[3+2] Cycloaddition of Masked *o*-Benzoquinones with Azomethine Ylides

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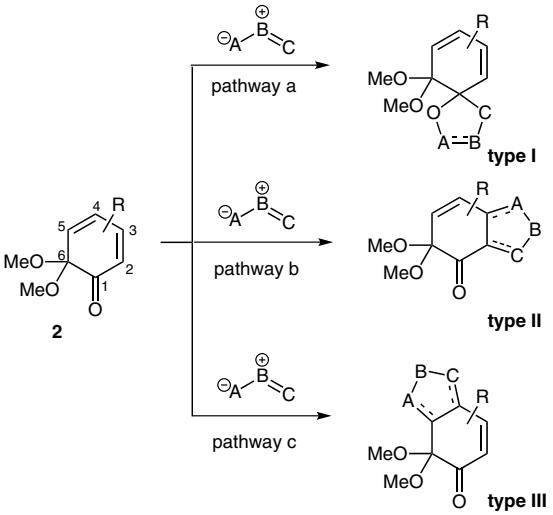
Abstract: A simple and efficient access to highly functionalized isoindolone derivatives via a [3+2] cycloaddition process between in situ generated azomethine ylides with various stable (isolable) masked *o*-benzoquinones is described. This approach allows a rapid and general synthesis of isoindolones with substituents to further manipulate and elaborate the structural complexity.

Key words: masked *o*-benzoquinones, [3+2] cycloadditions, azomethine ylides, isoindolones, isoindolines

Masked *o*-benzoquinones (MOB) or orthoquinone monoketals are extremely useful synthons in organic synthesis.[1] Liao and co-workers have successfully demonstrated the usefulness of MOB by employing them in inter- and intramolecular Diels–Alder reactions, hetero-Diels–Alder reactions to obtain functionally rich cycloadducts which in turn were utilized as key intermediates for the synthesis of natural products.[2] Recently, several other research groups have effectively exploited MOB chemistry for the synthesis of natural products with unique structural frameworks.[3] However, MOB are known to be very reactive and undergo spontaneous self-dimerization to provide Diels–Alder dimers.[1,4] During extensive studies on developing synthetic strategies employing MOB chemistry, it was found that a suitably substituted MOB can be stabilized and could be isolated for further synthetic transformations.[1b,5] MOB with its inherent multifunctional structure is a versatile building block not only for Diels–Alder reactions but also for a repertoire of other reactions including photorearrangements,[6a] Michael additions,[6b] 1,2-additions,[6c] epoxidations,[6d] cyclopropanations,[6e,f] and the construction of anthraquinones.[6g] Inspite of such undisputed synthetic value, to our knowledge MOB were seldom utilized in 1,3-dipolar cycloadditions. Herein, we report the results of this endeavor and provide preliminary results on the reaction of isolable MOB **2** with azomethine ylides **3**[7] and **4**.[8]

The anticipated reaction between azomethine ylide and MOB would provide highly substituted isoindolones. Compounds with an isoindole core are viewed as privileged structures in medicinal chemistry.[9] For example, it was reported that compounds with an isoindole moiety were employed for the treatment of neurobehavioral disorders,[9c] as local anesthetics[9a] and were also known for their high contraceptive activity.[9a] Moreover, isoindole derivatives were utilized to label the terminal amino groups in various biological objects.[9d] In addition, isoindoline compounds are known for their HSP-90 modulator[9e] and IKK2 inhibitory activities.[9f] Furthermore, hypoglycemic mitiglinide,[9g] an octahydroisoindole derivative is used for the treatment of diabetes, and tandospirone[9h] is used as an antidepressant.

As shown in Scheme 1, MOB **2** has three reactive sites namely C2=C3, C4=C5, and C1=O; thus, upon reaction with 1,3-dipoles could provide products of type I, II, and/or III, respectively. It is well-established that 1,3-dipolar compounds of the azomethine ylide kind on reaction with Michael acceptors provide products of type II. Consequently pathway a could be ruled out.[10]



Scheme 1 Possible products in the reaction between MOB and a dipolarophile

However, MOB is a dienone system where pathway b or c could compete to provide products of type II or III, respectively. Therefore, we commenced our study by choosing 5,6,6-trimethoxy cyclohexa-2,4-dienone (**2a**) as the model substrate to optimize the reaction conditions.

