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Reactions of 1,1-diaryl-2-isopropylidene-3-methylenecyclopropanes with *C,N*-diarylnitrones and nitrile oxides

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ABSTRACT

The reactions of unactivated bis(methylene)cyclopropanes with nitrones and nitrile oxides have been investigated. The 1,1-diaryl-2-isopropylidene-3-methylenecyclopropanes react with the *C,N*-diarylnitrones to give a mixture of 2,2-dimethyl-1,6-diaryl-3-(diarylmethylene)piperidin-4-ones and 5-methyl-1-aryl-1-(arylamino)-4-(diarylmethylene)hex-5-en-3-ones. 2,3-Dihydro-3-methylenepyridin-4(1*H*)-ones are obtained by reaction of 1,1-diaryl-2-isopropylidene-3-methylenecyclopropanes with nitrile oxides.

1,3-Dipolar cycloaddition reactions have long been recognized as important for the synthesis of heterocyclic rings.[1] Nitrones and nitrile oxides are remarkably versatile building blocks in organic synthesis, and are known to take part in 1,3-dipolar cycloaddition reactions with a wide range of dipolarophiles. Cycloadditions of nitrones and nitrile oxides to alkenes are well established reactions in which isoxazolidines and isoxazolines are formed, often with a high degree of stereochemical control.[2] These cycloadducts have attracted considerable attention due to the potential biological activities of isoxazolines and isoxazolidines.[1a,b] Isoxazolidines and isoxazolines have also been used as precursors to γ-amino alcohols through the reductive cleavage of the N–O bond, and are potential precursors for the synthesis of natural products such as alkaloids and β-lactam antibiotics.[2a] The groups of Brandi and de Meijere have systematically studied 1,3-dipolar cycloaddition reactions of methylenecyclopropanes with nitrones and nitrile oxides that afford the exocyclic [3+2] adducts in good yields.[3,4] Rearrangements of 5-spirocyclopropaneisoxazolines and 5-spirocyclopropaneisoxazolidines have shown potential for the synthesis of functionalized pyridones (Brandi–Guarna reaction)[5] which are precursors for the synthesis of natural alkaloids.[6] Recently, Wang reported the first example of the $Yb(OTf)_3$-catalyzed formal [3+3] cycloadditions of methylenecyclopropane-dicarboxylates with *C,N*-diarylnitrones with the formation of substituted 1,2-oxazines in good yields.[7] The chemistry of methylenecyclopropanes has been explored extensively. Novel intramolecular rearrangements and also cycloaddition reactions with compounds containing carbon–carbon or carbon–heteroatom multiple bonds, such as imines, aldehydes, ketones, and α,β-unsaturated ketones and aldehydes, have been studied.[2b,d,8] However, reactions of bis(methylene)cyclopropanes with nitrones and nitrile oxides have not been studied. In continuation of our earlier work,[9] we have studied the reactions of non-activated bis(methylene)cyclopropanes with nitrones and nitrile oxides. The choice of bis(methylene)cyclopropanes **1** as dipolarophiles in this process appeared particularly interesting in order to expand the synthetic utility of this methodology.

The starting 1,1-diaryl-2-isopropylidene-3-methylenecyclopropanes **1a–d** are easily accessible via thermolysis of the corresponding 1-(2-methylpropenylidene)-2,2-diarylcyclopropanes.[10] In earlier studies we investigated the reaction of the *C,N*-diarylnitrone **2a** with bis(methylene)cyclopropane **1a**. Heating of **1a** and nitrone **2a** (1.5 equiv) in benzene (80 °C, 40 h) led to a mixture of compounds **4a** and **5a** in 13% and 18% yields, respectively (Table 1, entry 1). 5-spiroisoxazolidine **3** could not be isolated because

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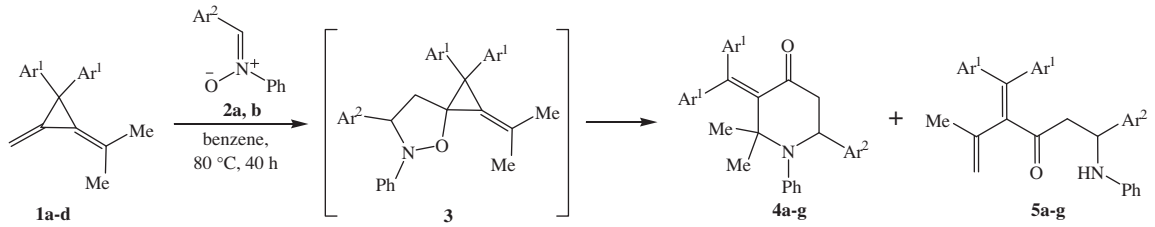
Table 1
Reactions of bis(methylene)cyclopropanes **1a–d** with nitrones **2a–c**



