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EDGE ARTICLE

Catalytic generation of *ortho*-quinone dimethides *via* donor/donor rhodium carbenes†

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Substrates engineered to undergo a 1,4-C–H insertion to yield benzocyclobutenes resulted in a novel elimination reaction to yield *ortho*-quinone dimethide (*o*-QDM) intermediates that undergo Diels–Alder or hetero-Diels–Alder cycloadditions. The analogous benzylic acetals or ethers avoid the C–H insertion pathway completely and, after hydride transfer, undergo a de-aromatizing elimination reaction to *o*-QDM at ambient temperature. The resulting dienes undergo a variety of cycloaddition reactions with high diastereo- and regio-selectivity. This is one of the few examples of catalytic generation of *o*-QDM without the intermediacy of a benzocyclobutene and represents one of the mildest, ambient temperature processes to access these useful intermediates. This proposed mechanism is supported by DFT calculations. Moreover, the methodology was applied to the synthesis of (±)-isolariciresinol in 41% overall yield.
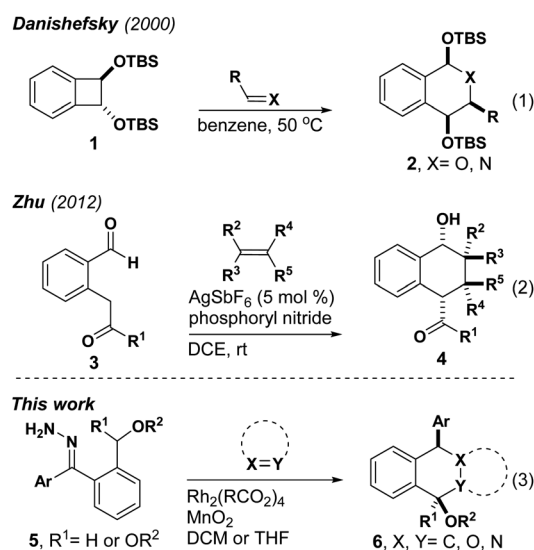
Introduction

Metal carbenes are useful intermediates for a variety of reactions that assemble complex molecules with high efficiency and atom economy.[1–6] While early studies involved carbenes appended with electron-withdrawing groups, donor/acceptor carbenes developed by Davies and co-workers opened up new avenues for reactivity and selectivity.[3,5] Recent advances with donor/donor carbenes have revealed complementary reactivity, increased functional group tolerance and an evolving level of reaction diversity.[1] Importantly, donor/donor carbenes (DDCs) resist attack by heteroatom nucleophiles, which enables the design of reactions that would normally suffer from side reactions that limit the range of reactivity observed for more electrophilic carbenes.

ortho-Quinone dimethide (*o*-QDM) was first discovered in 1957.[7] These reactive dienes are typically formed by the thermal ring opening of benzocyclobutenes. While this process can involve thermolysis at high temperatures, Danishefsky reported an extremely useful substrate that forms *o*-QDM at 50 °C (Scheme 1).[8] Given that multistep syntheses are often required to access *o*-QDM precursors, recent work has focused on accessing these useful intermediates using catalysis. Zhu has reported that a silver catalyst forms *o*-QDM from dicarbonyl substrate 3.[9] During our investigations of C–H insertion reactions to form benzocyclobutenes, we observed direct formation

of *o*-QDMs from donor/donor carbenes. These intermediates could be generated and trapped *in situ* with electron deficient alkenes, carbonyls and imines in stereoselective Diels–Alder and hetero-Diels–Alder reactions, respectively. This is the first example of generating *o*-QDMs from carbene intermediates and one of small number of examples of accessing these intermediates catalytically[9–15] at ambient temperature (Scheme 2).

