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Rearrangements and Intramolecular Diels−Alder Reactions of Normal and Vinylogous Aza-Morita−Baylis−Hillman Products Leading to Isoindoline Derivatives

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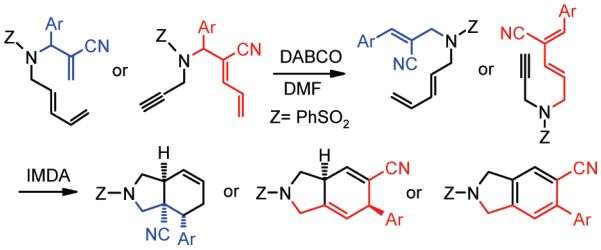

Aza-Morita−Baylis−Hillman (aza-MBH) products derived from arylimines and methyl acrylate or acrylonitrile were *N*-alkylated with (*E*)-5-bromopenta-1,3-diene, and the resulting trienes were subjected to intramolecular Diels−Alder (IMDA) cyloadditions to afford the corresponding *trans*- and *cis*-fused tetrahydroisoindolines as the major and minor products, respectively. Catalysis with boron trichloride improved the IMDA diastereoselectivities of the nitrile derivatives, while yields were improved in both the nitrile and ester series. Treatment of the nitrile-substituted trienes with DABCO in DMF resulted in unexpected transposition of the *N*-(pentadienyl)sulfonamide group to the β-position of the acrylonitrile moiety. Subsequent IMDA cycloadditions produced *cis*-fused positional isomers of the previous tetrahydroisoindolines. When the products of vinylogous aza-MBH reactions in the nitrile series were *N*-propargylated, the resulting dienynes underwent a similar transposition and IMDA reaction, producing *trans* and *cis* diastereomers of the corresponding dihydroisoindolines as the major and minor products, respectively. In all but one case, only the former products were observed in the presence of methylaluminum dichloride, while the corresponding aromatized isoindolines were obtained when the IMDA reactions were carried out in the presence of DDQ. Thus, a variety of aryl-substituted isoindoline products with different levels of unsaturation and complementary substitution patterns and stereochemistry are readily available through these processes.

Introduction

The Morita−Baylis−Hillman reaction was discovered more than 40 years ago[1,2] but was largely ignored for several decades. More recently, it has attracted considerable attention as a widely applicable synthetic method for coupling the α-position of an alkene, activated by a suitable electron-withdrawing group (EWG), with the carbonyl group of an aldehyde or related electrophile. The reaction is typically catalyzed by a tertiary amine or phosphine and proceeds by conjugate addition of the nucleophilic catalyst to the activated alkene, followed by attack of the resulting zwitterion upon the aldehyde carbonyl group, proton transfer, and finally elimination of the catalyst (Scheme 1). Numerous

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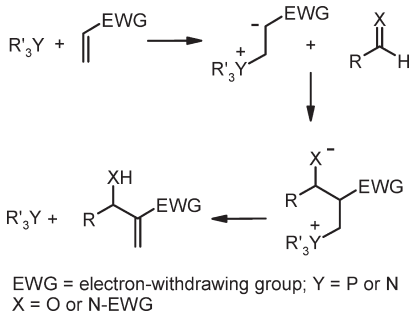
SCHEME 1

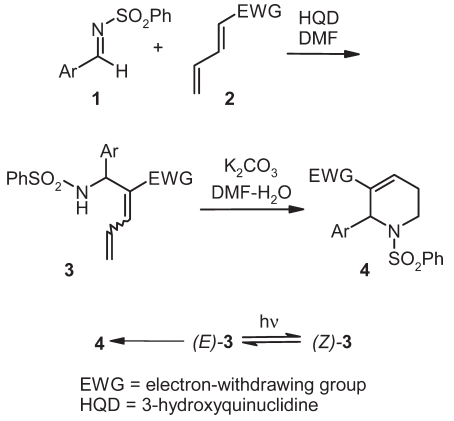


variations in the structures of the reactants and catalyst are tolerated,[2] and several mechanistic investigations have been completed.[3] Enantioselective variations, frequently effected by the use of chiral catalysts,[4] and numerous studies of further transformations of the products have been reported.[2] A particularly useful modification is based on employing aldimines instead of aldehydes, resulting in the aza-Morita–Baylis–Hillman (aza-MBH) reaction.[5,6] This permits the formation of allylic amines instead of the more conventional allylic alcohol products.

We recently reported the use of activated dienes **2** in place of simple alkenes in a novel vinylogous aza-MBH reaction with imines **1**. The activating groups can be sulfonyl,[7a,b] ester,[7b] ketone,[7b] or nitrile[7c] moieties, resulting in products **3** with predominantly (where EWG is Ts, CO_2Me, or C(=O)Ph) or exclusively (where EWG is C(=O)Me) the *E*-configuration. In contrast, the corresponding nitriles (where EWG is CN) were obtained as essentially pure *Z*-isomers. In the case of the *E*-isomers of the products **3**,[7a,b] a subsequent intramolecular conjugate addition afforded substituted piperidines **4**. Although the corresponding *Z*-isomers were unreactive in this process, in situ photoisomerization of *E*,*Z* mixtures of the aza-MBH adducts **3** (where EWG is Ts) during the cyclization reaction resulted in equilibration of the *E*- and *Z*-isomers, with the ultimate consumption of both geometrical isomers (Scheme 2).[7a,b]

During further investigations of useful transformations of aza-MBH products, we prepared the corresponding *N*-allyl and *N*-propargyl derivatives **5** from (*Z*)-**3**, which underwent

SCHEME 2



intramolecular Diels–Alder (IMDA) reactions to afford the corresponding 1-aryl-substituted tetra- or dihydroisoindoline derivatives **6**–**8**.[8] The corresponding *E*-isomers were unsuitable for this purpose because of their competing intramolecular conjugate additions, as was shown in Scheme 2. The products were converted into the corresponding isoindolines **9** by aromatization and isoindolinones **10** by further oxidation (Scheme 3).