Entry	Ar^1	Ar^2	Yield of **4**[a] (%)	Yield of **5**[a] (%)
1[b]	Ph (**1a**)	Ph (**2a**)	13 (**4a**)	18 (**5a**)
2[c]	Ph (**1a**)	4-ClC_6H_4 (**2b**)	17 (**4b**)	27 (**5b**)
3[d]	4-MeC_6H_4 (**1b**)	Ph (**2a**)	16 (**4c**)	13 (**5c**)
4[e]	4-MeC_6H_4 (**1b**)	4-ClC_6H_4 (**2b**)	19 (**4d**)	18 (**5d**)
5[f]	4-ClC_6H_4 (**1c**)	4-ClC_6H_4 (**2b**)	11 (**4e**)	19 (**5e**)
6[g]	4-$MeOC_6H_4$ (**1d**)	Ph (**2a**)	6 (**4f**)[h]	43 (**5f**)
7[i]	4-$MeOC_6H_4$ (**1d**)	4-ClC_6H_4 (**2b**)	8 (**4g**)[j]	41 (**5g**)
8[k]	Ph (**1a**)	CONHPh (**2c**)	—	—

[a] Isolated yield.
[b] 21% of starting material **1a** was recovered.
[c] 19% of starting material **1a** was recovered.
[d] 23% of starting material **1b** was recovered.
[e] 21% of starting material **1b** was recovered.
[f] 24% of starting material **1c** was recovered.
[g] 19% of starting material **1d** was recovered.
[h] Spectral yield.
[i] 22% of starting material **1d** was recovered.
[j] Spectral yield.
[k] Mixture of unidentified products.

rearrangement occurs smoothly under the reaction conditions to give the products **4a** and **5a**. In the ^{1}H NMR spectrum of the crude reaction mixture the signals due to proposed intermediate **3** were not found. The reaction products were isolated by preparative thin layer chromatography on silica. The compositions and structures of the products were established by elemental and spectral analyses.[11] The structures of compounds **4a** and **5a** were confirmed by X-ray diffraction analysis (Figs. 1 and 2).[12,13] Running the reaction in benzene at 20 °C for 56 h did not lead to the formation of **4** and **5**. The ^{1}H NMR spectra of the crude reaction mixture contained only signals due to the starting bis(methylene)cyclopropane and nitrone. A similar reaction occurred on the treatment of bis(methylene)cyclopropane **1a** with nitrone **2b** to give a mixture of compounds **4b** and **5b** in 17% and 27% yields, respectively (Table 1, entry 2). The reactions of bis(methylene)cyclopropanes **1b,c** and nitrones **2a,b** proceed in an analogous manner: mixtures of bis(methylene)cyclopropanes **1b** and **1c**, respectively, and nitrones **2a** or **2b** in benzene afforded, on heating (80 °C, 40 h), mixtures of the corresponding products **4** and **5** (Table 1, entries 3–5). Moreover, increasing the electron density of the aryl functionalities in bis(methylene)cyclopropane **1d** by introducing two electron-donating methoxy groups led to the formation of ketones **5f** and **5g** (41–43%) as the major products (Table 1, entries 6 and 7). Sig-

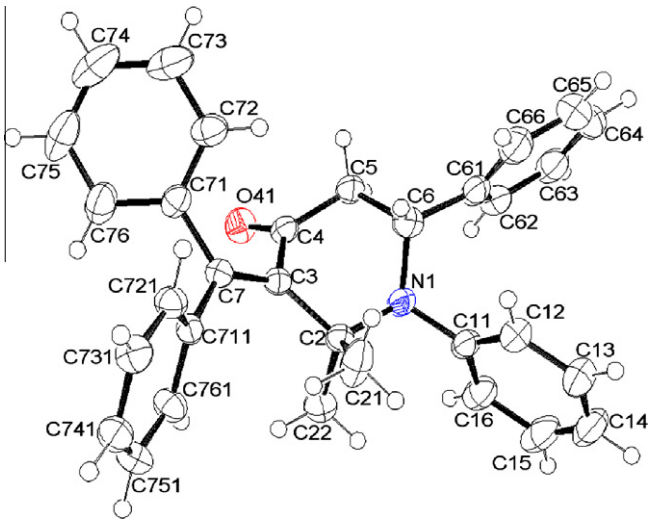


Figure 1. ORTEP representation of **4a**.