During our studies of enantioselective synthesis of isochromans by C–H insertion, we observed benzocyclobutene 7 as a side product. Recognizing the potential for this product to serve as a precursor to *o*-QDM, we heated it in the presence of *N*-

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Scheme 1 *o*-QDM generation methods.
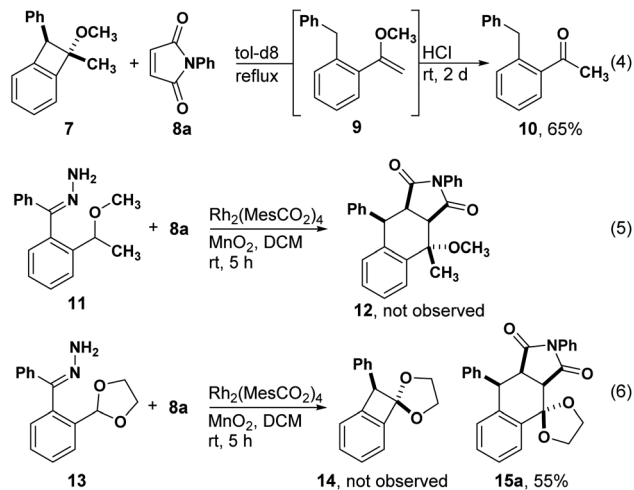
Scheme 2 Discovery of Rh-catalyzed o-ODM generation.

Table 1 Acetal substrate scope for Diels–Alder Reactions[a]

phenyl maleimide **8** with the hope of observing a stereoselective Diels–Alder reaction. Acetophenone **10** was the only observed product, which we presume emanates from enol ether **9** through a known process.[16,17] We next attempted to intercept the presumed o-QDM intermediate through a one-pot process and did not observe any Diels–Alder products. Finally, we prepared acetal **13**, which would avoid enol ether formation. Although we were unable to isolate any products of C–H insertion, e.g. benzocyclobutene **14**, Diels–Alder product **15** was isolated in good yield, suggesting that o-QDM was forming directly without the intermediacy of **14**. Herein we report the development of this o-QDM-forming method for acetals and ethers and propose a mechanism for its formation based on DFT calculations.