At the outset, a mixture of sarcosine, paraformaldehyde, and MOB **2a** in toluene was refluxed for six hours in the presence of $MgSO_4$. To our delight, adduct **5a** was obtained as the only product in 76% yield via [3+2] cycloaddition of MOB **2a** with transiently generated azomethine ylide **3** (Scheme 2, Table 1, entry 1). Further optimization revealed that yield of cycloaddition product **5a** could be improved to 89% by conducting the reaction in a sealed tube under the same reaction conditions (Table 1, entry 2).

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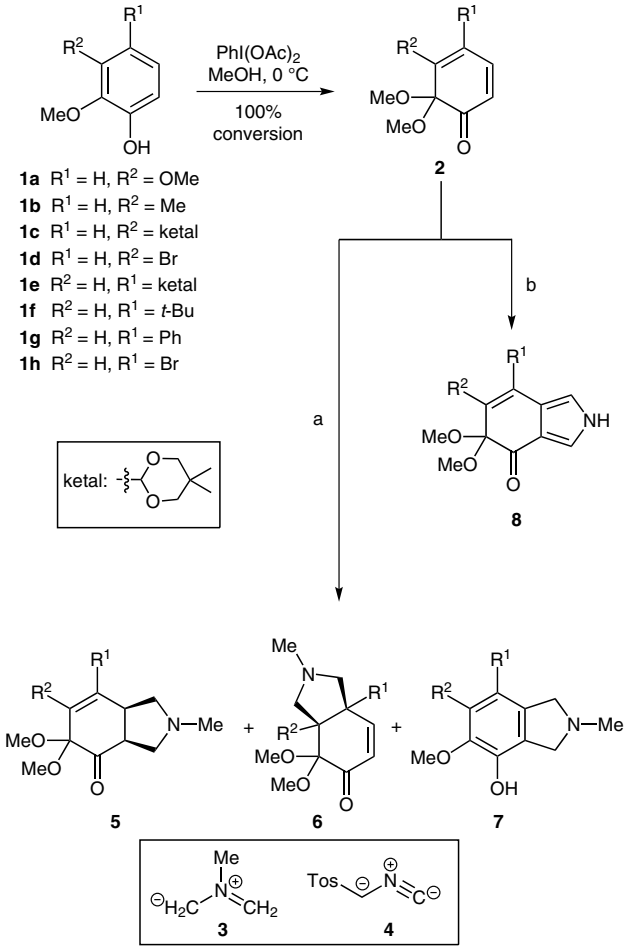


Scheme 2 Synthesis of isolable MOB **2** from 2-methoxyphenols **1** and their reactions with in situ generated azomethine ylides **3** and **4**. *Reagents and conditions*: (a) sarcosine (2.5 equiv), $(CH_2O)_n$ (6.0 equiv), toluene, reflux (in situ generation of azomethine ylide **3**); (b) TOSMIC, KO*t*-Bu, THF (in situ generation of azomethine ylide **4**).

With these conditions in hand, the scope of the MOB partner was explored. All the MOB utilized in the present study are prepared by the treatment of a methanolic solution of commercially available (for **1a** and **1h**) or readily accessible phenols **1** with diacetoxyiodobenzene at 0 °C to room temperature for 30 minutes. High yields (up to 98%) of pure MOB **2** were achieved after column chromatographic purification (Scheme 2).[11] Accordingly, MOB **2b** and **2c** were utilized in this reaction. The reactions of MOB **2b** and **2c** with azomethine ylide **3** were sluggish and needed 16 hours reaction time for their complete consumption. The desired cycloadducts **5b** and **5c** were obtained in moderate yields (ca. 60%), in addition corresponding aromatized products **7b** and **7c** were produced in 33% and 24% yields, respectively. Besides, MOB **2c** provided 14% of the other isomer **6c** (Figure 1). The formation of aromatized products **7b** and **7c** can be presumed to be produced from the initially generated cycloadducts **5b** and **5c**, respectively.[12] Under the optimized reaction conditions, bromo-substituted MOB **2d**[13] participated in the cycloaddition with the in situ generated azomethine ylide **3** to provide the isoindolone **5d** in 89% yield.

