46**, 5193–5203; (*d*) M. P. Plesniak, H.-M. Huang and D. J. Procter, *Nat. Rev. Chem.*, 2017, **1**, 0077; (*e*) Y. Okada and K. Chiba, *Chem. Rev.*, 2018, **118**, 4592–4630; (*f*) H.-M. Huang, M. H. Garduño-Castro, C. Morrill and D. J. Procter, *Chem. Soc. Rev.*, 2019, **48**, 4626–4638; (*g*) C.-H. Xu, Y. Li, J.-H. Li, J.-N. Xiang and W. Deng, *Sci. China: Chem.*, 2019, **62**, 1463–1475.

7 For recent reviews, see: (*a*) M. Kitamura and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 539–547; (*b*) J. C. Walton, *Acc. Chem. Res.*, 2014, **47**, 1406–1416; (*c*) H. Huang, X. Ji, W. Wu and H. Jiang, *Chem. Soc. Rev.*, 2015, **44**, 1155–1171; (*d*) X. Zhu and S. Chiba, *Chem. Soc. Rev.*, 2016, **45**, 4504–4523; (*e*) D. S. Bolotin, N. A. Bokach, M. Y. Demakova and V. Y. Kukushkin, *Chem. Rev.*, 2017, **117**, 13039–13122; (*f*) N. J. Race, I. R. Hazelden, A. Faulkner and J. F. Bower, *Chem. Sci.*, 2017, **8**, 5248–5260; (*g*) L. M. Stateman, K. M. Nakafuku and D. A. Nagib, *Synthesis*, 2018, **50**, 1569–1586; (*h*) J. Davies, S. P. Morcillo, J. J. Douglas and D. Leonori, *Chem.–Eur. J.*, 2018, **24**, 12154–12163; (*i*) S. P. Morcillo, *Angew. Chem., Int. Ed.*, 2019, **58**, 14044–14054.

8 E. M. Dauncey, S. P. Morcillo, J. J. Douglas, N. S. Sheikh and D. Leonori, *Angew. Chem., Int. Ed.*, 2018, **57**, 744–748.

