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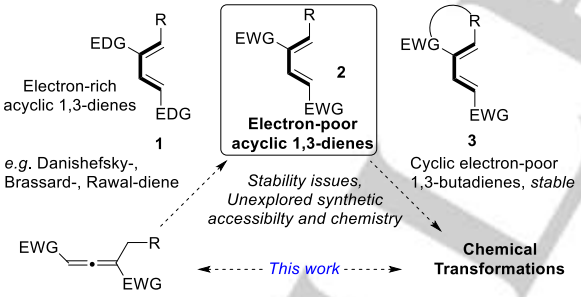
Unravelling Synthesis and Chemistry of Stable, Acyclic and Double-Deficient 1,3-Butadienes: An *endo*-Selective Diels-Alder Route to Hedgehog Pathway Inhibitors

Xiaoyi Xin,[a] Stefan Zimmermann,[a,b] Jana Flegel,[a,b] Felix Otte,[b] Lena Knauer,[b] Carsten Strohmann,[b] Slava Ziegler[a] and Kamal Kumar*[a]

Abstract: The first synthetic access to stable and acyclic 1,3-butadienes with two electron-withdrawing carbonyl groups and their potential to deliver novel molecular scaffolds *via* intriguing *endo*-selective Diels-Alder cycloadditions is presented. The bicyclic scaffolds emanating from cycloaddition chemistry of electron-deficient dienes afforded potent hedgehog signaling pathway inhibitors.

Conjugated 1,3-dienes represent an important class of building blocks that had been extensively utilized to form carbo- and heterocyclic molecules largely through their exquisite cycloaddition reactions.[1] Besides offering access to numerous complex molecules of natural and synthetic origin, the cycloaddition and annulation chemistry of dienes have inspired the development of diverse ligands and catalytic systems.[2] The emergence of concepts like frontier orbital control and the stereoselectivity rules have a historic connection with the cycloaddition chemistry of dienes.[3] The chemistry of carbadienes is largely covered by electron-rich 1,3-butadienes like the Danishefsky–Kitahara´s-,[4] Brassard´s-,[5] and Rawal´s-diene.[6] These dienes bear at least two electron-donating groups (**1**, Scheme 1) from where they derive their peculiar electron-rich nature and also dictate the chemo- and regio-selectivities in cycloaddition reactions. In contrast, their *double-deficient* counterparts (**2**) – dienes with two electron-withdrawing groups at relative 1,3-position are often unstable and tend to oligomerize and therefore had only rarely been synthesized.[7]



Scheme 1. Different 1,3-dienes and the proposal for the synthesis and chemistry of acyclic electron-poor 1,3-dienes.

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A deeper understanding of their chemical reactivity and thereby their potential in organic synthesis remains largely unexplored. Here we report a facile synthesis of electron-deficient, acyclic and stable 1,3-butadienes and unravel their intriguing cycloaddition chemistry affording novel carbo- and heterocyclic small molecules which led to the discovery of a novel class of small molecule inhibitors of Hedgehog signaling pathway.

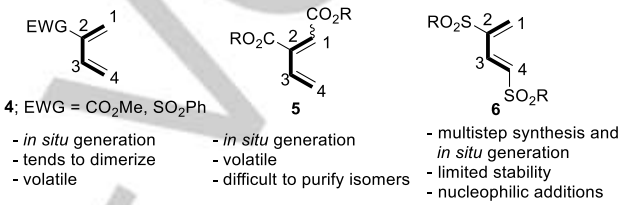

Figure 1. Representative acyclic electron-poor 1,3-carbadienes reported in literature.

