Exploring α-Chromonyl Nitrones as 1,5-Dipoles

Kathrin Wittstein,[a,b] Ana B. García,[a] Markus Schürmann,[c] Kamal Kumar*[a,b]

[a] Max-Planck-Institut für Molekulare Physiologie, Otto-Hahn-Str. 11, 44227 Dortmund, Germany
Fax +49(231)1332496; E-mail: Kamal.Kumar@mpi-dortmund.mpg.de

[b] Technische Universität Dortmund, Fachbereich Chemie, Chemische Biologie, 44221 Dortmund, Germany

[c] Technische Universität Dortmund, Anorganische Chemie, 44221 Dortmund, Germany

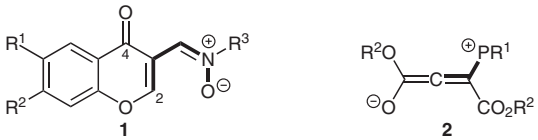
Received 17 October 2011

Abstract: *N*-Phenyl-*C*-chromonyl nitrones **1** and the allenoate zwitterion **2**, generated by addition of phosphine to acetylenedicarboxylates, undergo a cascade reaction sequence involving an unprecedented [5+3] annulation followed by deoxygenative rearrangement leading to dihydropyridine-fused benzopyrones. Unusual electronic control by the N-substituents of **1** directs the annulation pathway, leading to two different ring-systems.

Keywords: nitrones, dipolar cycloadditions, acetylene carboxylates, cascade reactions, zwitterions

Ring systems form the core of many natural products and drug molecules and provide the spatial arrangement for interacting with proteins and other macromolecules.[1] Although the biological relevance of scaffolds that exist in natural products or privileged frameworks of drugs (for instance, benzodiazepines) makes them useful starting points for compound library synthesis,[2] there is always a demand and scope for novel molecular architectures in medicinal chemistry and drug discovery reasearch.[3] Consequently, new annulation reactions that provide access to new ring systems are highly desirable. We have been exploring the annulation chemistry of electronically similar substrates with the expectation that this might provide interesting and novel scaffolds that are amenable to the synthesis of focused compound collections.[4] For instance, we have recently developed a [4+2] annulation between electron-deficient oxadienes and electron-poor acetylenes, leading to tricyclic benzopyrones.[4a–c] In a continuation of this program, and seeking access to unprecedented ring-systems based on the privileged benzopyrone scaffold, we wanted to examine whether the two dipoles, a nitrone **1**[5] and a zwitterion **2**[6] (generated in situ by addition of phosphine to acetylenedicarboxylates; Figure 1) would undergo an annulation reaction.

Similar to nitrones **3**, benzopyrone nitrones of type **1** have been reported to undergo [3+2] cycloadditions with both electron-rich and electron-deficient olefins.[5] We were curious to realize the potential of nitrone **1** as a 1,5-dipole in annulation chemistry because this would provide novel ring-systems embodying the benzopyrone scaffold. In general, a 1,5-dipolar cycloaddition/annulation reaction of any conjugated nitrone[7] remains unprecedented.[8] Herein, we report the first case of trapping nitrone **1** as a 1,5-dipole in a cascade sequence of annulation–rearrangement reaction with a phospha-zwitterion derived from dimethyl acetylenedicarboxylate (DMAD), leading to novel dihydropyridine fused benzopyrones.



1a; $R^1 = R^3 = Me$, $R^2 = H$
1b; $R^1 = Cl$, $R^2 = R^3 = Me$
1c; $R^1 = Me$, $R^2 = H$, $R^3 = Bn$
1d; $R^1 = R^2 = H$, $R^3 = Bn$
1e; $R^1 = Cl$, $R^2 = H$, $R^3 = Bn$
1f; $R^1 = Me$, $R^2 = H$, $R^3 = Ph$
1g; $R^1 = Cl$, $R^2 = Me$, $R^3 = Ph$
1h; $R^1 = R^2 = H$, $R^3 = Ph$
1i; $R^1 = i$-Pr, $R^2 = H$, $R^3 = Ph$

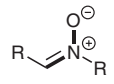
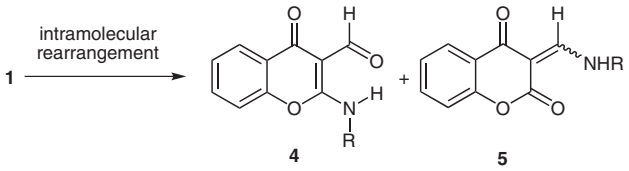