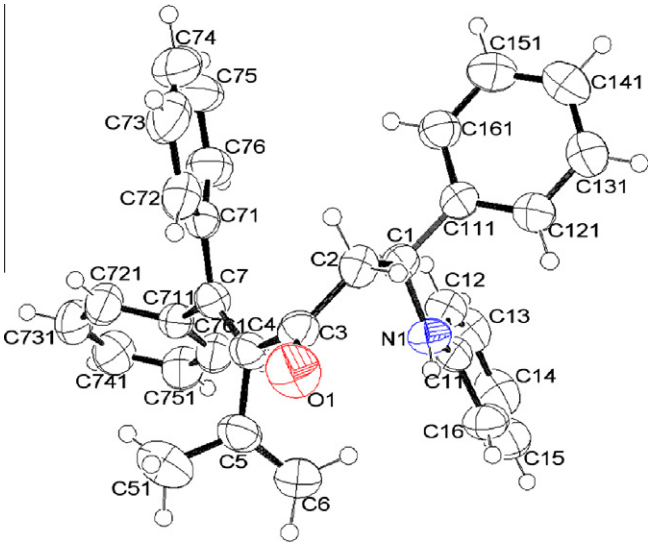
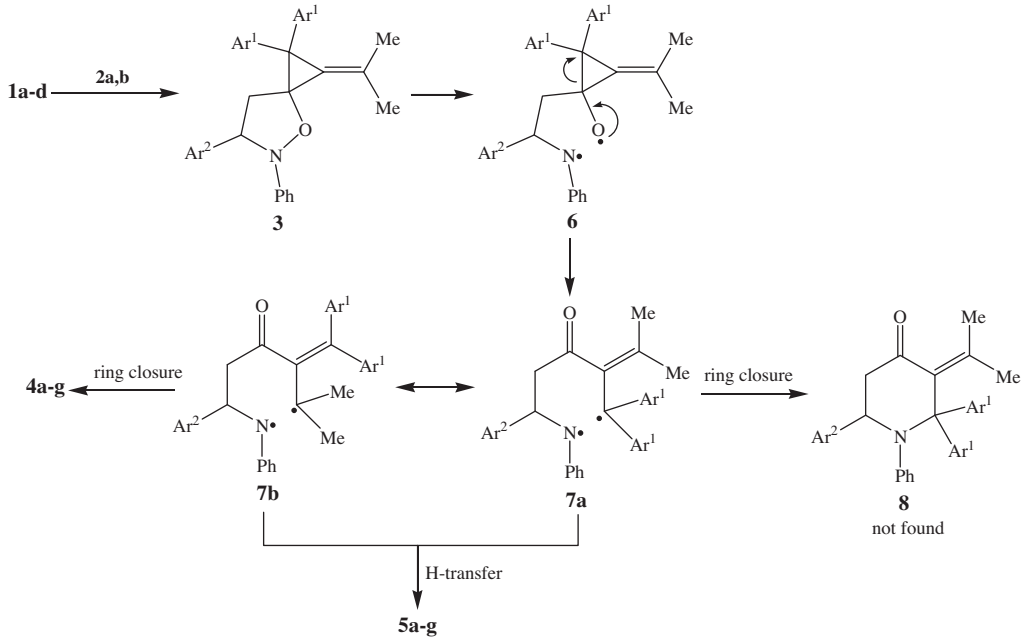
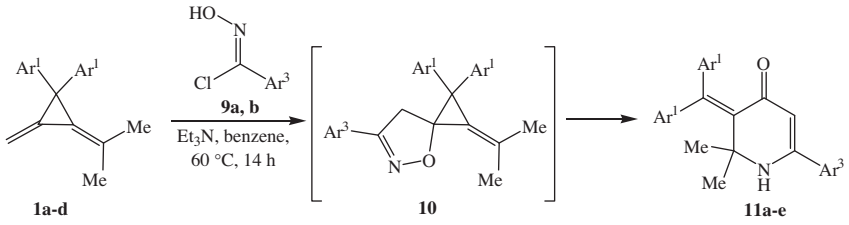


Figure 2. ORTEP representation of **5a**.



Scheme 1. Proposed reaction mechanism for the formation of compounds **4** and **5**.