Although cyclic electron-deficient dienes[8] (**3**, Scheme 1) are relatively stable and have marked their presence in organic chemistry literature;[9] acyclic, stable and electron-poor butadienes (**2**) remain largely inaccessible despite the dedicated efforts from some groups in the last quarter of twentieth century. McIntosh,[10] Bäckvall[11] and Spino[12] group synthesized and explored the dienes **4** (Fig. 1) supporting only one electron-withdrawing group in the Diels-Alder cycloaddition reactions.[13] However, these dienes were prone to nucleophilic additions and undesired dimeric cycloadditions.[11a, 14] In particular, dienes with an ester moiety had to be generated *in situ* for any further transformation.[13, 15] In successful cases, both electron-rich and poor olefins reacted with dienes **4** to produce Diels-Alder adducts.[16] Diene **5** with 1,2-dicarbonyl functions also showed similar limitations and displayed a relatively lesser dienic character. Padwa et al developed a multistep synthesis of 2,4-bis-sulfonyl 1,3-butadienes (**6**, Fig. 1).[17] The high electrophilicity of the terminal olefin in **6** and sulfone being a leaving group invite further nucleophilic additions and the tendency of dienes **6** to follow dimeric cycloaddition in the presence of unreactive dienophiles,[11a] were the major concerns which limited their further exploitation as viable building blocks.

Taking cognizance of the fact that cyclic electron-poor dienes are stable, we assumed that introduction of substitutions on the butadiene with two electron-withdrawing groups at 1- and 3- positions may offer stable acyclic dienes. Also, such dienes may have enhanced synthetic potential owing to the two modifiable electron-withdrawing functional groups. Unlike the reported isomerization of γ-alkyl allene esters into dienes,[18] no isomerization of α,γ-disubstituted allene ester (**7**, R = H or Me) into the desired diene (**9**) was observed upon treatment with triphenylphosphine (Scheme 2a).[19]

Addition of phosphine to allenoates (**7**) produces zwitterions (**8**) which may exist as cyclic phosphorane (**8´**)[20] and have been successfully used in various annulation reactions.[21] We assumed

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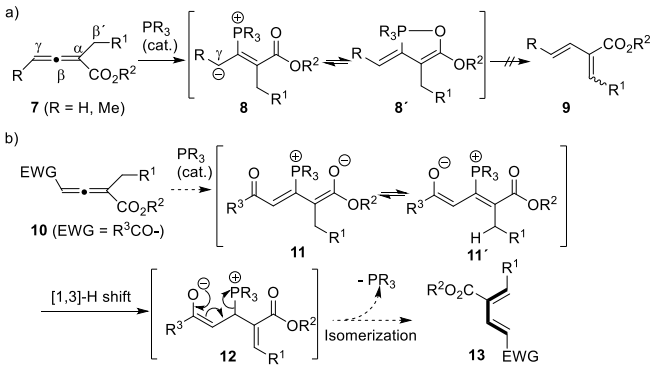
that an introduction of an electron-withdrawing group at γ-position of allene (**10**) may stabilize the corresponding phosphonium enolate (**11**-**11´**) and favours the isomerization to the desired 1,3-diene (**13**, Scheme 2b). Moreover, avoiding a terminal olefin by introducing substitution R^1 may lend more stability to the diene and disfavour their oligomerization.



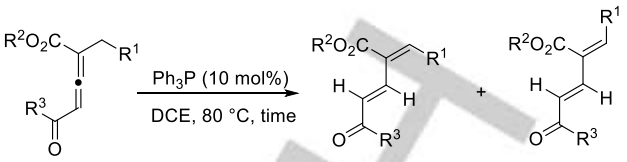
Scheme 2. a) An attempted transformation of allene **7** into diene **9**; b) proposed isomerization of α,γ-disubstituted allene esters (**10**) into dienes (**13**).

To our delight, treatment of allenoate **10a** (see Supp. Information for synthesis of allenes **10**) with 10 mol% of Ph_3P in 1,2-dichloroethane (DCE) and at 80 °C, delivered electron-deficient diene **13a** as two isomers i.e. *E,E*-**13a** and *Z,E*-**13´a** in 72 and 26% respectively (Table 1, entry 1). Different electron-poor and -rich aryl groups were tolerated in the diene synthesis without much influencing the efficiency of the reaction or the ratio of two isomeric dienes formed (entries 2-7). The attempted isomerization of α-methyl allene ester **10h** to terminal diene **13h** led to a complex mixture of oligomers (entry 8). The α-ethyl allene ester however, nicely yielded diene **13i** and **13´i** with a methyl substitution (entry 9). This result highlights the importance of substitution (R^1) in affording stable dienes. Electron-poor dienes with different alkyl and aryl ketones (**13j-l**, entries 10-12) were also synthesized in high yields except for **13m** where the diene supported a bulky tertiary butyl ester (entry 13). The stereochemistry of diene products was corroborated by single crystal X-ray analysis of **13l** and **13´f**.[22]