Isoindolines and their congeners display a remarkable variety of biological activities. They serve as inhibitors of the enzymes prolyl dipeptidases DPP8 and DPP9,[9] which are of interest in therapies for Type II diabetes, while other members of this class inhibit COX-2,[10] a key target for anti-inflammatory drugs. Certain derivatives serve as antagonists of the receptors ET_A,[11] NMDA,[12] and 5-HT_{2C},[13] which are implicated in vasoconstriction, neurodegenerative diseases, and neuropsychiatric disorders, respectively. Some isoindolines act as selective serotonin uptake inhibitors,[14] while others exhibit antitumor,[15] diuretic,[16] and herbicidal[17] activity. Many of the biologically active isoindolines contain additional aryl and other substituents. While numerous methods have been reported for the synthesis of isoindoline derivatives, they are

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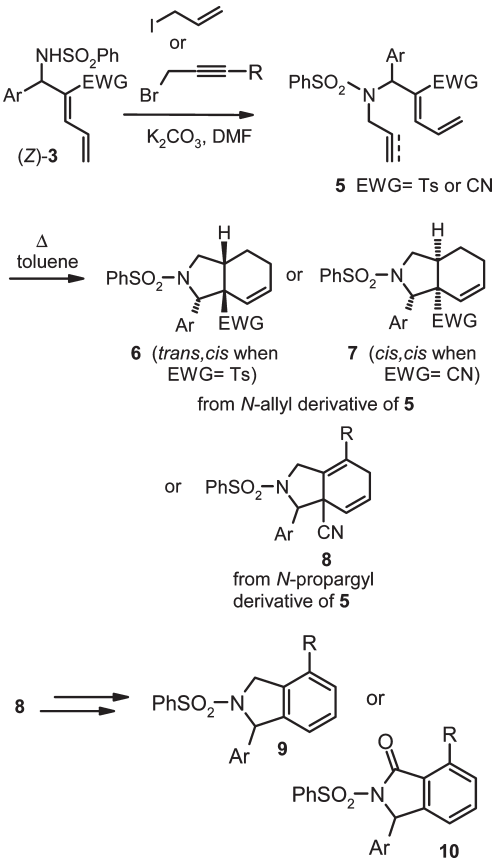
SCHEME 3



generally limited with respect to the level of unsaturation of the products and the types and locations of substituents. Versatile synthetic approaches that are able to provide these products with diverse substituent patterns and in various oxidation states are therefore in demand.

We now report that aza-MBH products derived either from simple alkenes or dienes undergo a facile isomerization of the sulfonamide moiety to the terminal position of the alkene or diene. When the sulfonamide is suitably *N*-functionalized with pentadienyl or propargyl substituents, the isomerization and subsequent IMDA cycloaddition can be exploited in the preparation of complementary isoindoline derivatives that differ in stereo- and regiochemistry compared to those we had prepared previously[8] via Scheme 3.

Results and Discussion

The aza-MBH adducts **11** and **12** were obtained from the simple activated alkenes methyl acrylate and acrylonitrile according to literature procedures.[18] The products were then *N*-alkylated in good yield with (*E*)-5-bromopenta-1,3-diene[19] to provide trienes **13** and **14** (Scheme 4). It was expected that the latter compounds would provide IMDA cycloadducts similar to **6** and **7** in Scheme 3, but differing in the position of the double bond and possibly the stereochemistry. In contrast to the preparation of **6** and **7** from **5**, where