Figure 1 Dipolar species used to probe reactivity

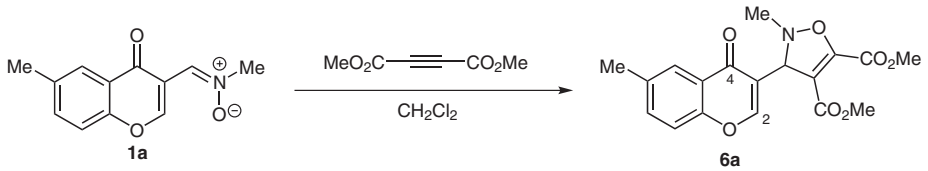
However, rearrangement of nitrones **1** to products **4** and **5** is quite facile (Scheme 1)[9] and, in the absence of reactive partners, could prove to compete strongly with the envisaged annulation/cycloaddition reactions.



Scheme 1 Rearrangement of nitrone **1** yields **4** and **5**

Although [3+2] cycloaddition reactions of nitrone **1** with electron-deficient olefines have been reported, similar attempts with electron-poor alkynes remain unprecedented. Before employing the zwitterion **2** with nitrone **1**, a reaction of *N*-methylnitrone **1a** with DMAD in dichloromethane at room temperature was attempted (Scheme 2); this led to the formation of [3+2] adduct **6a** (35% yield; Table 1, entry 1) along with the nitrone rearrangement products **4** and **5**. No trace of a plausible [5+2] cycloadduct was observed. Increasing the reaction temperature led only to increased amounts of the rearranged products (Table 1, entry 2).

SYNLETT 2012, 23, 227–232
Advanced online publication: 03.01.2012
DOI: 10.1055/s-0031-1290070; Art ID: B56411ST



Scheme 2

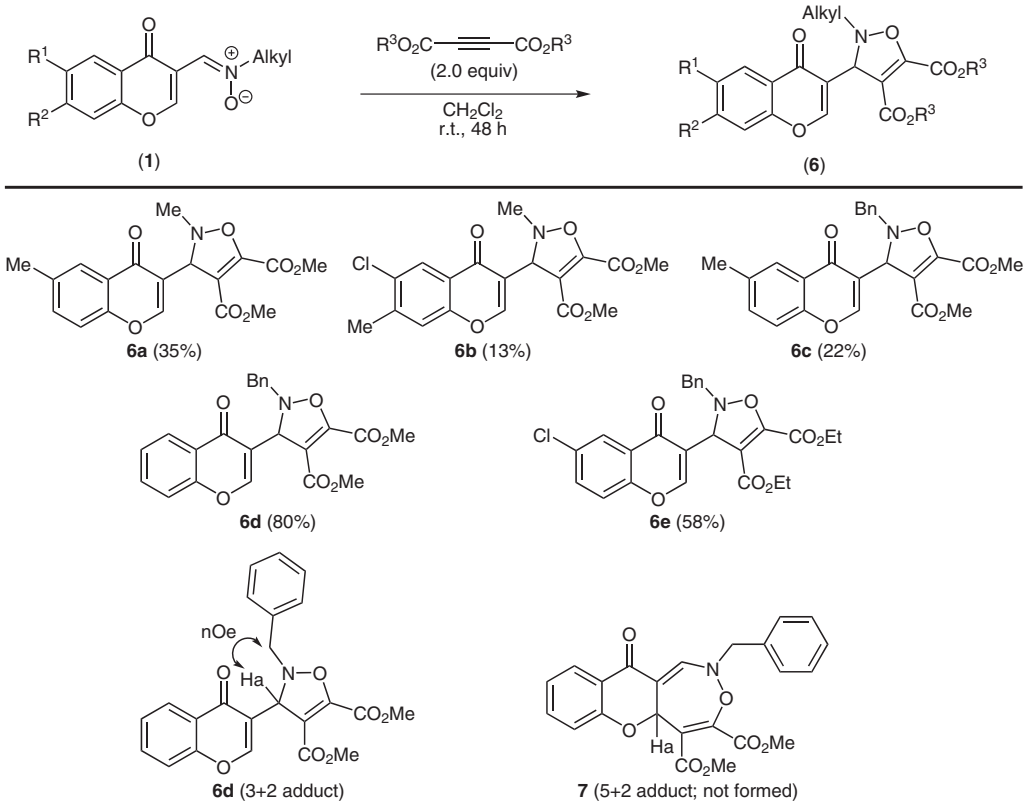
Table 1 [3+2] Cycloaddition of Nitrone **1** with DMAD