Both **13a** and **13´a** were stable at room temperature (Scheme 3, eq. i and ix and Supp. Information) in DCE even at higher temperature (eqs iii and x). At higher temperature in toluene (microwave (μW) irradiation, 200 °C), diene *E,E*-**13a** remained stable with slight conversion to **13´a** (eq ii), however, the latter isomerized to **13a** and also displayed dimerization and decomposition (see Supp. Information). Interestingly, in DMSO-d_6 both the dienes reached a ratio of *ca*. 60:40 in favor of *E,E*-**13a** (eqs iv and xi). In the presence of catalytic triphenylphosphine and at high temperature, both dienes **13a** and **13´a** acquired a ratio of 74:26 with *Z,E*-**13´a** as minor isomer (Scheme 3, eqs v and vii). Intriguingly, the phosphine mediated conversion of *Z,E*-**13´a** at room temperature delivered almost 1:1 ratio of the two dienes.

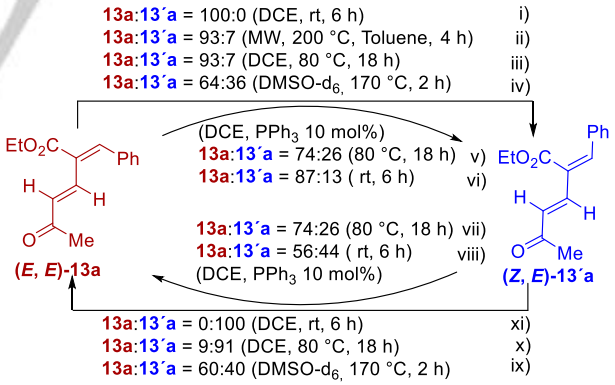
Our interest in cycloaddition chemistry of the electron-deficient 1,3-butadienes (**13**) stems from developing synthetic methods to novel and diverse molecular scaffolds that can be used to build compound collections for biological screenings.[23] We assumed that a single bond rotation in dienes **13** under the

Table 1. Phosphine catalyzed synthesis of electron-deficient 1,3-dienes.



No	R^1	R^2	R^3	Time (h)	Yield (%)[a] (*E*, *E*)-**13**	Yield (%)[a] (*Z*, *E*)-**13´**
1	Ph	Et	Me	18	**13a**, 72	**13´a**, 26
2	2-Me-C_6H_4	Et	Me	18	**13b**, 58	**13´b**, 41
3	4-Me-C_6H_4	Et	Me	18	**13c**, 68	**13´c**, 25
4	3-MeO-C_6H_4	Et	Me	18	**13d**, 72	**13´d**, 27
5	4-CF3-C_6H_4	Et	Me	18	**13e**, 68	**13´e**, 31
6	4-Br-C_6H_4	Et	Me	18	**13f**, 67	**13´f**, 29
7	4-NO_2-C_6H_4	Et	Me	18	**13g**, 57	**13´g**, 35
8	H	Et	Me	18	**13h**, -[b]	**13´h**, -[b]
9[c]	Me	Et	Me	60	**13i**, 54	**13´i**, 24
10	Ph	Et	Et	18	**13j**, 66	**13´j**, 26
11	Ph	Et	Bn	18	**13k**, 76	**13´k**, 23
12	Ph	Et	Ph	72	**13l**, 67	**13´l**, 20
13	Ph	^{t}Bu	Me	72	**13m**, 47	**13´m**, 30

[a] Isolated yields. [b] Oligomerization products were formed. [c] 20 mol% of Ph_3P was used.