Table 2
Reactions of bis(methylene)cyclopropanes **1a–d** with nitrile oxides **10a–c**



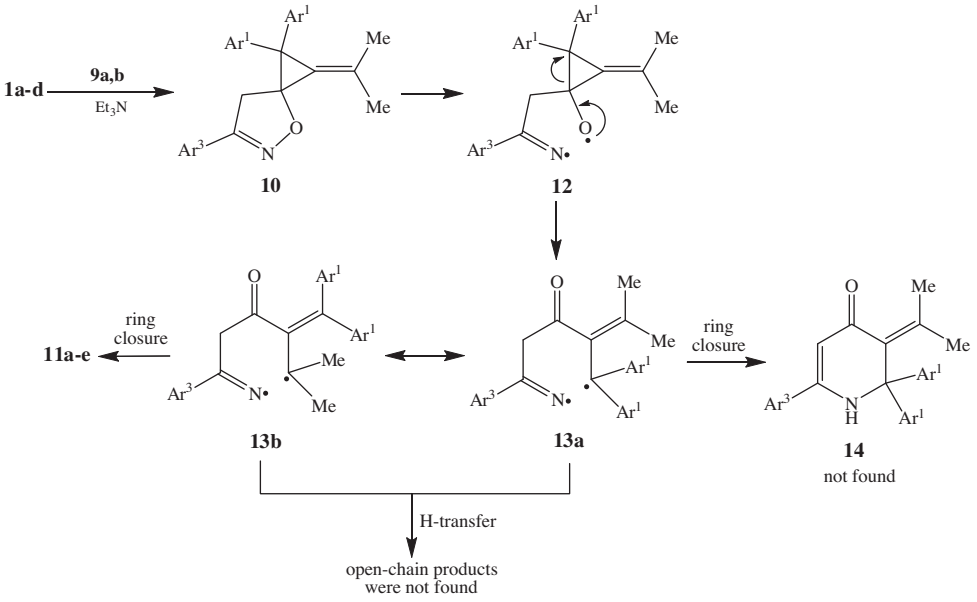
Entry	Ar^1	Ar^3	Yield of **11**[a,b] (%)
1	Ph (**1a**)	4-ClC_6H_4 (**9b**)	28 (**11a**)[c]
2	4-MeC_6H_4 (**1b**)	Ph (**9a**)	32 (**11b**)[d]
3	4-ClC_6H_4 (**1c**)	Ph (**9a**)	15 (**11c**)[e]
4	4-$MeOC_6H_4$ (**1d**)	Ph (**9a**)	22 (**11d**)[f]
5	4-$MeOC_6H_4$ (**1d**)	4-ClC_6H_4 (**9b**)	25 (**11e**)[g]
6	Ph (**1a**)	EtO_2C (**9c**)	—[h]

[a] Isolated yield.
[b] 3,4-$(Ar^3)_2$furoxanes—dimers of the corresponding nitrile oxides—were isolated from the reaction mixtures in all cases.
[c] 35% of starting material **1a** was recovered.
[d] 29% of starting material **1b** was recovered.
[e] 37% of starting material **1c** was recovered.
[f] 41% of starting material **1d** was recovered.
[g] 38% of starting material **1d** was recovered.
[h] Mixture of unidentified products.

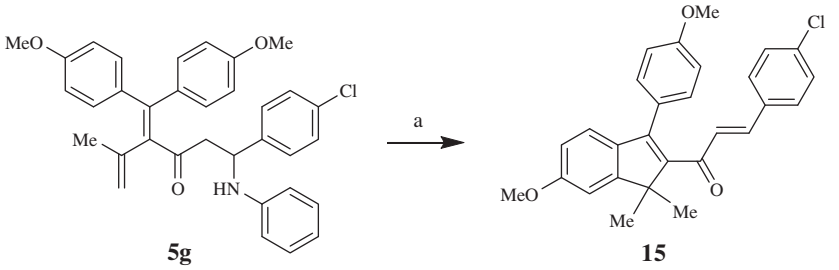
nals for the corresponding piperidin-4-ones **4f,g** were detected in the ^1H NMR spectra of the reaction mixtures (spectral yields 6–8%), but it was impossible to separate them as individual compounds. Increasing the nitrone concentration in the reaction mixture (up to 2.0–2.5 equiv) and the reaction time (up to 56 h) did not lead to significant increases in the yields of the products **4** and **5**. At the same time, increased amounts of unidentified products were observed in these cases which made product separation difficult. The reaction of bis(methylene)cyclopropane **1a** with amidonitrone **2c** gave a mixture of unidentified products (Table 1, entry 8).