Table 1 Reaction of MOB with in situ Generated Azomethine Ylide **3**[a]

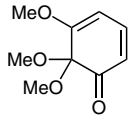
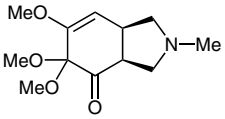
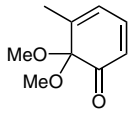
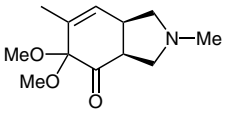
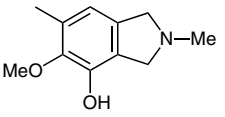
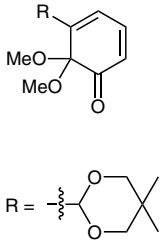
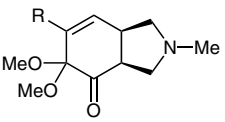
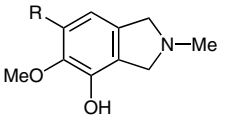
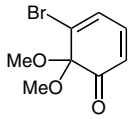
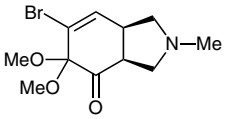
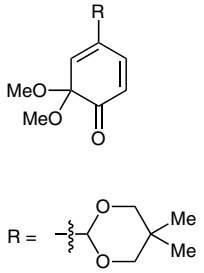
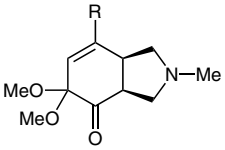
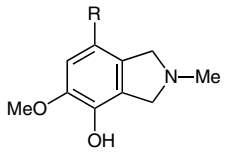
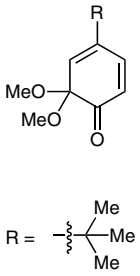
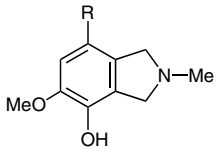
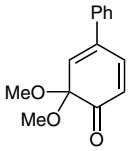
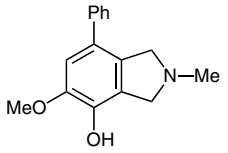
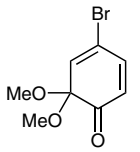
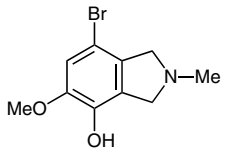
Entry	MOB	Reaction time (h)	Product/Yield	Yield (%)
1[b]	 **2a**	6	 **5a**	76
2	**2a**	6	**5a**	89
3	 **2b**	16	 **5b**	62
			 **7b**	33
4[c]	 **2c**	16	 **5c**	56
			 **7c**	24
5	 **2d**	6	 **5d**	89
6[d]	 **2e**	7	 **5e**	54

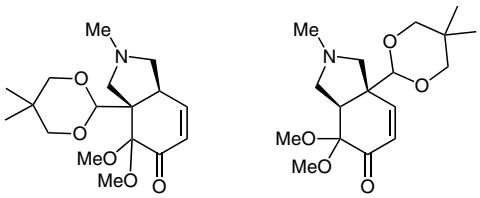
Table 1 Reaction of MOB with in situ Generated Azomethine Ylide **3**[a] (continued)

Entry	MOB	Reaction time (h)	Product/Yield	Yield (%)
			 **7e**	38
7	 **2f**	16	 **7f**	87
8	 **2g**	16	 **7g**	60
9	 **2h**	16	 **7h**	85

[a] Reaction conditions: MOB (1.0 equiv), sarcosine (5.0 equiv), paraformaldehyde (10.0 equiv), $MgSO_4$ (3.0 equiv) were refluxed in dry MeCN in a sealed tube.
[b] Reaction was conducted under conventional reflux (using reflux condensor) and argon atmosphere.
[c] Isoindolone **6c** was also isolated in 14% yield.
[d] Isoindolone **6e** was also isolated in 3% yield.