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SCHEME 4

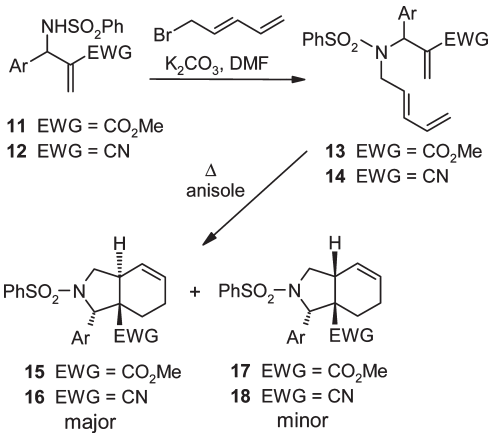


TABLE 1. Preparation and IMDA Cycloadditions of 13 and 14

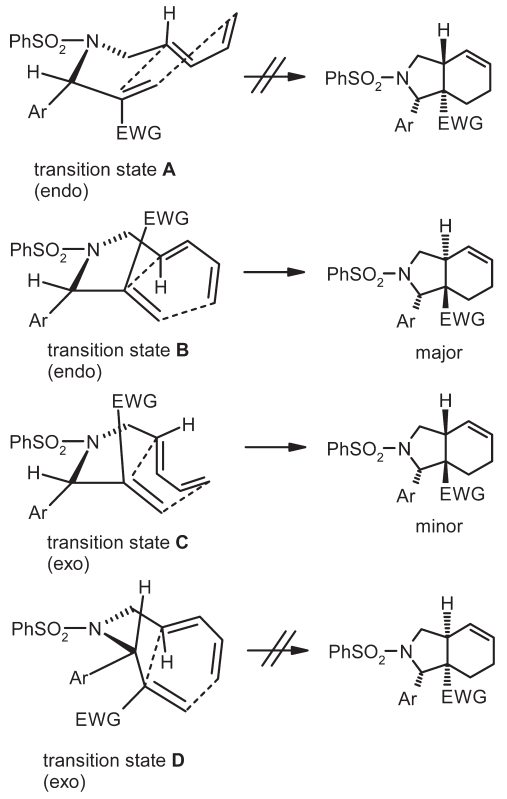
entry	Ar	EWG	products **13** and **14** (yield, %)[a]	IMDA products (yield, %)[a]	dr[b]
1	Ph	CO_2Me	**13a** (98)	**15a** + **17a** (89)	65:35
2	*p*-Cl-Ph	CO_2Me	**13b** (97)	**15b** + **17b** (67)	75:25
3	*p*-MeO-Ph	CO_2Me	**13c** (94)	**15c** + **17c** (72)	70:30
4	*p*-NC-Ph	CO_2Me	**13d** (99)	**15d** + **17d** (77)	70:30
5	1-naphthyl	CO_2Me	**13e** (98)	**15e** + **17e** (86)	75:25
6	Ph	CN	**14a** (98)	**16a** + **18a** (61)	75:25
7	*p*-Cl-Ph	CN	**14b** (98)	**16b** + **18b** (84)	75:25
8	*p*-MeO-Ph	CN	**14c** (94)	**16c** + **18c** (88)	70:30
9	*p*-NO_2-Ph	CN	**14f** (−)	**16f** + **18f** (70)[c]	70:30

[a]Isolated yields of **13** and **14** and of unseparated mixtures of **15** + **17** and **16** + **18** are reported. [b]Diastereomeric ratio (dr) determined by integration of ^{1}H NMR spectra of the unseparated mixtures. [c]Overall yield from **12f** is shown.

the *N*-substituent comprised the dienophile and reacted with a diene moiety activated by an electron-withdrawing group via inverse electron demand, cycloadditions of **13** and **14** were expected to proceed through normal electron demand. When trienes **13** and **14** were refluxed in anisole, IMDA cycloadditions afforded the corresponding tetrahydroisoindoline products as mixtures of two diastereomers **15** and **17** for the methyl esters and **16** and **18** in the nitrile series. Yields are summarized in Table 1 and were generally moderate to good, with both electron-withdrawing and electron-donating substituents on the aryl moiety tolerated by the reaction conditions. Diastereoselectivities ranged from 65:35 (entry 1) to 75:25 (entries 2, 5, 6, and 7). The major isomers **15a**−**15e**, **16a**−**16c**, and **16f** could be isolated essentially free of their minor diastereomers, but minor isomers **17** and **18** could not be completely separated from their counterparts, except for **17c**.

The structures of the major diastereomers **15b** and **16c** were unequivocally confirmed by X-ray crystallography (see Supporting Information), which indicated *trans*-fused rings and a *trans* orientation of the aryl substituent with the electron-withdrawing group. This stereochemistry is consistent with *endo* transition state **B** in Scheme 5, in contrast to the previous *cis*-fused products **6** and **7** that had been obtained by inverse electron demand IMDA reactions (Scheme 3). The stereochemistry of the minor diastereomer **17c** in the ester series was also confirmed by X-ray crystallography (see Supporting Information), which indicated the *cis*-fused ring system arising from the *exo* transition state **C** in Scheme 5. Presumably, transition state *endo*-**B** is favored over *exo*-**C** because of

SCHEME 5



secondary orbital interactions that compensate for the incipient formation of the less stable *trans*-fused product. The failure to observe products derived from transition states **A** and **D** is attributed to the destabilizing steric interactions between the aryl moiety and the ester or nitrile group. The stereochemistry of the other products in Table 1 was inferred by analogy and from the similarity of their respective NMR spectra to those of the corresponding compounds of known configuration described above.

Attempts to increase the diastereoselectivity and decrease the required temperature of the IMDA reaction of **14a** by means of Lewis acid catalysis are summarized in Table 2. While the inclusion of several Lewis acids permitted the reactions to proceed at temperatures as low as −78 °C (entries 3 and 6), boron trichloride afforded the highest diastereomeric ratio (dr) of 90:10 (entries 5 and 9−11), while the conditions of entries 10 and 11 provided the highest yields of 98% and 93%, respectively. A decrease to 0.5 equiv of boron trichloride decreased the yield slightly (entry 11), while the use of only 0.1 equiv resulted in a very sluggish reaction and markedly lower yield. The most satisfactory combination of d.r and yield was therefore obtained in entry 10 in 1,2-dichloroethane at 0 °C−room temperature with 1 equiv of the catalyst.