9 J. Ke, Y. Tang, H. Yi, Y. Li, Y. Cheng, C. Liu and A. Lei, *Angew. Chem., Int. Ed.*, 2015, **54**, 6604–6607.

10 X. Tang, L. Huang, Y. Xu, J. Yang, W. Wu and H. Jiang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4205–4208.
11 R. O. Torres-Ochoa, A. Leclair, Q. Wang and J. Zhu, *Chem.–Eur. J.*, 2019, **25**, 9477–9484.
12 (*a*) X. Shen, J.-J. Zhao and S. Yu, *Org. Lett.*, 2018, **20**, 5523–5527; (*b*) L. Chen, L.-N. Guo, Z.-Y. Ma, Y.-R. Gu, J. Zhang and X.-H. Duan, *J. Org. Chem.*, 2019, **84**, 6475–6482.
13 Z. Li, R. O. Torres-Ochoa, Q. Wang and J. Zhu, *Nat. Commun.*, 2020, **11**, 403–409.
14 (*a*) Y. Wei and N. Yoshikai, *J. Am. Chem. Soc.*, 2013, **135**, 3756–3759; (*b*) X. Tang, L. Huang, C. Qi, W. Wu and H. Jiang, *Chem. Commun.*, 2013, **49**, 9597–9599; (*c*) Q. Wu, Y. Zhang and S. Cui, *Org. Lett.*, 2014, **16**, 1350–1353; (*d*) M.-N. Zhao, Z.-H. Ren, L. Yu, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.*, 2016, **18**, 1194–1197; (*e*) H. Huang, J. Cai, X. Ji, F. Xiao, Y. Chen and G.-J. Deng, *Angew. Chem., Int. Ed.*, 2016, **55**, 307–311; (*f*) W. W. Tan, Y. J. Ong and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2017, **56**, 8240–8244; (*g*) C. Zhu, R. Zhu, H. Zeng, F. Chen, C. Liu, W. Wu and H. Jiang, *Angew. Chem., Int. Ed.*, 2017, **56**, 13324–13328; (*h*) B. Zhao, H.-W. Liang, J. Yang, Z. Yang and Y. Wei, *ACS Catal.*, 2017, **7**, 5612–5617; (*i*) H.-B. Yang and N. Selander, *Chem.–Eur. J.*, 2017, **23**, 1779–1783; (*j*) D. Bai, X. Wang, G. Zheng and X. Li, *Angew. Chem., Int. Ed.*, 2018, **57**, 6633–6637; (*k*) J. Yang, B. Zhao, Y. Xi, S. Sun, Z. Yang, Y. Ye, K. Jiang and Y. Wei, *Org. Lett.*, 2018, **20**, 1216–1219; (*l*) W. Liang, K. Jiang, F. Du, J. Yang, L. Shuai, Q. Ouyang, Y.-C. Chen and Y. Wei, *Angew. Chem., Int. Ed.*, 2020, **59**, 19222–19228; (*m*) F. Du, S.-J. Li, K. Jiang, R. Zeng, X.-C. Pan, Y. Lan, Y.-C. Chen and Y. Wei, *Angew. Chem., Int. Ed.*, 2020, **59**, 23755–23762.
15 For recent reviews regarding the radical-triggered 1,5-HAT reactions, see: (*a*) J. Robertson, J. Pillai and R. K. Lush, *Chem. Soc. Rev.*, 2001, **30**, 94–103; (*b*) Ž. Čeković, *Tetrahedron*, 2003, **59**, 8073–8090; (*c*) S. Chiba and H. Chen, *Org. Biomol. Chem.*, 2014, **12**, 4051–4060; (*d*) M. Yan, J. C. Lo, J. T. Edwards and P. S. Baran, *J. Am. Chem. Soc.*, 2016, **138**, 12692–12714; (*e*) L. Capaldo and D. Ravelli, *Eur. J. Org. Chem.*, 2017, 2056–2071; (*f*) X.-Q. Hu, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 1960–1962; (*g*) L. M. Stateman, K. M. Nakafuku and D. A. Nagib, *Synthesis*, 2018, **50**, 1569–1586; (*h*) X. Wu and C. Zhu, *Chem. Commun.*, 2019, **55**, 9747–9756; (*i*) G. Kumar, S. Pradhan and I. Chatterjee, *Chem.–Asian J.*, 2020, **15**, 651–672; (*j*) D.-Q. Dong, J.-C. Song, S.-H. Yang, Q.-X. Qin, Z.-L. Wang, E.-X. Zhang, Y.-Y. Sun, Q.-Q. Han and S. Yue, *Chin. Chem. Lett.*, 2022, **33**, 1199–1206.
16 For recent examples regarding the radical-triggered 1,5-HAT reactions, see: (*a*) Y.-F. Wang, H. Chen, X. Zhu and S. Chiba, *J. Am. Chem. Soc.*, 2012, **134**, 11980–11983; (*b*) P. Yu, J.-S. Lin, L. Li, S.-C. Zheng, Y.-P. Xiong, L.-J. Zhao, B. Tan and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 11890–11894; (*c*) G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu and R. R. Knowles, *Nature*, 2016, **539**, 268–271; (*d*) J. C. K. Chu and T. Rovis, *Nature*, 2016, **539**, 272–275; (*e*) J. Zhang, Y. Li, F. Zhang, C. Hu and Y. Chen, *Angew. Chem., Int. Ed.*, 2016, **55**, 1872–1875; (*f*) C. Wang, K. Harms and E. Meggers, *Angew. Chem., Int. Ed.*, 2016, **55**, 13495–13498; (*g*) E. A. Wappes, K. M. Nakafuku and D. A. Nagib, *J. Am. Chem. Soc.*, 2017, **139**, 10204–10207; (*h*) W. Yuan, Z. Zhou, L. Gong and E. Meggers, *Chem. Commun.*, 2017, **53**, 8964–8967; (*i*) A. Hu, J.-J. Guo, H. Pan, H. Tang, Z. Gao and Z. Zuo, *J. Am. Chem. Soc.*, 2018, **140**, 1612–1616; (*j*) Y. Xia, L. Wang and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 12940–12944; (*k*) H. Guan, S. Sun, Y. Mao, L. Chen, R. Lu, J. Huang and L. Liu, *Angew. Chem., Int. Ed.*, 2018, **57**, 11413–11417; (*l*) S. P. Morcillo, E. M. Dauncey, J. H. Kim, J. J. Douglas, N. S. Sheikh and D. Leonori, *Angew. Chem., Int. Ed.*, 2018, **57**, 12945–12949; (*m*) X.-X. Wu, H. Zhang, N.-N. Tang, Z. Wu, D.-P. Wang, M.-S. Ji, Y. Xu, M. Wang and C. Zhu, *Nat. Commun.*, 2018, **9**, 3343; (*n*) Z. Li, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 13288–13292; (*o*) D. Kurandina, D. Yadagiri, M. Rivas, A. Kavun, P. Chuentragool, K. Hayama and V. Gevorgyan, *J. Am. Chem. Soc.*, 2019, **141**, 8104–8109; (*p*) S. Wu, X. Wu, D. Wang and C. Zhu, *Angew. Chem., Int. Ed.*, 2019, **58**, 1499–1503; (*q*) K. Wu, L. Wang, S. Colón-Rodríguez, G.-U. Flechsig and T. Wang, *Angew. Chem., Int. Ed.*, 2019, **58**, 1774–1778.
17 CCDC 2048559 (**3a**) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.
18 Please see the ESI† for more details.
19 (*a*) A. R. Forrester, M. Gill, C. J. Meyer, J. S. Sadd and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 606–611; (*b*) A. R. Forrester, M. Gill, J. S. Sadd and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 612–615.
20 (*a*) M. S. Kharasch and G. Sosnovsky, *J. Am. Chem. Soc.*, 1958, **80**, 756; (*b*) J. Eames and M. Watkinson, *Angew. Chem., Int. Ed.*, 2001, **40**, 3567–3571; (*c*) M. B. Andrus and J. S. Lashley, *Tetrahedron*, 2002, **58**, 845–866; (*d*) S. Wertz, D. Leifert and A. Studer, *Org. Lett.*, 2013, **15**, 928–931; (*e*) K. Foo, E. Sella, I. Thomé, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5279–5282; (*f*) W. Jian, L. Ge, Y. Jiao, B. Qian and H. Bao, *Angew. Chem., Int. Ed.*, 2017, **56**, 3650–3654; (*g*) B. Qian, S. Chen, T. Wang, X. Zhang and H. Bao, *J. Am. Chem. Soc.*, 2017, **139**, 13076–13082; (*h*) Y. Li, L. Ge, M. T. Muhammad and H. Bao, *Synthesis*, 2017, **49**, 5263–5284.
21 $Pd(PPh_3)Cl_2$ (99.9%) was purchased from Strem Chemicals.
22 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215–241.
23 Y. Lan, *Computational Methods in Organometallic Catalysis*, Wiley-VCH, Germany, 2021.