Subsequently, we turned our attention to the 4-substituted MOB **2e**–**h**. Thus, MOB **2e** provided cycloadduct **5e** in 54% and aromatized product **7e** in 38% along with 3% of isoindolone **6e** under the standard reaction conditions (Figure 1). MOB **2f** (*t*-Bu), **2g** (4-Ph), **2h** (4-Br) bearing different substitutions at the 4-position exclusively furnished the aromatized isoindoline products **7f** (87%), **7g** (60%), and **7h** (85%), respectively. As a result, MOB **2f**–**h** provided a straightforward route for the synthesis of isoindolines **7f**–**h** bearing multifunctional groups with an opportunity to further elaborate the structures.

Noticeably, MOB with different substitutions on the ring were all compatible under the standard conditions either producing the isoindolone and/or isoindoline derivatives in very good total yields. At this juncture, it is important



6c 14% **6e** 3%

Figure 1 Other isomers obtained in the reaction between MOB **2c** and **2e** with azomethine ylide **3**

to note that in the cycloaddition reaction disubstituted double bond was preferred over the trisubstituted perhaps due to the steric factors. Electron-donating substitutions like OMe and Br at 5-position of MOB **2a** and **2d**, respectively, activate the C2=C3 double bond by conjugation towards the cycloaddition. Hence these reactions were completed in shorter reaction times (ca. 6 h). For MOB **2b** and **2c** longer reaction times (ca. 16 h) were required for complete consumption of these MOB. As the reaction time increased, the formed isoindolines were prone to aromatization which is evident from the formation of isoindolines **7b** and **7c**. Substitutions at the 4-position of MOB **2f**–**h** are not effecting/activating the C2=C3 double bond and, moreover, are in close proximity (steric affect) to the reacting center. This might be the reason for the observed increase in reaction time to 16 hours in these cases. Consequently, both increase in reaction time along with the steric influence due to the presence of substitutions at 4-position facilitated easy aromatization to furnish compounds **7f**–**h**. Thus, the factors influencing the aromatization are a cumulative effect of reaction time, steric and electronic factors. As of now it is unclear why only the ketal-substituted MOB provided the cycloadducts of type **6c** and **6e**. We believe that the cycloadducts **5a**–**e** can be easily transformed to the corresponding aromatized compounds (isoindolines).[14] MOB **2** with $R^1 = R^2 = H$ are known for their self-dimerization[2b] quite easily and are not isolable due to which such substrates were not utilized in this study.

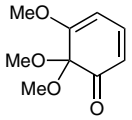
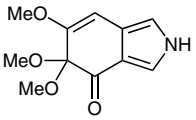
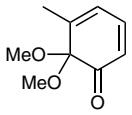
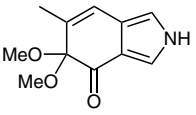
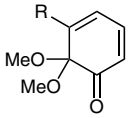
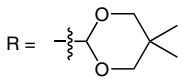
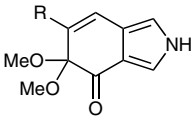
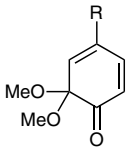
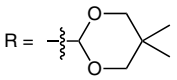
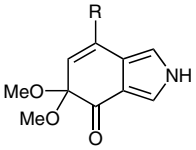
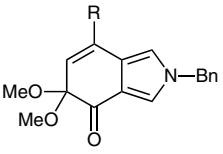
Next, we investigated the possibility of utilizing MOB **2** in the reaction with TOSMIC **4**. MOB **2a** obtained after the oxidation of 2,3-dimethoxy phenol (**1a**) was as such utilized for the next transformation without column chromatographic purification. Thus obtained MOB **2a** and TOSMIC were taken in dry THF to which KO*t*-Bu in dry THF was added dropwise and stirred at room temperature for three hours. To this reaction mixture water was added and extracted with ethylacetate (three times). All organic fractions were combined and concentrated under reduced pressure followed by column chromatography to provide the desired product **8a** in only 35% yield along with 25% of unreacted MOB **2a**. No better result was generated upon increasing the equivalents of KO*t*-Bu or TOSMIC. But when the same reaction was repeated with a column purified MOB **2a**, the yield was dramatically improved to 73%. Subsequently, column purified MOB **2b** and **2c** were subjected to standard reaction conditions to provide

the desired products **8b** and **8c** in 78% and 60% yield, respectively. Next, it was decided to utilize MOB **2e**,**g**,**h** in the reaction, which have a substitution at the 4-position. Contrary to our expectation, none of the expected products **8e**, **8g**, or **8h** could be isolated; however, TLC analysis of the corresponding reaction mixture indicated complete consumption of the respective MOB substrate.