Entry	Additive (equiv)	Temp	Yield **6a** (%)[a]
1	–	r.t.	35
2	–	40 °C	15
3	Ph_3P (0.2)	r.t.	30
4	Ph_3P (1.2)	r.t.	32
5	$(PhCF_3)_3P$ (1.2)	r.t.	30
6	$(NMe_2)_3P$ (1.2)	r.t.	–
7	DABCO (1.3)	r.t.	–
8	Ph_3P (1.2) + H_2O (3 M LiOH)	r.t.	–

[a] Isolated yield.

Zwitterionic nucleophiles, generated by addition of phosphines to acetylenecarboxylates or allenic esters, often add to the highly electrophilic C2 position of conjugated chromone systems, including 3-formylchromone and its corresponding imines.[4a–c,10] Therefore, we were expecting a similar addition of allenoate **2** on the C2 of nitrone **1**, which may trap it as a 1,5-dipole. To this end, reactions of zwitterion **2**, generated by different Lewis base nucleophiles (Table 1, entries 3–8), were attempted with **1**. Employing triphenylphosphine neither provided the [5+2] adduct nor enhanced the yield of **6a** (Table 1, entries 3 and 4). Electron-poor phosphine $(PhCF_3)_3P$ was as good as Ph_3P at yielding **6a** (entry 5) but did not provide any [5+2] cycloadduct. In contrast, electron-rich phosphine and tertiary amine DABCO did not provide any cycloadduct at all (Table 1, entries 6 and 7). Garicia-Tellado and coworkers had reported an 'on-water' [3+2] cycloaddition of nitrones with allenoate **2**.[11] However, in our hands, these reaction conditions also failed to yield any cycloadduct of DMAD with **1** (Table 1, entry 8).

N-Methyl- and *N*-benzyl-*C*-chromonyl nitrones also provided the corresponding [3+2] cycloadducts with acetylenedicarboxylates (Scheme 3). Interestingly, while *N*-methyl nitrones provided only moderate yields of adducts **6a** and **6b**, reactions of *N*-benzyl nitrones were both cleaner and higher yielding (**6c**–**e**). It should be noted that most



Scheme 3 [3+2] Cycloaddition of *N*-alkyl-*C*-chromonyl nitrones with acetylenedicarboxylates

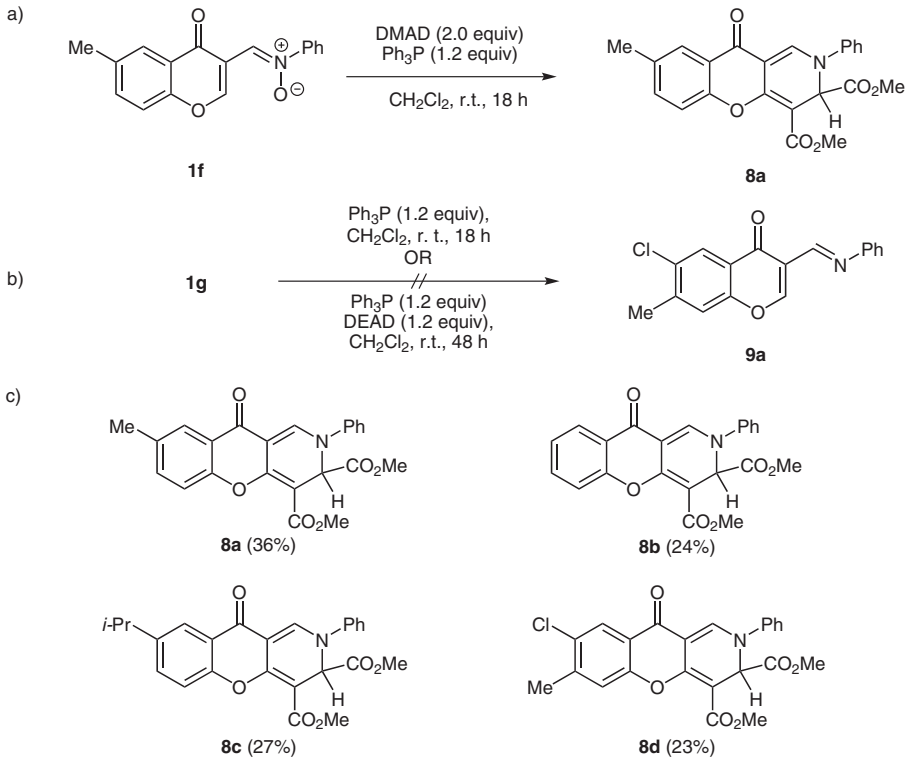
of the spectroscopic data fits well with both of the molecular structures of [3+2] (**6**) and [5+2] adducts (**7**), rendering structural assignment quite difficult. However, a strong NOE interaction between the H_a proton with the benzylic protons in **6d** favored the formation of [3+2] adducts (Scheme 3). Furthermore, a carbon signal for the vinylogous ester (C4 appearing at δ = 176.5 ppm) and C2 (δ = 155 ppm) clearly indicated the intact chromone moiety in **6d**.[5a]