Unfortunately, similar attempts to enhance the diastereoselectivity of the cycloadditions of esters **13** with Lewis acids were unsuccessful, although boron trichloride did improve the combined yields of products **15** and **17** in refluxing 1,2-dichloroethane. Consequently, further IMDA reactions of trienes **13** and **14** were conducted with 1 equiv of boron trichloride in refluxing 1,2-dichloroethane for the esters **13** and at 0 °C−room temperature for nitriles **14**. The results are shown in Table 3. Thus, while high combined yields were

TABLE 2. Lewis Acid Catalyzed IMDA Reactions of 14a (Ar = Ph; EWG = CN)

entry	Lewis acid	equiv	temp (°C)[a]	solvent[b]	**16a** + **18a** (yield, %)[c]	dr[d]
1	$AlCl_3$	1	0−rt	DCM	(45)	80:20
2	$MeAlCl_2$	1	0−rt	DCM	(82)	80:20
3	BBr_3	1	−78	DCM	(45)	85:15
4	$BF_3 \cdot OEt_2$	1	0	DCM	(38)	85:15
5	BCl_3	1	0−rt	DCM	(70)	90:10
6	BCl_3	1	−78	DCM	(68)	85:15
7	BCl_3	1	−55	DCM	(73)	85:15
8	BCl_3	2	0	DCM	(63)	85:15
9	BCl_3	1	rt	DCM	(70)	90:10
10	BCl_3	1	0−rt	DCE	(98)	90:10
11	BCl_3	0.5	0−rt	DCE	(93)	90:10

[a]rt = room temperature. [b]DCM = dichloromethane; DCE = 1,2-dichloroethane. [c]Isolated yields are reported. [d]Determined by integration of ^{1}H NMR spectra of the crude mixtures.

TABLE 3. Boron Trichloride Catalyzed IMDA Cycloadditions of Trienes 13 and 14[a]

entry	Ar	EWG	products (yield, %)[b]	dr[c]
1	Ph	CO_2Me	**15a** + **17a** (90)	65:35
2	*p*-Cl-Ph	CO_2Me	**15b** + **17b** (95)	75:25
3	*p*-MeO-Ph	CO_2Me	**15c** + **17c** (98)	70:30
4	*p*-NC-Ph	CO_2Me	**15d** + **17d** (94)	70:30
5	1-naphthyl	CO_2Me	**15e** + **17e** (90)	75:25
6	Ph	CN	**16a** + **18a** (98)	90:10
7	*p*-Cl-Ph	CN	**16b** + **18b** (86)	90:10
8	*p*-MeO-Ph	CN	**16c** + **18c** (92)	90:10

[a]All reactions were conducted in 1,2-dichloroethane with 1 equiv of BCl_3; those with EWG = CO_2Me were performed at reflux and those with EWG = CN were carried out at 0 °C−rt. [b]Isolated yields are reported. [c]Determined by integration of ^{1}H NMR spectra of the crude mixtures.

observed in both the ester and nitrile series, high diastereoselectivities were confined to the latter. An exception was noted with the *p*-nitrophenyl derivative **14f** (Ar = *p*-nitrophenyl), which failed to produce the corresponding cycloadduct under these conditions.

Numerous methods have been reported for the cleavage of *N*-benzenesulfonyl groups from their parent amines.[20a] As an illustrative example, *N*-desulfonylation of tetrahydroisoindoline **16c** was carried out in 85% yield with magnesium in methanol[20b] (see Supporting Information), while several other methods (HBr/phenol, sodium amalgam-Na_2HPO_4-MeOH, sodium in isopropanol) afforded less satisfactory results.

Several examples have been reported in which allylic substitutions of activated hydroxyl groups from MBH adducts derived from aldehydes (i.e., X = O in Scheme 1) were effected by bromide,[21] azides,[22] amines, and other nitrogen nucleophiles.[22a,23] However, similar reactions in the case of

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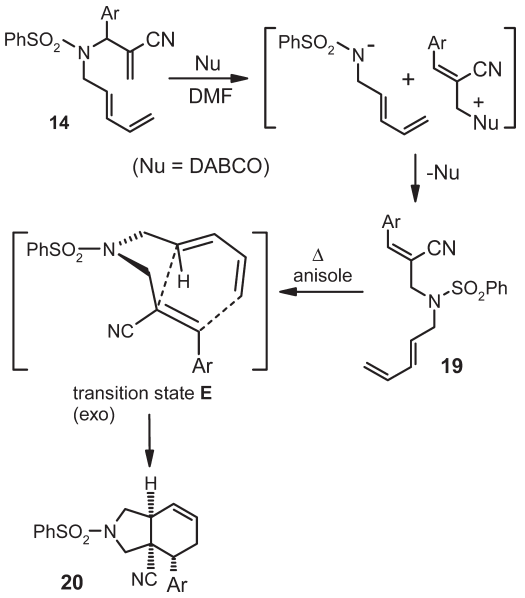
SCHEME 6



aza-MBH products (where X = NTs in Scheme 1) are confined to examples of overall allylic substitutions of *p*-toluenesulfonamide groups by the *p*-toluenesulfonamide anion, as reported by Xu and Shi[24] and by Kim et al.,[25] who employed a multistep process mediated by methoxide anion generated from DMF dimethyl acetal. We now report that the aza-MBH derivatives **14** underwent the base-catalyzed isomerizations shown in Scheme 6, in which the entire *N*-(2,4-pentadienyl)sulfonamide group was translocated to the β-position of the unsaturated nitrile moiety to afford **19**. These processes occurred smoothly at room temperature in DMF with catalytic amounts of DABCO in the nitrile series, whereas the corresponding esters **13** produced complex mixtures under similar conditions. The rearranged products **19** then underwent IMDA cycloadditions in refluxing anisole, affording tetrahydroisoindolines **20** in moderate yields as single diastereomers. The results are summarized in Table 4. Attempts to further improve the yields by means of Lewis acid catalysis were unsuccessful. The stereochemistry of **20g** was determined to be *cis*,*cis* by X-ray diffraction (see Supporting Information), which implicates the *exo* transition state **E** in this process and confirms the *cis* orientation of the nitrile and aryl groups in the dienophile component of triene **19g**. Thus, in this case, the dominant stereochemistry appears to be determined by the greater thermodynamic stability of the *cis*-fused rings, rather than by secondary orbital interactions.