Results and discussion

We began our studies by treating hydrazone **13a** with manganese dioxide, Rh₂(MesCO₂)₄ and N-phenyl maleimide in DCM obtaining the desired tetralin **15a** in 55% yield with 87 : 13 dr (Table 1). Encouraged by this result, we next examined the substrate scope of dienophiles in this reaction (Table 1). We were pleased to isolate the desired Diels–Alder products from various N-substituted maleimides (**15a–c**) and hydrazones with different electronic properties (**15d** and **15e**), respectively. The X-ray structure of **15b** demonstrated the endo-product as the major configuration. In addition to the glycol derived hydrazone, substrates with pinacol-derived or dimethoxy acetal groups could also afford the corresponding products **15f** and **15g**. When a hydrazone with propanediol-derived acetal was used, the product was unstable to column chromatography, affording vinyl ether product **15h**. Diethyl fumarate led the cyclization product in 55% yield, while the analogous maleate substrate was far less reactive (**15i** and **15j**). Notably, unsymmetric alkenes containing oxazolidinone groups showed good regioselectivity and diastereoselectivity (**15k**), and the reaction was feasible for amide substituted alkenes in THF (**15l**). Fumaronitrile proved to be another good dienophile (**15m** and
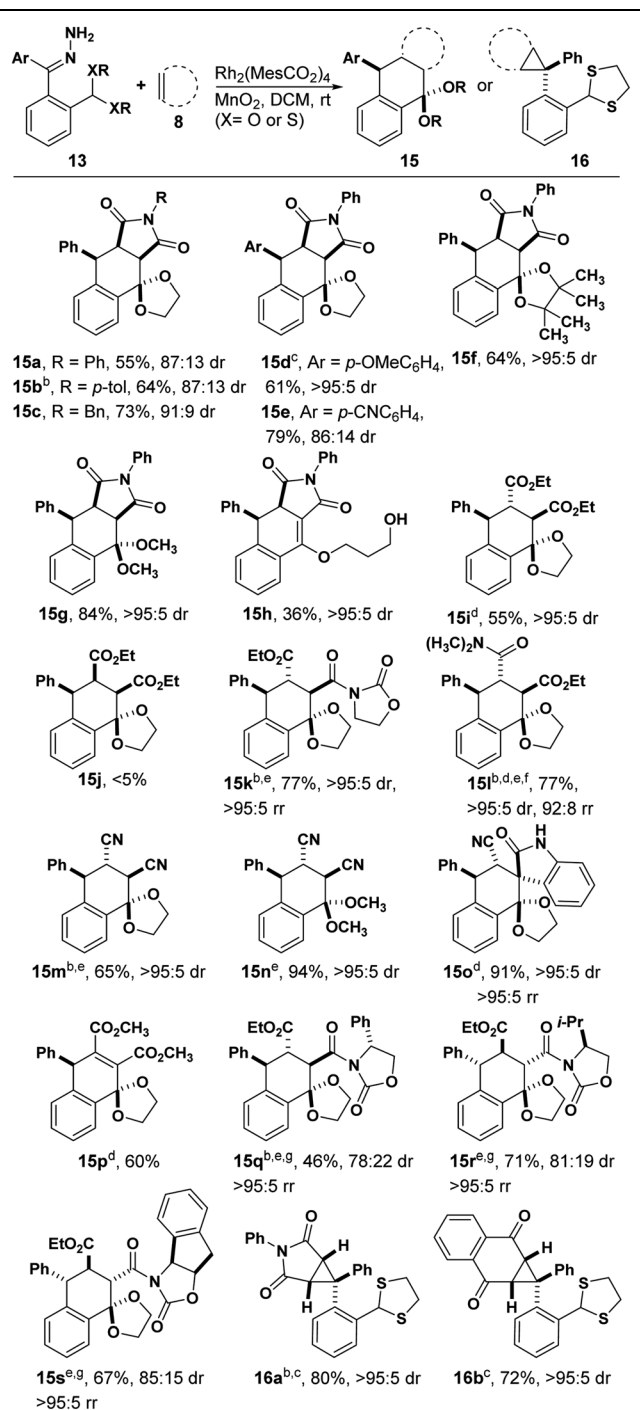
[a] Reaction conditions: 13 (0.1 mmol), 8 (0.12 mmol), Rh₂(MesCO₂)₄ (1 mol%), MnO₂ (0.8 mmol) in DCM (6 mL); isolated yields; dr was determined by ¹H NMR of unpurified reaction mixture. [b] The structure and configuration were further determined by X-ray structure. [c] Rh₂(R-PTAD)₄ was used as catalyst. [d] Rh₂(MesCO₂)₄ and dienophile were added after hydrazone and MnO₂ had been stirred in solvent for 2 h. [e] 1.0 equiv. of dienophile was used. [f] THF was used instead of DCM. [g] Major diastereoisomer yield.