To our surprise, when *N*-phenyl nitrone **1f** was employed in the reaction with DMAD, no [3+2] cycloaddition product was obtained. Anticipating an addition of nucleophilic zwitterion **2** to **1f**, the reaction was attempted with a catalytic amount (20 mol%) of triphenylphosphine. However, only trace amounts of a new addition product was obtained. The yield of the latter increased with the amounts of PPh_3 and reached a maximum using 1.2 equivalent of phosphine (Scheme 4). The structure of this adduct was unambiguously established by X-ray crystallographic analysis to be a dihydropyridine fused benzopyrone (**8a**).[12] Other nucleophiles presented in Table 1, however, failed to deliver **8a** under a range of reaction conditions (using 20 mol% to 2.0 equivalents; from room temperature to 50 °C; and up to 72 h reaction time) and only nitrone rearranged products were obtained. Furthermore, electron-rich tributylphosphine did not yield **8a** at all. Dichloromethane proved to be the solvent of choice among the solvents tested (toluene, THF, MeCN, MeOH, H_2O/LiOH) in the triphenylphosphine-mediated synthesis of dihydropyridine-fused benzopyrone **8a** and provided a moderate yield of **8a**. However, the intramolecular rearrangement of nitrone **1** remained the favored transformation and could not be avoided. Other substituted nitrones were also successfully employed to yield novel dihydropyridine-fused benzopyrones in moderate yields (Scheme 4c).[13–15]

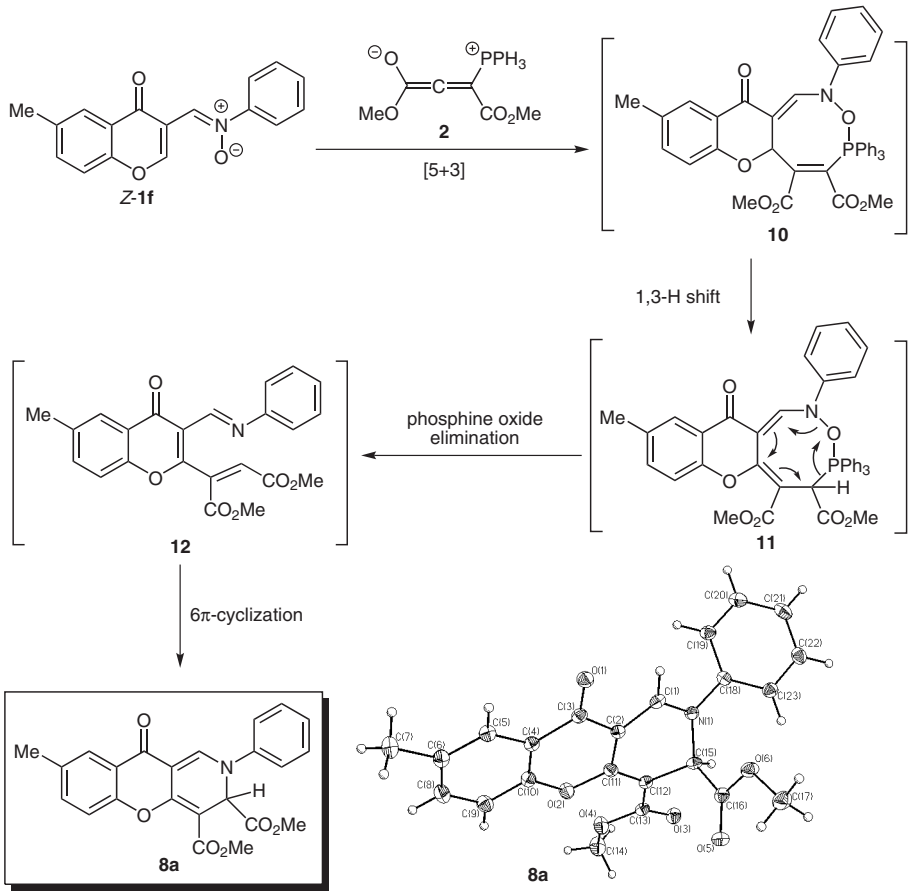
Formation of cycloadduct **8** in the above reactions was quite an unexpected result. We considered whether triphenylphospine had induced any deoxygenation[16] of nitrone leading to an azadiene **9** that might involve DMAD to form **8**. In separate experiments, treatment of **1g** with triphenylphosphine under the annulation reaction conditions and also in the presence of acceptor diethyl azodicarboxylate (DEAD) did not result in any deoxygenation (Scheme 4b), which thus ruled out this reaction pathway.