Scheme 3. Interconversion of ***E,E*-13a** and ***Z,E*-13'a**.

reaction conditions may offer the *s*-cis conformation to entertain the Diels-Alder (DA) reaction. We chose to first explore *N*-methyl maleimide (NMM) as electron-poor dienophile,[10, 12a, 12b, 24] in DA reaction with dienes **13**. To this end, when the *E,E*- or *Z,E*-diene **13a** or **13´a** respectively were heated with NMM in toluene under μW irradiation (300 W, 200 °C) for 4h, a complex and unresolvable product mixture was formed. Performing the reaction in xylene at 150 °C or in toluene at lower temperatures (rt to 80 °C) provided similar results. Interestingly, when DMSO was employed as solvent in the reaction of diene **13a** with NMM

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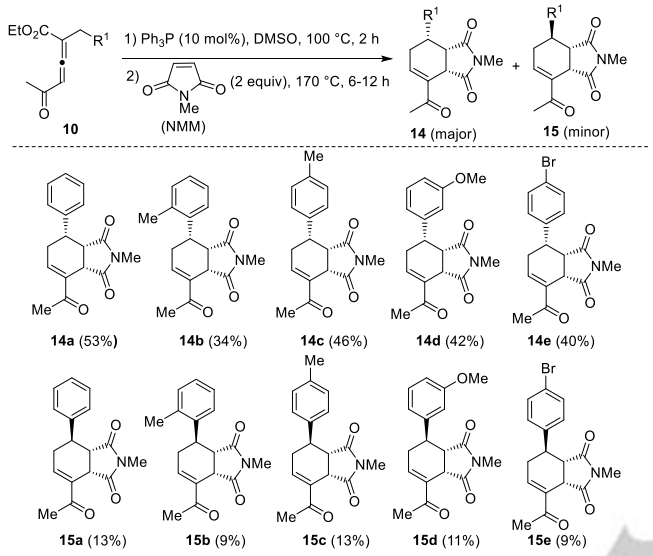
at 170 °C, the reaction afforded a decarboxylated cycloadduct **14a** as the major product and the diastereomer **15a** as the minor product.[22] Reaction conditions were established to deliver the cycloadduct **14a** directly from the allenes esters **10** in a one-pot, two-step process. Different allene esters supporting electron-poor and -rich aromatic groups were used in this one-pot cascade reaction sequence to provide novel bicyclic molecular scaffolds **14** and **15** in acceptable yields (Scheme 4).



Scheme 4. A cascade reaction sequence of Diels-Alder-isomerization-decarboxylation of electron-poor 1,3-dienes with NMM.

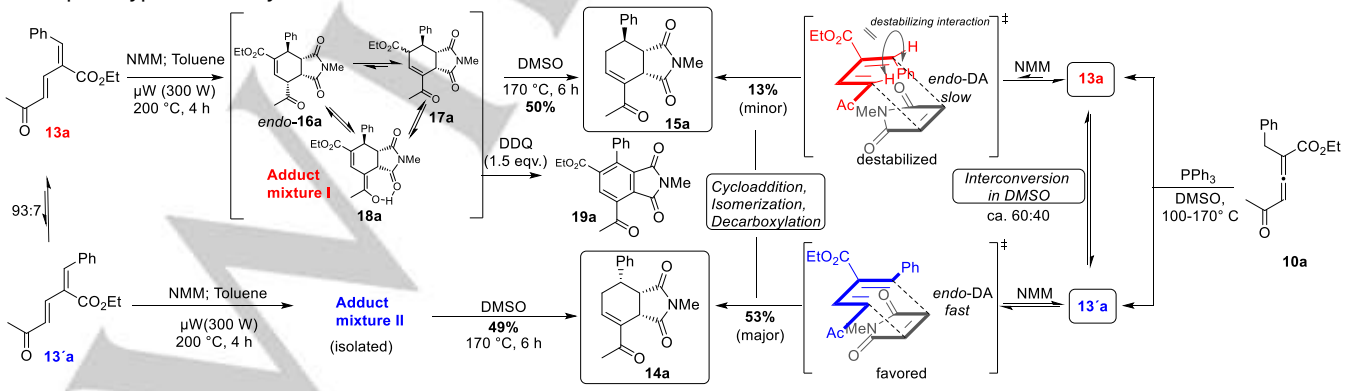
Further experiments were performed to get more insights into this unique chemistry of electron-poor dienes. In two separate control reactions of **13a** and **13´a** with NMM (2.0 eqv) in DMSO-d_6 at 170 °C, **14a** was formed as major cycloadduct and diene *Z,E*-**13´a** was consumed faster than diene *E,E*-**13a** (Supp. Fig. 1).The reactions of **13a** and **13´a** with NMM were also performed in toluene under μW irradiation (200°C, 300 W) for 4 h. After a short flash column chromatography to remove the unreacted dienes and excess of NMM, an inseparable mixture was obtained (see Supp. Information). Interestingly, the two adduct-mixtures **I** & **II** obtained from the reactions of **13a** and **13´a** when separately dissolved in DMSO and further heated at 170 °C for 6 h, followed a Krapcho type decarboxylation[25] to form adducts **15a** and **14a** respectively as the major products (Scheme 5). The NMR analysis of reaction adduct-mixture **I** hinted towards the presence of major cycloaddition product **17a** wherein olefin isomerization had already occurred and along with another product with H-bonded enol moiety (**18a**).[26] DDQ-mediated oxidation of the adduct-mixture-**I** afforded a highly substituted *N*-methyl-phthalamide (**19a**) and further corroborated that the decarboxylation followed the DA-cycloaddition reaction in DMSO.