15n). An isatin-derived alkene offered spiro compound **15o** in 91% yield, and computational NMR suggested a trans configuration of phenyl and cyano groups (see ESI†). The observation of product with the indicated regioselectivity can be attributed to steric hindrance between the phenyl and the isatin moiety. Furthermore, an alkyne dienophile is also compatible with this reaction, affording product **15p** in 60% yield. Chiral dienophiles afforded their respective tetralins **15q**, **15r** and **15s** in good yields with excellent regioselectivity, albeit with modest levels of chiral induction from the oxazolidinone. The major isomers were isolated and the stereo- and regiochemistry for **15q** were confirmed by X-ray crystallography. When a thioacetal-containing hydrazone was used, [4 + 2] cyclization was replaced by cyclopropanation, affording **16a** and **16b**, respectively. The observation of single stereoisomer suggests that the bulky thioacetal groups blocked one face of the carbene. This result also reveals that changes to the electronic structure of donor/donor carbenes can lead to completely different reaction pathways.[18]
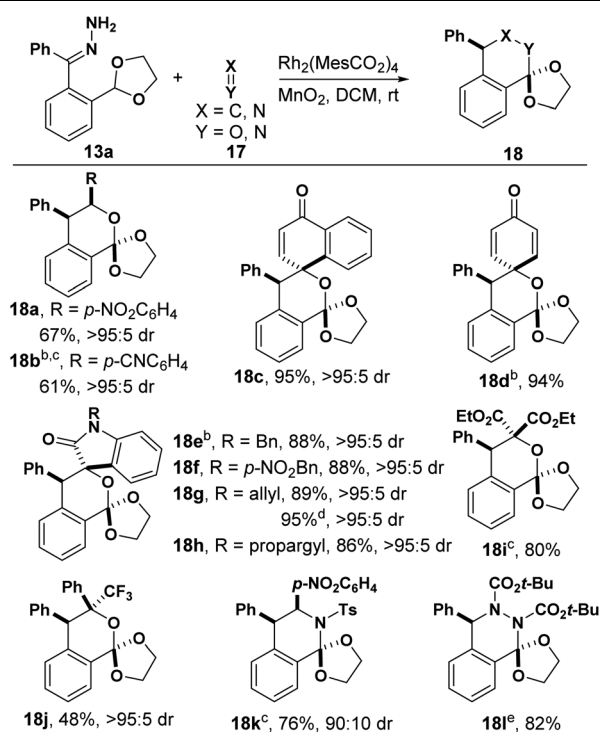
We next investigated hetero-Diels–Alder reactions between o-QDMs formed from hydrazones and C=X/X=X double bonds (Table 2). Electron-deficient aldehydes lead to isochroman products **18a** and **18b**, while benzaldehyde failed to react under the same conditions. An X-ray structure of **18a** indicated that the phenyl group and p-nitrophenyl (PNP) group were assembled in a cis configuration. Generally, quinones are a class of reactive dipolarophiles because of the activated C=C double bond.[19,20] Surprisingly, this [4 + 2] cycloaddition occurred on the carbonyl group instead of the activated C=C double bond (**18c** and **18d**), which has been observed in a related reaction.[19] The structure of **18d** was further confirmed by X-ray diffraction (see ESI†). A variety of isatins were examined next (**18e–h**). The products were isolated in excellent yields and diastereoselectivity in all cases. It should be noted that both alkene and alkyne substitution are tolerated in this transformation (**18g** and **18h**). Furthermore, diethyl ketomalonate afforded the corresponding product **18i** in 80% yield. A trifluoromethyl group was successfully introduced into product **18j** with trifluoro acetophenone as the dienophile. We were pleased to see N-containing heterocycle **18k** was obtained when an imine was used as dienophile, as well as dihydrophthalazine **18l** from an azo compound, illustrating the broad substrate scope of this method.

Motivated by the positive results obtained above, we decided to test the effect on reactivity induced by replacing acetal with methyl ether (Table 3). Treating **13f** with N-phenyl maleimide at 55 °C using THF as the solvent and $Rh_2(MesCO_2)_4$ as the catalyst afforded the desired tetralin **19a** in 69% with >95 : 5 dr. The relative stereochemistry of **19a** was confirmed by X-ray crystallography.

With these optimized conditions, we began developing the substrate scope by testing hydrazones with different electronic properties (Table 4). Electron-poor hydrazone afforded tetralin **19b** in 77% yield with perfect diastereoselectivity. On the other hand, electron-rich hydrazones did not yield the desired tetralin, instead a complex mixture of products was observed. Reacting **13f** with different fumarates afforded tetralins (**19c–e**) in good yields with high diastereoselectivity. Surprisingly, the reaction with trimethyl aconitate and t-butyl acrylate, which did not show any reactivity with **13a**, afforded tetralins **19f** and **19g**