The absence of a positive result was inconclusive in these cases; the reason being the ^{1}H NMR of the crude reaction mixture with MOB **2e** as starting material has shown the peaks corresponding to the product **8e**. At this stage, we attribute the failure of isolation of the isoindolone product(s) **8e**, **8g**, or **8h** to their instability which might be air- and light-sensitive.[15] Thus, another approach that would reduce such uncertainties was desired. It was decided to in situ trap the free NH produced during the reaction. Consequently, in the modified reaction procedure, after the complete consumption of MOB **2e** as indicated by TLC analysis, 1.5 equivalents of KO*t*-Bu were added to the reaction mixture along with the dropwise addition of benzylbromide. The reaction mixture was allowed to stir at room temperature for another two hours. Gratifyingly, this procedure provided compound **9e** in 30% yield as the only product. Increasing the reaction temperature to 50 °C or performing the reaction at reflux in an attempt to improve the yield of the adduct **9e** failed. However, the yield of compound **9e** could be improved to 63% (Table 2, entry 9) by conducting the initial cycloaddition reaction at 0 °C for five hours followed by the addition of KO*t*-Bu (1.0 equiv) and benzylbromide (3.0 equiv) at the same temperature and allowing the reaction mixture to stir at room temperature for eight hours.

In summary, we have successfully presented the [3+2] cycloaddition reactions of azomethine ylides **3** and **4** with readily available MOB **2**, which furnished the highly substituted isoindoline structures **5**–**9** in good yields. The products described in this study are densely functionalized and are versatile building blocks for the synthesis of more complex molecules. In general, excellent site selectivities were observed where the disubstituted double bond preferentially reacted over the trisubstituted double bond. Further investigations to broaden the scope of this methodology with the hope of accessing intermediates for biologically important products are in progress.

Table 2 Reaction of MOB with TOSMIC (Azomethine Ylide **4**)[a]

Entry	MOB	Product/Yield	Yield (%)
			
1[b]	**2a**	**8a**	35
2	**2a**	**8a**	73
			
3	**2b**	**8b**	78
	 		
4	**2c**	**8c**	60
	 		
5	**2e**	**8e**	0
6	**2g** R = Ph	**8g**	0
7	**2h** R = Br	**8h**	0
			
8[c]	**2e**	**9e**	30
9[d]	**2e**	**9e**	63

[a] Reaction conditions: MOB (1.0 equiv), TOSMIC (1.3 equiv), KO*t*-Bu (2.0 equiv), THF, r.t., 3 h.
[b] Unpurified MOB **2a** was utilized.
[c] After step a, to the crude reaction mixture was added KO*t*-Bu (1.5 equiv), BnBr (1.8 equiv), and stirred for 2 h.
[d] After step a at 0 °C for 5 h, to the crude reaction mixture at 0 °C was added KO*t*-Bu (1.0 equiv), BnBr (3.0 equiv), and stirred for 8 h at r.t.

General Procedure for the Preparation of MOB

To a solution of 2-methoxyphenol (1.0 mmol) in anhyd MeOH (6.0 mL) was added DAIB (1.2 mmol) at r.t. After stirring for 20 min, MeOH was evaporated, and flash column was performed using EtOAc and hexanes as eluent to obtain the corresponding MOB.

Typical Experimental Procedure for the Synthesis of Isoindoline 5a

To solution of **2a** (185 mg, 1.0 mmol), sarcosine (180 mg, 2.00 mmol), paraformaldehyde (180 mg, 6.00 mmol) in toluene was added $MgSO_4$ (360 mg, 3.00 mmol). The reaction mixture was allowed to reflux in a sealed tube. After the completion of reaction, the solvent was evaporated in vacuo, and the residue was chromatographed over silica gel by using hexanes–EtOAc as eluent to give isoindoline **5a** in 89% yield.