Based on above results we propose that in DMSO, the phosphine transforms allene ester **10a** into dienes **13a** and **13´a** in ~ 60:40 ratio. Due to an internal destabilizing interaction between aryl group and the proton in the *s-cis* conformation of *E,E*-**13a** (Scheme 5, right), the corresponding highly congested *endo*-transition state is not favored. The *endo*-transition state derived from *s-cis-Z,E*-**13´a** has no such destabilizing interaction and reacts faster with NMM in a DA reaction to yield **14a**. The faster consumption of **13´a** further shifts the equilibrium of the diene interconversion towards *Z,E*-diene-**13´a** and consequently, **14a** is formed as the major product (Scheme 5, right). As no *exo*-cycloaddition derived product was observed in the reaction, we assume that secondary orbital interactions might have contributed to stabilize the *endo*-transition state.[27] Unlike a number of reactive, substituted acyclic dienes which deliver thermodynamically favored *exo*-DA adducts, the electron-poor 1,3-dienes **13** afforded *endo*-DA-derivatives.[6a, 28]

Notably, the diene interconversion is not well supported in toluene and therefore isolated diene **13a** could be used in DA reaction with NMM to form the adduct mixture-**I** which upon heating in DMSO afforded **15a** – the other diastereomer as the major adduct (Scheme 5).

Extending the scope of cycloadditions of electron-deficient dienes, 4-phenyl and 4-methyl 1,2,4-triazoline-3,5-diones (**20**) were used as electron-poor hetero-dienophiles. A one-pot reaction condition was established for the reaction of allene esters **10** with aza-dienophiles **20** to form bicyclic triazolindiones (**21a-m**) with four-point variations in very high yields (Scheme 6).

When combined with dienes under prolonged heating, acyclic and cyclic ketene acetals furnished corresponding addition products **22** and **23a-c** (Scheme 6). Interestingly, **22** is stable under normal conditions whereas the surrogate intermediate oxidizes relatively quickly towards the biphenyl in the case of **23a-c** (see Supp. Information).



Scheme 5. Control experiments to unravel the cycloaddition chemistry of electron-poor 1,3-dienes and a mechanistic proposal for stereoselective synthesis of two diastereomeric adducts **14a** and **15a.**