A plausible mechanism for the formation of adduct **8** is depicted in Scheme 5. We assume that the two dipoles, for instance, nitrone **1f** and zwitterion **2** derived from DMAD and triphenylphosphine, add initially in a [5+3] annulation (either in a concerted or stepwise manner) yielding an eight-membered-ring intermediate **10**. Larger rings facilitate hydride shifts[17] and a 1,3-hydride shift in **10** provides intermediate **11**. The latter eliminates phosphine oxide leading to imine **12,** which eventually undergoes 6π electrocyclization to yield the tricyclic benzopyrone **8a** (Scheme 5).

To gain further insights into this cascade annulation–rearrangement sequence, the deuterium labeled nitrone **1h**-d_2 (see the Supporting Information) was treated with DMAD and triphenylphosphine and the expected deuterated adduct **8b**-d_2 was obtained in 21% yield (Scheme 6). Although 75% of the deuterium at C3 (the highly acidic α-



Scheme 4 Synthesis of dihydropyridine-fused benzoypyrones through phosphine-mediated annulation

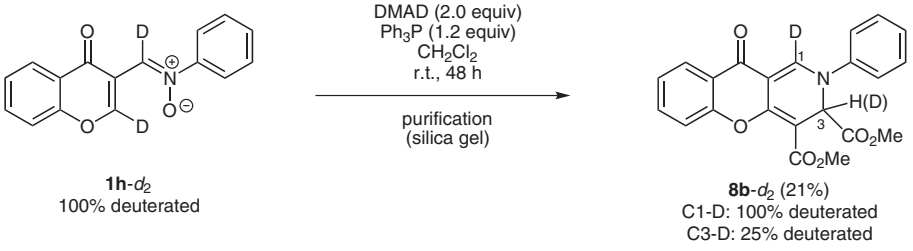


Scheme 5 Proposed reaction mechanism for the cascade annulation leading to dihydropyridine-fused benzopyrones **8**

position next to an ester and a nitrogen) was exchanged with protons during silica gel column chromatographic purification, the experiment provided ample evidence for the suggested 1,3-hydride shift occurring after [5+3] annulation.

The non-catalytic [3+2] cycloaddition of *N*-alkyl nitrones **1a–e** with acetylenedicarboxylates seems to be driven by a $HOMO_{(nitrone)}$:$LUMO_{(acetylenedicarboxylates)}$ interaction[18] that favors 1,3-dipolar cycloaddition. However, the different reactivity of *N*-phenyl-*C*-chromonyl nitrones **1f–i** could originate from the differing electronic nature of *N*-aryl nitrones as well as their preferred *Z*-configuration.[5a,19] It is noteworthy that the facile rearrangement of nitrones **1** begins with an intramolecular 1,5-cyclization[9] that is clearly facilitated by a *Z*-configuration of **1**. Larger amounts of rearranged products **4** and **5** (or moderate yields of **8**) obtained with *N*-aryl-*C*-chromonyl nitrones **1f–i** clearly supports its preferred *Z*-configuration. We assume that the *Z*-configuration of **1f–i** facilitates the initial [5+3] annulation, leading to intermediate **10**, which eventually provides benzopyrones **8** (Scheme 5).