We next investigated the as yet unexplored rearrangements analogous to those in Scheme 6 in the products of vinylogous aza-MBH reactions, in which an activated diene is employed instead of a monoalkene. The installation and transposition of the *N*-(propargyl)benzenesulfonamide moieties of dienynes **22** would result in the reversal of the frontier MO interactions of subsequent IMDA reactions, relative to those in Scheme 6. Thus, the propargylic *N*-substituent would now serve as an electron-rich dienophile and interact with an electron-deficient diene moiety. The resulting cycloadducts would be expected to exhibit not only different substitution patterns and levels of unsaturation, but perhaps also stereochemistries complementary to the ones in Schemes 4 and 6 and to those we had previously synthesized[8] via Scheme 3.

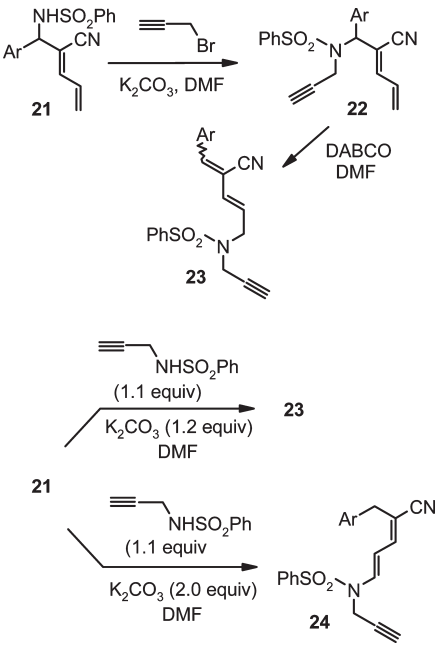
(24) Xu, Y.-M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417–425.
(25) Lee, H. J.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **1999**, *40*, 4363–4366.

TABLE 4. Rearrangements and IMDA Cycloadditions of 14

entry	Ar	rearrangement product (yield, %)[a]	IMDA product (yield, %)[a]
1	Ph	**19a** (97)	**20a** (59)
2	*p*-Cl-Ph	**19b** (95)	**20b** (73)
3	*p*-MeO-Ph	**19c** (98)	**20c** (71)
4	*p*-NO_2-Ph	**19f** (−)	**20f** (72)[b]
5	*m*-Cl-Ph	**19g** (96)	**20g** (72)
6	*p*-MeO_2C-Ph	**19h** (85)	**20h** (58)

[a]Isolated yields are reported. [b]Overall yield from **12f** via **14f** and **19f** is shown.

SCHEME 7



The *N*-propargyl derivatives **22a**, **22b**, **22e**, **22g**, and **22h** were easily obtained from the corresponding aza-MBH adducts **21**[7c] and propargyl bromide. They underwent rearrangements similar to those in Scheme 6 in the presence of catalytic amounts of DABCO to afford the corresponding transposed products **23**. Migration of the *N*-(propargyl)-benzenesulfonamide group occurred exclusively to the δ-position of the dienyl nitrile moiety, and β-substituted products were not isolated (Scheme 7). The results are summarized under method A in Table 5. Other catalysts such as aqueous sodium hydroxide or DBU produced more complex mixtures or slower reactions and DABCO was found to be the optimal catalyst of those investigated. We postulate that a vinylogous substitution of the sulfonamide group by the catalyst, followed by the further direct substitution of the latter by the sulfonamide anion occurs in a fashion similar to that shown in Scheme 6. The transposed products **23** were obtained as inseparable mixtures of geometrical isomers. Attempts at chromatographic separation failed to improve their purity and in some cases resulted in further decomposition. It was therefore more expedient to perform subsequent transformations (vide infra) directly on the crude products.

TABLE 5. Preparation of Dienynes 23 and 24

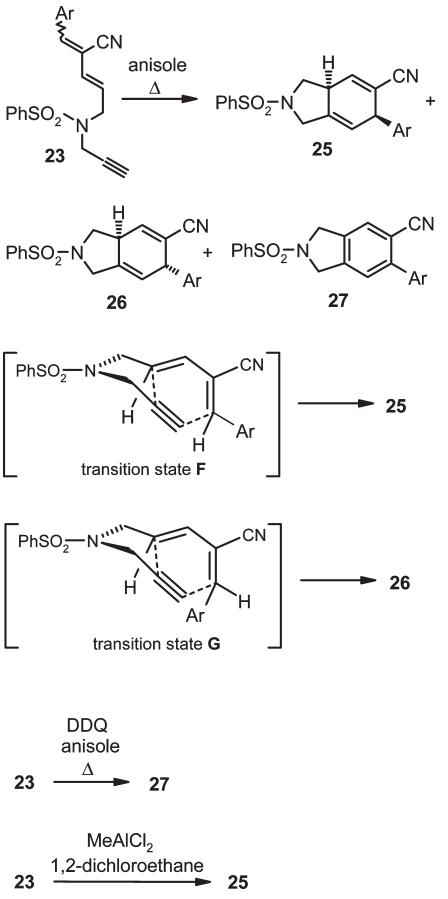
entry	starting material	method[a]	Ar	product (yield, %)[b]
1	**22a**	A	Ph	**23a** (87)
2	**21a**	B		**23a** (96)
3	**21a**	C		**24a** (68)
4	**22b**	A	*p*-Cl-Ph	**23b** (90)
5	**21b**	B		**23b** (92)
6	**21b**	C		**24b** (67)
7	**22e**	A	1-naphthyl	**23e** (92)
8	**21e**	B		**23e** (85)
9	**21e**	C		**24e** (65)
10	**22g**	A	*m*-Cl-Ph	**23g** (88)
11	**21g**	B		**23g** (81)
12	**21g**	C		**24g** (60)
13	**22h**	A	*p*-MeO_2C-Ph	**23h** (69)
14	**21h**	B		**23h** (83)
15	**21h**	C		**24h** (73)