Isoindoline 5a
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05–2.13 (m, 1 H), 2.34 (s, 3 H), 2.76–2.82 (m, 1 H), 2.86–2.91 (m, 2 H), 3.31 (s, 3 H), 3.33–3.38 (m, 2 H), 3.47 (s, 3 H), 3.61 (s, 3 H), 4.91 (d, *J* = 2.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.5 (CH), 41.9 (CH_3), 46.2 (CH), 50.9 (CH_3), 51.5 (CH_3), 54.9 (CH_2), 55.2 (CH_3), 62.7 (CH_2), 98.3 (C), 102.7 (CH), 151.7 (C), 202.2 (C).

Isoindoline 5b
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (dd, *J* = 1.2, 2.4 Hz, 3 H), 2.23 (dd, *J* = 6.0, 8.4 Hz, 1 H), 2.32 (s, 3 H), 2.63 (app dd, *J* = 8.4, 9.6 Hz, 1 H), 2.72–2.76 (m, 1 H), 2.90 (dd, *J* = 5.2, 9.6 Hz, 1 H), 3.25 (s, 3 H), 3.32–3.39 (m, 2 H), 3.40 (s, 3 H), 5.70–5.73 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (CH_3), 40.9 (CH), 41.9 (CH_3), 46.2 (CH), 49.7 (CH_3), 50.8 (CH_3), 55.2 (CH_2), 61.9 (CH_2), 99.6 (C), 133.3 (CH), 136.0 (C), 204.0 (C).

Isoindoline 5e
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74 (s, 3 H), 1.19 (s, 3 H), 2.06 (t, *J* = 9.6 Hz, 1 H), 2.36 (s, 3 H), 2.78 (dd, *J* = 6.6, 9.6 Hz, 1 H), 3.02 (app dd, *J* = 9.6, 9.6 Hz, 1 H), 3.11–3.17 (m, 1 H), 3.29 (s, 3 H), 3.40 (s, 3 H), 3.43–3.49 (m, 2 H), 3.52–3.64 (m, 4 H), 4.76 (s, 1 H), 6.06 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.1 (CH_3), 30.2 (C), 42.1 (CH_3), 42.8 (CH), 46.9 (CH), 50.0 (CH_3), 50.3 (CH_3), 54.6 (CH_2), 60.5 (CH_2), 77.3 (CH_2), 77.5 (CH_2), 96.4 (C), 101.0 (CH), 125.7 (CH), 143.2 (C), 203.7 (C).

Isoindoline 6e
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (s, 3 H), 1.20 (s, 3 H), 2.29 (s, 3 H), 2.41 (d, *J* = 9.6 Hz, 1 H), 2.48 (t, *J* = 9.6 Hz, 1 H), 2.71 (t, *J* = 9.6 Hz, 1 H), 3.11 (s, 3 H), 3.27–3.29 (m, 1 H), 3.31 (s, 3 H), 3.33–3.45 (m, 2 H), 3.52 (d, *J* = 11.2 Hz, 1 H), 3.61 (dd, *J* = 2.8, 10.8 Hz, 1 H), 3.75 (dd, *J* = 2.8, 10.8 Hz, 1 H), 4.64 (s, 1 H), 5.99 (d, *J* = 10.4 Hz, 1 H), 6.73 (dd, *J* = 1.2, 10.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (CH_3), 23.0 (CH_3), 30.4 (C), 42.2 (CH_3), 44.1 (CH), 48.4 (CH_3), 50.2 (CH_3), 52.7 (C), 55.6 (CH_2), 61.6 (CH_2), 77.8 (2 × CH_2), 97.7 (C), 102.3 (CH), 125.5 (CH), 151.3 (CH), 193.0 (C).

Isoindoline 7b
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3 H), 2.56 (s, 3 H), 3.73 (s, 3 H), 3.82–3.84 (m, 2 H), 3.88–3.91 (m, 2 H), 6.52 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (CH_3), 42.5 (CH_3), 58.1 (CH_2), 60.5 (CH_3), 60.9 (CH_2), 115.4 (CH), 124.6 (C), 129.4 (C), 137.2 (C), 143.7 (C), 144.5 (C).