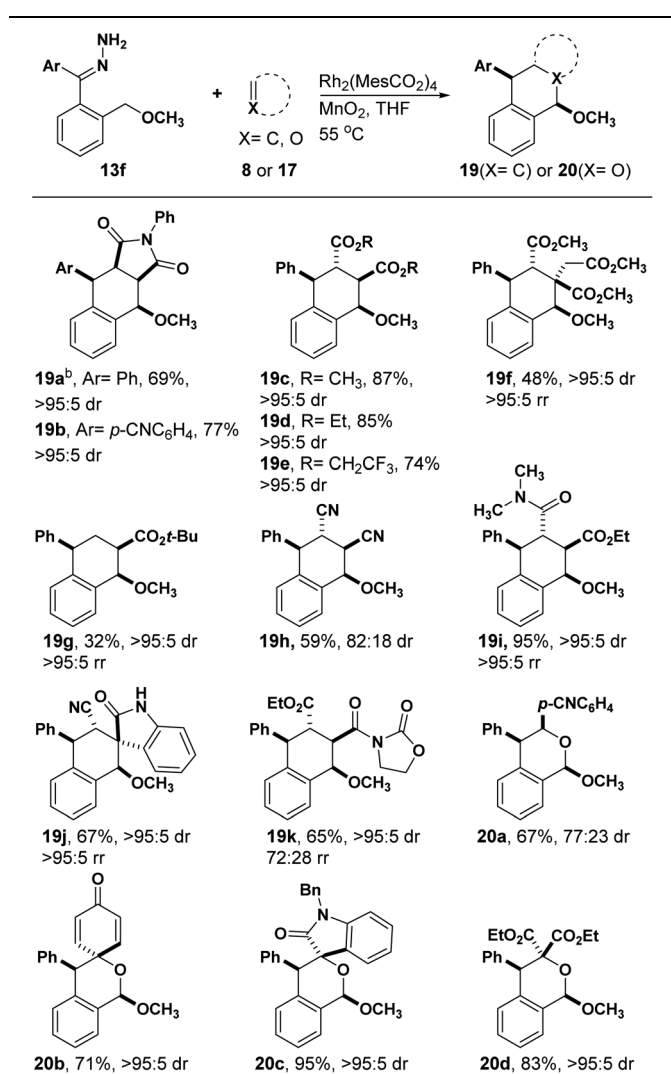**Table 2** Acetal substrate scope for the hetero-Diels–Alder Reaction[a]

18a, R = p-NO$_2$C$_6$H$_4$
67%, >95:5 dr
18b[b,c], R = p-CNC$_6$H$_4$
61%, >95:5 dr

18c, 95%, >95:5 dr

18d[b], 94%

18e[b], R = Bn, 88%, >95:5 dr
18f, R = p-NO$_2$Bn, 88%, >95:5 dr
18g, R = allyl, 89%, >95:5 dr
95%[d], >95:5 dr
18h, R = propargyl, 86%, >95:5 dr

18i[c], 80%

18j, 48%, >95:5 dr

18k[c], 76%, 90:10 dr

18l[e], 82%

[a] Reaction conditions: **13a** (0.1 mmol), **17** (0.12 mmol), $Rh_2(MesCO_2)_4$ (1 mol%), MnO_2 (0.8 mmol) in DCM (6 mL); isolated yields; dr was determined by ^1H NMR of unpurified reaction mixture. [b] The structure and configuration were determined by X-ray structure. [c] $Rh_2(MesCO_2)_4$ and dienophile were added after hydrazone and MnO_2 had been stirred in DCM for 2 h. [d] 0.5 mmol scale. [e] 0.2 mmol scale.

Table 3 Optimization of methyl ether Diels–Alder reaction

| Entry[a]	[Rh] Cat.	Solvent	T (°C)	Yield[b]	dr[c]
1	$Rh_2(MesCO_2)_4$	DCM	rt	25%	>95 : 5
2	$Rh_2(PTCC)_4$	DCM	rt	40%	>95 : 5
3	$Rh_2(PTCC)_4$	THF	rt	60%	>95 : 5
4	$Rh_2(PTCC)_4$	THF	55	65%	>95 : 5
5	$Rh_2(MesCO_2)_4$	THF	55	69%	>95 : 5

[a] Reaction conditions: **13f** (0.1 mmol), **8a** (0.1 mmol), MnO_2 (0.8 mmol), solvent (6 mL), [Rh] (1 mol%), reaction mixture stirred for 1 h before adding [Rh]. [b] Isolated yield. [c] dr was determined by ^1H NMR of unpurified reaction mixture.