[a]Method A: DABCO, DMF. Method B: *N*-(propargyl)benzenesulfonamide (1.1 equiv), K_2CO_3 (1.2 equiv), DMF. Method C: *N*-(propargyl)-benzenesulfonamide (1.1 equiv), K_2CO_3 (2.0 equiv), DMF. [b]Isolated yields are reported.

A NOESY experiment with **23a** revealed that the major geometrical isomer produced an interaction between the two protons located β to the nitrile group (singlet at δ 7.05 and doublet at δ 6.41 ppm, respectively), indicating the *Z* geometry for the trisubstituted double bond, while the ^{1}H NMR coupling constant $J = 15.4$ Hz confirmed the *trans* configuration of the disubstituted double bond of both geometrical isomers. Similar assignments to the major isomers of **23b**, **23e**, **23g**, and **23h** were made on the basis of their NMR spectra. We also discovered that treatment of aza-MBH adducts **21a**, **21b**, **21e**, **21g**, and **21h** with a slight excess (1.1 equiv) of *N*-(propargyl)-benzenesulfonamide and potassium carbonate (1.2 equiv) in DMF produced good yields of the same δ-substituted products as obtained from the DABCO-catalyzed reactions (Scheme 7 and method B in Table 5). Interestingly, the use of a larger excess of potassium carbonate (2.0 equiv) and longer reaction times under otherwise similar conditions resulted in the formation of the corresponding enamine derivatives **24**, which were obtained as essentially pure geometrical isomers (Scheme 7). These results are listed under method C in Table 5. A control experiment revealed that **24a** was produced from the isomerization of the initially formed **23a** under these conditions and not via an independent pathway. The assignment of *E*,*Z*-configuration to products **24** is tentative as NOESY and ROESY experiments failed to give clear results for the trisubstituted alkene moiety, while the coupling constants of ca. 14 Hz suggest the *trans* configuration for the disubstituted double bond.

The rearranged dienynes **23a**, **23b**, **23e**, **23g**, and **23h** were then subjected to IMDA cycloadditions in refluxing anisole, affording ca. 2:1 mixtures of the corresponding diastereomers **25** and **26**, as well as varying amounts of the aromatized isoindolines **27**. The major products **25** were isolated in pure form by chromatography. However, the minor diastereomers **26** could not be separated from the aromatic isoindolines **27**.[26] The stereochemistry of the major isomer **25a** was determined by X-ray crystallography (see Supporting Information), while those of the other major epimers **25b**, **25e**, **25g**, and **25h** were inferred from the similarity of their NMR spectra to those of **25a**. The minor isomers **26** are tentatively assigned the structures of the epimers of **25** where the aryl substituent is *cis* to the ring-fusion hydrogen. This is consistent with the formation of **25** from the *Z* isomer (with respect to the trisubstituted double bond) of **23** via transition state **F** and of **26** from the corresponding *E* isomer via transition state **G** (Scheme 8). Equilibration between **25** and **26** subsequent to their initial formation was ruled out by control experiments in which **25a** and **26a** were separately refluxed in anisole without any noticeable formation of the other diastereomer.

SCHEME 8



The aromatized products **27** were evidently formed by in situ air oxidation of the initial IMDA products. The mixtures of **25**−**27** obtained above could be fully converted to the corresponding isoindolines **27** by refluxing in anisole with DDQ. Alternatively, the isoindolines were also obtained in excellent yields in one step, without the accompanying formation of **25** and **26**, by simply refluxing dienynes **23** in anisole with DDQ for 24 h (Scheme 8). Thus, pure samples of **27** could be obtained for characterization. The results are summarized in Table 6.

The use of several Lewis acids ($AlCl_3$, $MeAlCl_2$, BCl_3, BBr_3, $TiCl_4$) in the IMDA step to improve the yield of the dihydroisoindoline product **25a** and the selectivity of its formation relative to its diastereomer **26a** was also investigated. The most favorable conditions were observed when the IMDA reaction of **23a** was repeated in refluxing 1,2-dichloroethane in the presence of 1 equiv of methylaluminum dichloride, providing **25a** in 93% yield with no detectable amount of **26a** (entry 1 in Table 6). Similarly, only one diastereomer could be detected in the cycloadditions of **23b**,

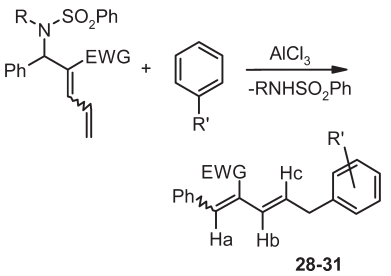
(26) A small amount of pure **26a** was obtained by conducting the reaction with exclusion of oxygen to avoid the formation of **27a**.