The addition of nitrones **2** to the bis(methylene)cyclopropanes **1** occurs at the unsubstituted double bond with the formation of spiroisoxazolidines **3**. The rearrangement of **3** starts with the homolytic cleavage of the N–O bond to afford the diradical **6** which, instantaneously, undergoes a cyclopropane ring-opening to form the highly reactive diradical intermediate **7** (Scheme 1).[14] Diradical **7a/7b** eventually cyclizes onto the pyridone moiety **4a–g** or produces open-chain aminoketones **5a–g** through hydrogen transfer. It is important to note that formation of the regioisomeric pyridones **8** was not observed in the reactions of bis(methylene)cyclopropanes **1a–d** with nitrones **2a,b**. This is possibly the result of steric hindrance in the transition state **7a**.

Next, the reactions of bis(methylene)cyclopropanes **1a–d** with nitrile oxides (generated from hydroximoyl chlorides **9a,b**) were investigated. Nitrile oxides are more reactive than nitrones in



Scheme 2. Proposed reaction mechanism for the formation of **11**.



Scheme 3. Conditions and yield: (a) glacial AcOH, reflux, 72 h, 36%.

1,3-dipolar cycloadditions toward unactivated alkenes.[1a–c,2a] On the other hand, they are also much less stable, mainly due to their facile dimerization to give furoxans.[2a] Benzonitrile oxide (generated in situ from the corresponding hydroximoyl chloride **9a** in the presence of Et_3N)[2a] was treated with **1b** in benzene at 60 °C to give a 32% yield of the dihydropyridinone **11b** (Table 1, entry 2). A threefold excess of hydroximoyl chloride **9a** was used for the reaction because the dimerization of nitrile oxides is strongly preferred if rather unreactive dipolarophiles such as bis(methylene)cyclopropanes **1** are used. The yield of **11b** was not more than 10% if equimolar amounts of the reagents were used. Running the reaction in benzene at 20 °C for 24 h and using a threefold excess of hydroximoyl chloride **9a** gave the product **11b** in pure form (less than 13%), together with extensive formation of 3,4-diphenylfuroxan. 5-spiroisoxazoline **10** could not be isolated because rearrangement occurred smoothly under the reaction conditions. In the ^1H NMR spectrum of the crude reaction mixture the signals of **10** were not observed. A similar reaction occurred on the treatment of bis(methylene)cyclopropanes **1a,c,d** with nitrile oxides generated from **9a,b** giving dihydropyridinones **11a,c–e** in 15–28% yields (Table 2, entries 1, 3–5). The reaction products were isolated by preparative thin layer chromatography on silica. The composition and structures of the products were established by elemental and spectral analyses.[15] The ^1H NMR spectra of compounds **11a–e** exhibited a signal for the olefinic proton at the C(5) atom at δ 5.4, a signal for the NH group at δ 5.5, and signals for methyl groups at the C(2) atom at δ 1.1 and δ 2.2. The shift of one methyl group signal to a higher field (δ 1.1) was due to the shielding effect induced by the aromatic ring of the diarylmethylene fragment. The ^{13}C NMR spectra of compounds **11a–e** exhibited signals for the CO groups at δ 188, and signals for the methyl groups (N-CMe_2) at δ 25 and δ 28 (see Supplementary data). The reaction of bis(methylene)cyclopropane **1a** with nitrile oxide generated from hydroximoyl chloride **9c** gave a mixture of unidentified products (Table 2, entry 6). 3,4-$(Ar^3)_2$Furoxanes—the dimers of the corresponding nitrile oxides—were isolated from the reaction mixtures in all cases. The rearrangement includes the cleavage of both the N–O bond of the isoxazoline ring (intermediate **12**) and the C–C bond of the cyclopropane ring to form a highly reactive diradical intermediate **13a/b** which cyclizes into the pyridone ring. The formation of regioisomeric pyridones **14** and open-chain enaminones[2b,f,3a] was not observed during the reactions of bis(methylene)cyclopropanes **1a–d** with nitrile oxides (Scheme 2).