In summary, for the first time, conjugated *N*-phenyl-*C*-chromonyl nitrones were trapped as 1,5-dipoles in a reaction with nucleophilic zwitterions generated by addition of triphenylphosphine to acetylenedicarboxylates. N-Substituents of nitrones **1** display amazing electronic control over the mode of cycloaddition/annulation reactions. Whereas the *N*-alkyl-substituted nitrones **1a–e** follow a non-catalytic [3+2] cycloaddition path, the corresponding *N*-phenyl analogues undergo a phosphine-mediated cascade reaction sequence of [5+3] annulation–rearrangement and yielded novel dihydropyridine fused



Scheme 6 Cascade annulation of DMAD with deuterated nitrone **1h**-d_2 provides evidence for the proposed 1,3-hydride shift

benzopyrones **8**. We believe that these results might be intriguing for further exploration of conjugated nitrones as 1,5-dipoles and their applications in organic synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This research work was supported by the Max Planck Gesellschaft. We thank Dr M. G. Sankar, MPI, Dortmund for his help in some control experiments.

References and Notes

(1) (a) Ertl, P.; Jelfs, S.; Muhlbacher, J.; Schuffenhauer, A.; Selzer, P. *J. Med. Chem.* **2006**, *49*, 4568. (b) Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 2879. (c) Böhm, H.-J.; Flohr, A.; Stahl, M. *Drug Discovery Today: Technol.* **2004**, *1*, 217. (d) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887.

(2) (a) Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3224. (b) Wetzel, S.; Klein, K.; Renner, S.; Rauh, D.; Oprea, T. I.; Mutzel, P.; Waldmann, H. *Nat. Chem. Biol.* **2009**, *5*, 696. (c) Renner, S.; van Otterlo, W. A. L.; Seoane, M. D.; Mocklinghoff, S.; Hofmann, B.; Wetzel, S.; Schuffenhauer, A.; Ertl, P.; Oprea, T. I.; Steinhilber, D.; Brunsveld, L.; Rauh, D.; Waldmann, H. *Nat. Chem. Biol.* **2009**, *5*, 585. (d) Nandy, J. P.; Prakesch, M.; Khadem, S.; Reddy, P. T.; Sharma, U.; Arya, P. *Chem. Rev.* **2009**, *109*, 1999.

(3) Ganesan, A. *Curr. Opin. Chem. Biol.* **2008**, *12*, 306.

(4) (a) Waldmann, H.; Khedkar, V.; Dückert, H.; Schürmann, M.; Oppel, I. M.; Kumar, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 6869. (b) Dückert, H.; Khedkar, V.; Waldmann, H.; Kumar, K. *Chem. Eur. J.* **2011**, *17*, 5130. (c) Baskar, B.; Dakas, P.-Y.; Kumar, K. *Org. Lett.* **2011**, *13*, 1988. (d) Wittstein, K.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 9076. (e) Waldmann, H.; Bruss, H.; Dückert, H.; Kumar, K. *Tetrahedron Lett.* **2011**, *52*, 2265.

(5) (a) Ishar, M. P. S.; Singh, G.; Kumar, K.; Singh, R. *Tetrahedron* **2000**, *56*, 7817. (b) Boruah, A. K.; Prajapati, D.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1995.

(6) (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

(7) (a) Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6613. (b) Lopez-Calle, E.; Höfler, J.; Eberbach, W. *Liebigs Ann.* **1996**, 1855.

(8) For reviews on cycloaddition reactions of nitrones, see: (a) Kanemase, S. *Heterocycles* **2010**, *82*, 87. (b) Nguyen, T. B.; Martel, A.; Gaulon, C.; Dhal, R.; Dujardin, G. *Org. Prep. Proced. Int.* **2010**, *42*, 387. (c) Bokach, N. A. *Russ. Chem. Rev.* **2010**, *79*, 89. (d) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808. (e) Rueck-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507. (f) Banerji, A.; Bandyopadhyay, D. *J. Indian Chem. Soc.* **2004**, *81*, 817. (g) Merino, P. *Nitrones and Analogues,* In *Science of Synthesis*; George Thieme Verlag: Stuttgart, **2004**, Chap. 13, 511. (h) Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205.

(9) (a) Ishar, M. P. S.; Kumar, K.; Singh, R. *Tetrahedron Lett.* **1998**, *39*, 6547. (b) Ghosh, T.; Bandyopadhyay, C. *Tetrahedron Lett.* **2004**, *45*, 6169.