TABLE 6. IMDA Cycloadditions and Aromatizations of Dienynes 23

entry	Ar	uncatalyzed IMDA products (yield, %)[a]	ratio **26**:**27**[b]	uncatalyzed IMDA and DDQ oxidation products (yield, %)[c]	$MeAlCl_2$-catalyzed IMDA products (yield, %)[d]
1	Ph	**25a** (37) **26a** + **27a** (38)	1.0:0.9	**27a** (91)	**25a** (93)
2	*p*-Cl-Ph	**25b** (26) **26b** + **27b** (49)	1.0:2.3	**27b** (82)	**25b** (85)
3	1-naphthyl	**25e** (33) **26e** + **27e** (46)	1.0:1.8	**27e** (81)	**25e** + **26e** (82)[e]
4	*m*-Cl-Ph	**25g** (34) **26g** + **27g** (47)	1.0:1.7	**27g** (86)	**25g** (86)
5	*p*-MeO_2C	**25h** (42) **26h** + **27h** (25)	1.0:0.06	**27h** (88)	**25h** (91)

[a]Isolated yields of **25** and of unseparated mixtures of products **26** and **27** are reported from **23** in the absence of DDQ and Lewis acids. [b]The ratios of **26**:**27** were determined by NMR integration. [c]Isolated yields of **27** are reported from the one-pot cycloadditions and DDQ oxidations of **23** in the absence of Lewis acids. [d]Performed in the presence of 1 equiv of $MeAlCl_2$ in 1,2-dichloroethane in the absence of oxygen; isolated yields are reported. [e]Obtained as an unseparated 2:1 mixture, as determined by NMR integration.

SCHEME 9



28-31

23g, and **23h** (entries 2, 4, and 5), whereas that of the 1-naphthyl derivative **23e** (entry 3) resulted in a 2:1 mixture of **25e** and **26e**.[27] These reactions were performed under nitrogen or argon atmospheres, thereby avoiding air oxidation of the products and preventing the formation of the corresponding isoindolines **27**.

These experiments demonstrate that the IMDA dienyne precursors **23** can be obtained effectively by the DABCO-catalyzed rearrangement of *N*-propargyl derivatives **22**. Subsequent cycloadditions of **23** in the presence of DDQ afforded high yields of the aromatic products **27**. On the other hand, IMDA reactions of **23** were also carried out under anaerobic conditions in the presence of the Lewis acid methylaluminum dichloride to afford dihydroisoindolines **25** in generally high yield and as single diastereomers. Thus, with the exception of entry 3 in Table 6, the choice of appropriate conditions makes it possible to obtain either **25** or the oxidized products **27** as essentially unique cycloadducts.

While attempting to improve the conditions for some of the above IMDA cycloadditions by the addition of Lewis acids, we discovered that exposure of several vinylogous aza-MBH products to 1 equiv of aluminum trichloride in toluene or other aromatic solvents resulted in intermolecular Friedel–Crafts reactions, producing **28**–**31** (Scheme 9). As expected, the most electron-rich solvent anisole afforded the highest yield (entry 3, Table 7), while unsubstituted benzene provided the lowest yield (entry 1). No products arising from reaction at the β-position of the dienyl nitrile moiety or by the direct substitution of the sulfonamide group were observed. The

(27) The precise role of the Lewis acid in improving the stereoselectivity of formation of **25** relative to **26** is not known. However, when **26b** (mixture with **27b**) in 1,2-dichloroethane was refluxed in the presence of methylaluminum dichloride, it did not produce any detectable **25b**. It is possible that the Lewis acid promotes *E*,*Z* isomerization of dienyne **23** prior to the IMDA reaction rather than the epimerization of **26** to **25** after the cycloaddition.

TABLE 7. Friedel–Crafts Reactions of Vinylogous MBH Adducts

entry	solvent	R	R′	EWG	product (yield, %)[a]	*o*:*p* ratio[b]
1	benzene	H	H	CN	(*Z*,*E*)-**28** (56)	
2	toluene	H	Me	CN	(*Z*,*E*)-**29** (80)	1:2
3	anisole	H	OMe	CN	(*Z*,*E*)-**30** (97)	1:9
4	toluene	propargyl	Me	CN	(*Z*,*E*)-**29** (88)	1:2
5	toluene	H	Me	Ts	(*E*,*E*)-**31** (74)	1:1

[a]Isolated yields are reported. [b]Ratios determined by NMR integration.

products were obtained as mixtures of *o*- and *p*-isomers when toluene and anisole were used, favoring the *p*-isomers. The *Z*-configuration for the trisubstituted double bond of **28**, where EWG = CN, was indicated by a NOESY experiment that produced a correlation between H_A and H_B (singlet at δ 6.96 ppm and doublet at δ 6.17 ppm with J = 15.5 Hz, respectively). No such correlation was detected in **31**, where EWG = Ts, tentatively suggesting that it may have the corresponding *E*-configuration. The disubstituted double bonds of all of the products were assigned the *E*-configuration, based on coupling constants J = 15–16 Hz for H_B and H_C. Aza-MBH adducts derived from simple alkenes rather than dienes have been reported to undergo similar Friedel–Crafts reactions, forming *E* double bonds preferentially in the case where the EWG is an ester substituent, but with complete selectivity for the *Z*-configuration where the EWG is a nitrile.[28] The latter examples are therefore in accord with our observations with the vinylogous nitrile systems **28**–**30**.