Table 4 Methyl ether substrate scope for Diels–Alder and hetero-Diels–Alder reactions[a]

19a[b], Ar= Ph, 69%, >95:5 dr
19b, Ar= p-CNC₆H₄, 77% >95:5 dr

19c, R= CH₃, 87%, >95:5 dr
19d, R= Et, 85% >95:5 dr
19e, R= CH₂CF₃, 74% >95:5 dr

19f, 48%, >95:5 dr >95:5 rr

19g, 32%, >95:5 dr >95:5 rr

19h, 59%, 82:18 dr

19i, 95%, >95:5 dr >95:5 rr

19j, 67%, >95:5 dr >95:5 rr

19k, 65%, >95:5 dr 72:28 rr

20a, 67%, 77:23 dr

20b, 71%, >95:5 dr

20c, 95%, >95:5 dr

20d, 83%, >95:5 dr

[a] Reaction conditions: **13f** (0.1 mmol), **8** or **17** (0.1 mmol), Rh₂(MesCO₂)₄ (1 mol%), MnO₂ (0.8 mmol) in THF (6 mL); isolated yields; dr was determined by ¹H NMR of unpurified reaction mixture. [b] The structure and configuration were determined by X-ray structure.

respectively in moderate yields with great regio- and diasteroselectivity. Fumaronitrile was less reactive and the diastereoselectivity of its corresponding tetralin product **19i** decreased to 82 : 18 with respect to **15m** and **15n**. Reactions with asymmetric dienophiles afforded the desired tetralins (**19i–k**) in moderate to excellent yields with >95 : 5 dr and 72 : 28 to >95 : 5 rr. We also investigated the reactivity of **13f** towards carbonyls to afford their respective heterocycles. Moderate reactivity and diastereoselectivity were observed in the reaction with p-cyanobenzaldehyde as the desired isochroman **20a** obtained in 67% yield with 77 : 23 dr. Reaction with ketones and isatins afforded cycloadducts (**20b–d**) in moderate to high yields with high diastereoselectivity.

We next tried to make lactones through cycloaddition and successive acidic deprotection (Scheme 3). For example,
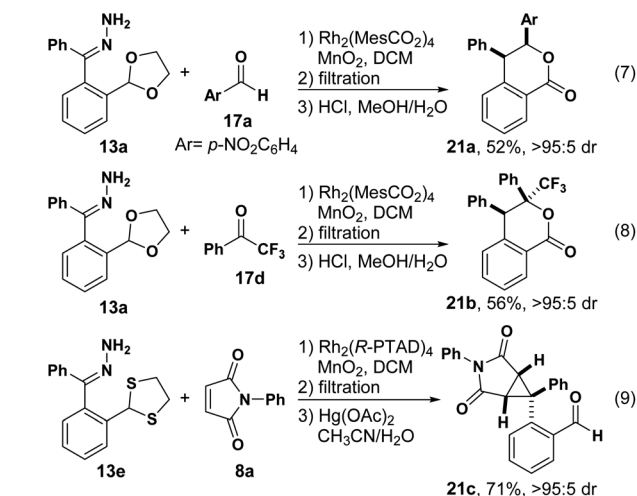
Scheme 3 Two-pot cycloaddition and acetal deprotection.

compound **21a** and **21b** were separated in moderate yield and excellent diastereoselectivity, respectively (eqn (7) and (8)). Using the presented method followed by deprotection with Hg(OAc)₂, aldehyde **21c** was provided smoothly with the cyclopropane untouched (eqn (9)).