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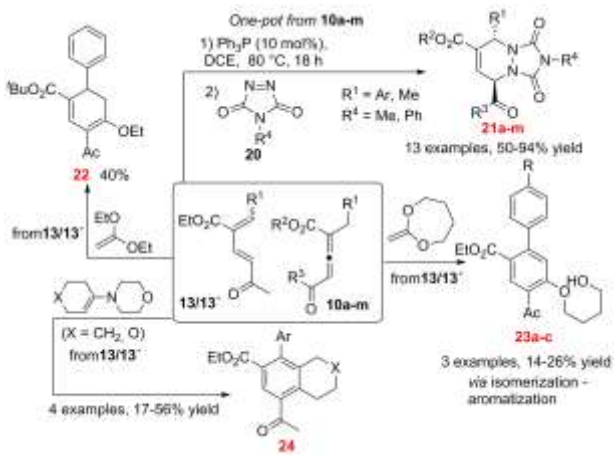

Scheme 6. Cycloaddition reaction of dienes **13**/**13´** with 1,2,4-triazoline-3,5-diones **20**, ketene acetals and enamines.

Furthermore, the electron-poor dienes displayed reactivity towards electron-rich enamines, however the reactions tend to deliver aromatic and structurally flat trisubstituted tetrahydronaphtalenes (X = CH_2, **24a-c**) and isochromane **24d** (X = O, Scheme 6). The reactions of electron-rich dienophiles with dienes **13**/**13´** supposedly proceed *via* inverse electron-demand Diels-Alder reaction, elimination and aromatization.

Cell-based phenotypic screenings[29] targeting modulation of cell signaling pathways, like hedgehog (Hh) pathway are important tools to identify leads for biological research.[30] Hh pathway is important for embryonic development, tissue regeneration and stem cell homeostasis. Aberrant activation of Hh signaling is involved in various types of cancer.[31] Consequently, novel Hh pathway inhibitors are in high demand.[32] The bicyclic cycloadducts were exposed to osteoblast differentiation assay in C3H10T1/2 cells as a primary screen to identify Hh inhibitors. The Smoothened (SMO) agonist Purmorphamine was employed to activate the Hh pathway, which induces osteoblast differentiation and leads to the expression of the osteoblast specific marker alkaline phosphatase.[33] The measurable activity of the latter correlates indirectly with the Hh pathway activity.[34] Remarkably, the bicyclic triazolindione **21f** inhibited Hh depended cell differen-tiation with a half-maximal inhibitory concentration (IC_{50}) of 0.2 µM. Further, the *N*-methylmaleimide adduct **14e** also bearing *p*-bromophenyl group caused Hh inhibition with an IC_{50} of 4.17 ± 0.78 µM, representing another bioactive bicyclic scaffold.

The inhibition of Hh signaling by adducts was further confirmed by an orthogonal, GLI-dependent reporter gene assay using Shh-LIGHT2 cells (Fig. 2a). In this assay, **21f** inhibited the GLI-dependent luciferase expression with an IC_{50} of 7.15 ± 1.91 µM. **14e**, **15b** and **15c** displayed an IC_{50} in the range of 9.5 - 11.2 µM (see Supp. Table 1). The ability of these molecules to bind to the seven-pass transmembrane protein SMO was explored using a competition experiment with BODIPY-cyclopamine in HEK293T cells ectopically expressing SMO. Interestingly, the BODIPY-fluorescence was considerably reduced after treatment with 20 µM **21f** (Fig. 2b), indicating that this compound might bind to the heptahelical bundle of SMO.[35] In case of carbocyclic adducts **14e**, **15b**, and **15c** a clear displacement could not be observed and therefore this compound class might inhibit the Hh pathway thorough a different, currently unknown mode of action.[36]