(10) Kumar, K.; Kapoor, R.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 2023.

(11) González-Cruz, D.; Tejedor, D.; de Armas, P.; Moralesa, E. Q.; García-Tellado, F. *Chem. Commun.* **2006**, 2798.

(12) Crystallographic data for **8a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC-848674). Copies of the data can be obtained free of charge at www.ccdc.cam.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ [fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk]

(13) Representative procedure for the synthesis of dihydropyridine fused benzopyrones **8a**: To a solution of nitrone **1f–i** (94 mg, 0.34 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dimethyl acetylenedicarboxylate (83 μL, 0.67 mmol, 2 equiv), followed by triphenylphosphine (88 mg, 0.4 mmol, 1.2 equiv). The resulting mixture was stirred at r.t. for 48 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (EtOAc–petroleum ether, 15–18%) to give **8a** (48 mg, 0.12 mmol, 36% yield) as a yellow solid

(14) Compound **8a**: R_f = 0.35 (EtOAc–petroleum ether, 40%); mp 226–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 1.8 Hz, 1 H), 7.87 (d, *J* = 1.9 Hz, 1 H,), 7.51–7.44 (m, 2 H), 7.41–7.34 (m, 4 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 6.10 (d, *J* = 1.7 Hz, 1 H), 3.87 (s, 3 H), 3.74 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.54, 170.29, 164.85, 156.97, 154.45, 147.13, 143.13, 135.75, 133.75, 129.83, 127.71, 125.89, 121.47, 120.24, 117.34, 105.59, 84.38, 61.98, 53.11, 51.62, 20.64; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{20}NO_6$: 406.12851; found: 406.12806

(15) Compound **8d**: R_f = 0.37 (EtOAc–petroleum ether, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 1.7 Hz, 1 H), 8.03 (s, 1 H), 7.48 (dd, *J* = 7.7 Hz, 2 H), 7.40–7.32 (m, 3 H), 7.21 (s, 1 H), 6.10 (d, *J* = 1.7 Hz, 1 H), 3.87 (s, 3 H), 3.74 (s, *J* = 5.1 Hz, 3 H), 2.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.24, 170.18, 164.68, 155.54, 154.47, 147.20, 143.81, 143.09, 130.19, 129.89, 127.88, 126.06, 121.55, 119.81, 119.66, 105.13, 84.92, 62.02, 53.19, 51.71, 20.70; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}ClNO_6$: 440.08954; found: 440.08909; *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}Cl^{37}NO_6$: 442.08659; found: 442.08630

(16) For deoxygenation of nitrones with phosphines and phosphites, see: (a) Cividino, P.; Dheu-Andries, M.-L.; Ou, J.; Milet, A.; Py, S.; Toy, P. H. *Tetrahedron Lett.* **2009**, *50*, 7038. (b) Horner, L.; Hoffmann, H. *Angew. Chem.* **1956**, *68*, 473. (c) Agolini, F.; Bonnett, R. *Can. J. Chem.* **1962**, *40*, 181. (d) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929. (e) Milliet, P.; Lusinchi, X. *Tetrahedron* **1979**, *35*, 43.

(17) Molnar, A.; Bucsi, I.; Bartok, M. *Tetrahedron* **1992**, *48*, 4929.

(18) (a) Bayón, P.; de March, P.; Figueredo, M.; Font, J.; Medrano, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4269. (b) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569. (c) Gilchrist, T. L.; Storr, R. C. In *Organic Reactions and Orbital Symmetry*; Cambridge University: Cambridge, **1972**, 132. (d) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, **1976**, 148–161. (e) Padwa, A.; Fisera, L.; Koehler, K. F.; Rodriguez, A.; Wong, G. S. K. *J. Org. Chem.* **1984**, *49*, 276.

(19) (a) Acharjee, N.; Banerji, A. *Indian J. Chem., Sect. A:*

Inorg., Bio-inorg., Phys., Theor. **2010**, *49*, 1444.
(b) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Acta Chem. Scand.* **1997**, *50*, 1234. (c) Banerji, A.; Biswas, P. K.; Gupta, M.; Saha, R.; Banerji, J. *J. Indian Chem. Soc.* **2007**, *84*, 1004. (d) Koyano, K.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3306. (e) Koyano, K.; Suzuki, H. *Tetrahedron Lett.* **1968**, *9*, 1859.