Isoindoline 7e
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (s, 3 H), 1.27 (s, 3 H), 2.56 (s, 3 H), 3.66 (AB_q, *J* = 10.8 Hz, 4 H), 3.83 (s, 3 H), 3.89 (br s, 2 H), 3.98 (br s, 2 H), 4.84 (br s, 1 H), 5.28 (s, 1 H), 6.89 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (CH_3), 23.2 (CH_3), 30.2 (C), 42.7 (CH_3), 56.2 (CH_3), 57.7 (CH_2), 59.7 (CH_2), 77.6 (2 × CH_2), 100.7 (CH), 107.5 (CH), 123.6 (C), 126.5 (C), 132.1 (C), 140.9 (C), 145.8 (C).

Typical Experimental Procedure for the Synthesis of Isoindoline 8a
To a solution of **2a** (185 mg, 1.0 mmol) and TOSMIC (255 mg, 1.3 mmol) in dry THF (6.0 mL) was added KO*t*-Bu (225 mg, 2.0 mmol) at r.t. The reaction mixture was allowed to stir at r.t. until the disappearance of MOB **2a** as indicated by TLC analysis. Solvent was evaporated, sat. aq NH_4Cl was added to the residue and extracted with EtOAc (3×). Organic layers were dried over Na_2SO_4, filtered, the solvent evaporated, and the residue was chromatographed over silica gel using CH_2Cl_2–MeOH as eluent to give isoindoline **8a** in 73% yield.

Isoindoline 8a
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.37 (s, 6 H), 3.78 (s, 3 H), 5.86 (s, 1 H), 6.54–6.61 (m, 1 H), 7.40–7.47 (m, 1 H), 8.62 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.9 (2 × CH_3), 55.5 (CH_3), 95.8 (C), 96.9 (CH), 114.7 (C), 117.3 (CH), 121.5 (C), 123.3 (CH), 153.1 (C), 188.7 (C).

Isoindoline 8b
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3 H), 3.27 (s, 6 H), 6.56–6.58 (m, 2 H), 6.44–6.45 (m, 1 H), 8.76 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8 (CH_3), 51.1 (2 × CH_3), 114.3 (CH), 119.6 (C), 121.3 (CH), 122.1 (CH), 123.1 (2 × C), 135.7 (C), 190.6 (C).

Isoindoline 9e
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (s, 3 H), 1.24 (s, 3 H), 3.38 (s, 6 H), 3.66 (AB_q, *J* = 10.8 Hz, 4 H), 5.01 (s, 2 H), 5.13 (d, *J* = 0.8 Hz, 1 H), 6.05 (d, *J* = 0.8 Hz, 1 H), 6.79 (d, *J* = 2.0 Hz, 1 H), 7.18–7.21 (m, 2 H), 7.29–7.36 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.2 (CH_3), 30.3 (C), 50.6 (2 × CH_3), 54.1 (CH_2), 77.5 (2 × CH_2), 94.8 (C), 100.7 (CH), 119.2 (CH), 120.4 (C), 124.2 (CH), 125.2 (CH), 127.8 (2 × CH), 128.4 (CH), 129.0 (2 × CH), 133.2 (2 × C), 135.4 (C), 188.3 (C).

References and Notes

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(12) For example, when column purified compound **5c** was subjected to the standard reaction conditions [sarcosine (1.0 equiv), paraformaldehyde (2.0 equiv), $MgSO_4$(1.5 equiv) in THF at reflux temperature for 12 h] aromatized product **7c** was isolated in 40% yield as expected along with 10% unreacted starting material (remaining was a complex mixture by ^{1}H NMR analysis with no indication for the formation of other possible cycloaddition products).

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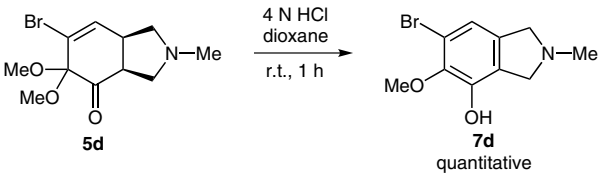
(14) For example, when compound **5d** was treated with 4 N HCl in dioxane for 1 h furnished compound **7d** (after NH_4OH wash) in quantitative yield (Scheme 3).



5d **7d** quantitative

Scheme 3

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