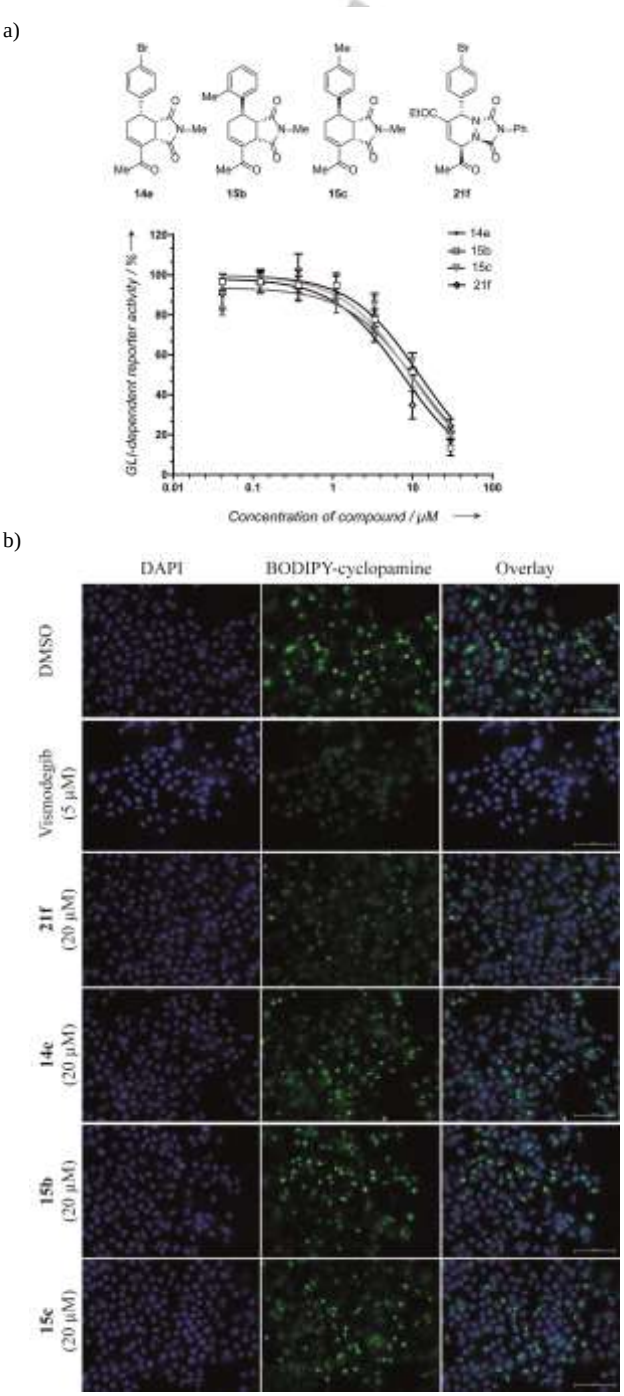

Figure 2. a.) Influence of the bicyclic triazolindione and *N*-methyl-maleimide compounds on GLI de-pendent reporter gene assay. Shh-LIGHT2 cells were treated with 2 µM Purmorphamine and different concentrations of compound or DMSO as a control for 48 h. The signal of the GLI-responsive *Firefly*-luciferase was divided by the control signal of the *Renilla*-luciferase and the DMSO control was set to 100%. The data are representative of three biological replicates (n=3), given as mean values ± standard deviation. b) Influence of active compounds on SMO-BODIPY-cyclopamine binding. HEK293T cells ectopically expressing SMO were fixed and treated with 5 nM BODIPY-cyclopamine (green) and compounds (20 µM) or vismodegib (5 µM), and DMSO as controls. Cells were stained with DAPI to visualize the nuclei (blue). Scale bar: 50 µm.

In summary, a facile synthesis of acyclic and stable electron-deficient 1,3-butadienes supporting two orthogonal carbonyl groups was developed and their prodigious potential in organic synthesis was presented with unique *endo*-selective Diels-Alder and cascade reactions. The intriguing chemistry of the electron-poor dienes delivered two novel bicyclic scaffold classes as promising inhibitors of the Hedgehog signaling pathway. We believe that the stable electron-poor dienes will open many doors to different chemical transformations as well as opportunities to unravel new insights into novel aspects of cycloaddition and annulation reactions and thereby will inspire new synthetic adventures and advances.

Keywords: 1,3-butadienes • electron-poor dienes • Diels-Alder reaction • allene esters • phosphine catalysis

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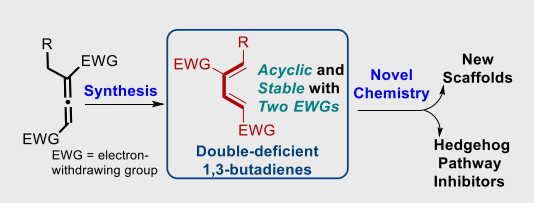

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