To further illustrate the application of this method, we next completed the stereoselective synthesis of isolariciresinol (Scheme 4), a natural product found in different plant species and is believed to possess anti-inflammatory and antioxidant properties.[21–23] From the relative stereochemistry observed in tetralins **15i** and (**19c–e**), it became obvious to us that the natural product tetralin core could be readily accessed using our methodology and it would take only a few transformations to arrive at the final target. Hydrazone **22** was readily obtained from vanillin in 7 steps and subjected to our one-pot sequential oxidation-carbene formation reaction. Using Rh₂(S-TCPTTL)₄ as the catalyst, the reaction with diethyl fumarate afforded tetralin **23** in 74% yield and >95 : 5 dr.
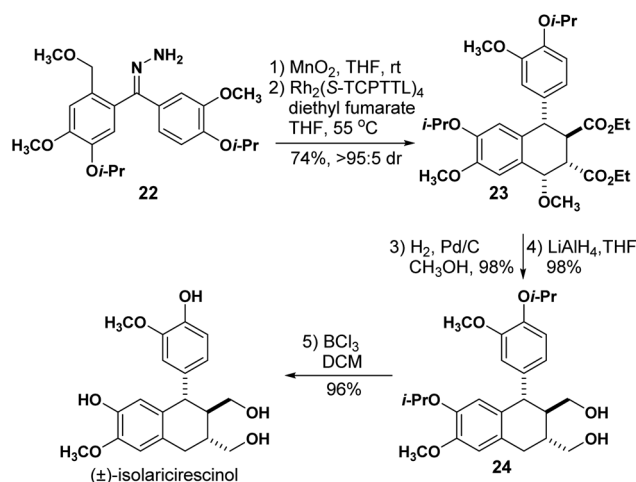
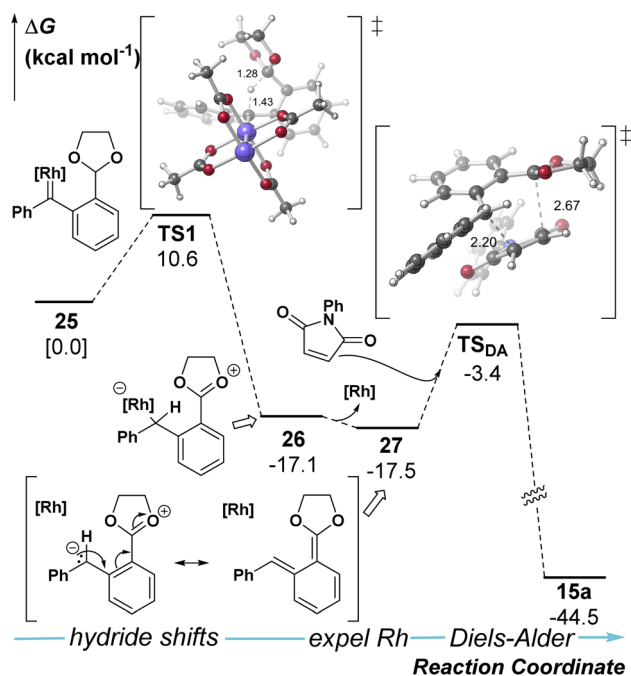**Scheme 4** Stereoselective synthesis of isolariciresinol.

Fig. 1 DFT calculations for QDM generation and Diels–Alder reaction.

While developing the methyl ether substrate scope (Table 4), we did not observe the desired tetralin for the electron-rich hydrazone. Although **22** is an electron-rich hydrazone, we believe that the additional meta alkoxy groups facilitated the *o*-QDM formation needed for the cycloaddition to take place. Treatment with H_2 and Pd/C allowed for the benzylic methoxy cleavage in 98% yield, and ester reduction with $LiAlH_4$ yielded diol **24** in 99% yield. Finally, isolariciresinol was obtained after cleaving the isopropyl protecting groups with BCl_3 in 96% yield resulting in a 41% overall yield. This synthesis installs all of the stereogenic centers in a single step and is completed in higher overall yield than the only previous synthesis reported to date.[24]

The mechanism was further investigated with density functional theory calculations (SMD(DCM)-B3LYP-D3/Def2-TZVPP// SMD(DCM)-B3LYP-D3/Def2-SVP) to examine the formation of *o*-QDM (Fig. 1, see ESI† for details). Our calculations predict that the hydride shift event is facile to the ylide intermediate **26** and occurs with the metal bound. At this stage, loss of Rh-catalyst reveals a metal-free *ortho*-quinone dimethide (*o*-QDM, **27**) which acts as the diene in the Diels–Alder step to obtain the final product **15a**.

Conclusion

In summary, we report a novel and easy access to *o*-QDM dienes that react with various dienophiles, affording tetralins and benzo-fused heterocycles in moderate to good yields. This method features broad substrate scope, excellent regio- and diastereoselectivity, as well as mild reaction conditions. Computational results revealed *ortho*-quinone dimethide as the key intermediate during the reaction. Application of this

methodology afforded the racemic synthesis of isolariciresinol in 41% overall yield.

Data availability

Experimental and computational work can be found in the ESI.†

Author contributions

The manuscript was written through contributions from all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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