Diene **5g** could be transformed into indene **15** in 36% yield by heating in glacial acetic acid (Scheme 3). Running the reaction in concentrated sulfuric acid leads to polymerization. It should be noted that the synthesis of novel indene derivatives may be of interest due to the many biologically active natural products and pharmaceutically important compounds which contain an indene fragment.[16] Indene derivatives are also used as ligands in organometallics and as functional materials.[17]

In conclusion, the first examples of the reactions of nitrones and nitrile oxides with non-activated bis(methylene)cyclopropanes have been described. The nitrones react with 1,1-diaryl-2-isopro-

pylidene-3-methylenecyclopropanes to give mixtures of 2,2-dimethyl-1,6-diaryl-3-(diarylmethylene)piperidin-4-ones and 5-methyl-1-aryl-1-(arylamino)-4-(diarylmethylene)hex-5-en-3-ones in moderate yields. 2,3-Dihydro-2,2-dimethyl-6-aryl-3-(diarylmethylene)pyridin-4(1*H*)-ones were obtained by the reaction of nitrile oxides with bis(methylene)cyclopropanes. The initially formed products of the 1,3-dipolar cycloaddition of nitrones and nitrile oxides to the unsubstituted double bonds of bis(methylene)cyclopropanes were not observed due to their smooth rearrangement under the reaction conditions.

Acknowledgements

We are grateful to Dr. Sergey Vyazmin and Dr. Elena Grinenko for recording IR spectra.

Supplementary data

Supplementary data (experimental procedures, characterization data, and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.093. These data include MOL files and InChiKeys of the most important compounds described in this article.

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11. ^{1}H NMR data for **4a**: δ_H (300 MHz, $CDCl_3$) 0.90 (s, 3H, Me), 1.44 (s, 3H, Me), 2.93 (dd, 1H, *J* = 14.5 and 4.4 Hz), 3.25 (dd, 1H, *J* = 14.5 and 10.2 Hz), 5.07 (dd, 1H, *J* = 10.2 and 3.6 Hz), 7.03–7.31 (m, 20H, Aryl). ^{13}C NMR: δ_c (75 MHz, $CDCl_3$) 25.0 (Me), 31.0 (Me), 52.2 (CH_2), 61.1 (CH), 64.0 (C), 125.7 (CH), 127.4 (CH), 127.6 (2CH), 127.9 (2CH), 128.3 (2CH), 128.5 (4CH), 128.7 (2CH), 128.9 (2CH), 129.0 (2CH), 132.0 (2CH), 142.2 (2C), 142.6 (C), 144.5 (C), 145.9 (C), 147.4 (C), 206.7 (CO). ^{1}H NMR data for **5a**: δ_H (300 MHz, $CDCl_3$) 1.67 (s, 3H, Me), 2.70–2.86 (m, 2H, CH_2), 4.68 (dd, 1H, *J* = 8.0 and 5.1 Hz, CH), 4.78 (s, 1H, =CH_2), 5.05 (s, 1H, =CH_2), 6.50 (d, 2H, *J* = 8.0 Hz, Aryl), 6.69 (t, 1H, *J* = 7.3 Hz, Aryl), 7.08–7.24 (m, 17H, Aryl), NH-signal is not be seen. ^{13}C NMR: δ_c (75 MHz, $CDCl_3$) 23.3 (Me), 51.5 (CH_2), 55.1 (CH), 114.2 (2CH), 118.1 (CH), 119.9 (CH_2), 126.7 (2CH), 127.5 (CH), 128.4 (2CH), 128.5 (CH), 129.02 (2CH), 129.04 (2CH), 129.1 (CH), 129.4 (2CH), 130.2 (2CH), 130.5 (2CH), 141.6 (C), 141.8 (C), 143.1 (C), 143.2 (C), 143.9 (C), 145.5 (C), 147.4 (C), 206.0 (CO).
12. Crystallographic data for the structure **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 846709. Copies of these data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).
13. Crystallographic data for the structure **5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 846710. Copies of these data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk)
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15. ^{1}H NMR data for **11a**: δ_H (300 MHz, $CDCl_3$) 1.10 (s, 3H, Me), 2.21 (s, 3H, Me), 5.34 (s, 1H, =*CH*), 5.56 (s, 1H, NH), 7.28–7.42 (m, 12H, Aryl), 7.53 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR: δ_c (75 MHz, $CDCl_3$) 25.3 (Me), 28.1 (Me), 72.1 (C), 101.0 (CH), 121.5 (CH), 128.0 (2CH), 128.6 (CH), 128.8 (2CH), 129.0 (2CH), 129.7 (2CH), 132.7 (C), 134.0 (C), 137.4 (C), 138.4 (C), 144.3 (C), 148.2 (C), 154.8 (C), 187.5 (CO).
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