In conclusion, we have demonstrated that a wide variety of isoindoline analogues, with different levels of unsaturation, as well as complementary regio- and stereochemistry, can be synthesized from aza-MBH or vinylogous aza-MBH products via IMDA cycloadditions of the corresponding *N*-pentadienyl and *N*-propargyl derivatives. The facile base-catalyzed rearrangement of the *N*-substituted benzenesulfonamide group to the terminal position of the nitrile-activated diene moiety prior to cycloaddition is noteworthy and permits further variation to the types of products that are made accessible. It is therefore possible to employ the pendant *N*-substituent as either the diene or dienophile component of the IMDA reaction and to perform the cycloaddition via either normal or inverse electron demand. While direct IMDA cycloadditions of *N*-substituted aza-MBH adducts provide only 1-aryl-substituted isoindoline

(28) Lee, H. J.; Seong, M. R.; Kim, J. N. *Tetrahedron Lett.* **1998**, *39*, 6223–6226.

derivatives (Schemes 3 and 4), the use of rearranged trienes or dienynes permits installation of the aryl substituent at either the proximal or distal position (4-aryl in Scheme 6 or 6-aryl in Scheme 8, respectively) of the six-membered ring. Similarly, the nitrile group, which is a potentially useful functionality for further transformations, can be incorporated at either the ring-fusion position or adjacent to the aryl substituent on the six-membered ring. This methodology therefore provides a concise route to diverse aryl-substituted isoindolines and their dihydro and tetrahydro analogues.

Experimental Section

NMR spectra were recorded in deuteriochloroform and mass spectra were obtained by electron impact, unless otherwise indicated. Chromatography refers to flash chromatography on silica gel (230−400 mesh). Compounds **3**[7,8] were prepared as described previously, while **11** and **12** were prepared by the same general procedure[18] as reported for the corresponding *N*-*p*-toluenesulfonyl derivatives. Compounds **13**, **14** and **23** could not be completely purified by rapid flash chromatography, while further attempts at chromatographic separation, particularly with **23**, resulted in gradual decomposition. Products **23** were therefore typically used in subsequent steps in crude form.

Typical Procedure for the Alkylation and Uncatalyzed IMDA Cycloaddition of 11 and 12 (see Table 1). Preparation of 13a, 15a, and 17a. The aza-MBH adduct **11a**[18a](Ar = phenyl; EWG = CO_2Me) (132 mg, 0.398 mmol), 1-bromo-2,4-pentadiene[19] (63.9 mg, 0.438 mmol), and potassium carbonate (82.4 mg, 0.597 mmol) were stirred in DMF (3 mL) at room temperature for 3 h. The reaction was poured into water and extracted with ethyl acetate. The combined organic fractions were washed with brine, dried, and concentrated under reduced pressure. The product was chromatographed over silica gel (toluene/ethyl acetate, 16:1) to afford 154 mg (98%) of methyl 3-[(*N*-benzenesulfonyl-*N*-penta-2,4-dienyl)amino]-2-methylene-3phenylpropanoate (**13a**) as a colorless oil: IR (film) 1725, 1340, 1161 cm^{-1}; ^1H NMR (400 MHz) δ 7.83−7.81 (m, 2 H), 7.60−7.55 (m, 1 H), 7.50−7.46 (m, 2 H), 7.25−7.23 (m, 2 H), 7.05−7.01 (m, 2 H), 6.46 (d, J = 0.9 Hz, 1 H), 6.16 (s, 1 H), 6.04 (dt, J = 16.9, 10.3 Hz, 1 H), 5.81−5.74 (m, 2 H), 5.11−5.00 (m, 3 H), 3.89 (t, J = 6.7 Hz, 2 H), 3.63 (s, 3 H); ^{13}C NMR (101 MHz) δ 166.2, 140.9, 139.4, 136.9, 135.9, 133.9, 132.5, 129.1, 128.8, 128.6, 128.5, 128.2, 128.0, 127.5, 61.9, 52.0, 47.8; mass spectrum (CI, m/z, %) 398 (100, $M^+ + 1$), 256 (100), 91 (53), 77 (64); HRMS calcd for $C_{16}H_{18}NO_2$ ($M^+ - SO_2Ph$): 256.1338, found 256.1337.

The above triene **13a** was refluxed in anisole (8 mL) for 24 h. The reaction mixture was concentrated in vacuo and chromatographed over silica gel (toluene/ethyl acetate, 16:1) to afford the product (138 mg, 89%) as a 65:35 mixture of diastereomers **15a** and **17a**. Recrystallization from ethyl acetate provided the pure major diastereomer of *N*-benzenesulfonyl-3-phenyl-1,2,3,4,5,7a-hexahydroisoindole-3a-carboxylic acid methyl ester (**15a**) as colorless crystals: mp 176−178 °C; IR (film) 1733, 1357, 1162, 1090 cm^{-1}; ^1H NMR (300 MHz) δ 7.78 (d, J = 8.4 Hz, 2 H), 7.56−7.43 (m, 3 H), 7.33−7.24 (m, 5 H), 5.74 (dd, J = 10.0, 1.6 Hz, 1 H), 5.42−5.37 (m, 1 H), 4.95 (s, 1 H), 3.91 (t, J = 7.8 Hz, 1 H), 3.63 (dd, J = 12.2, 7.6 Hz, 1 H), 3.19 (s, 3 H), 2.89−2.88 (m, 1 H) 1.98−1.86 (m, 3 H), 0.74−0.69 (m, 1 H); ^{13}C NMR (100 MHz) δ 173.1, 138.4, 138.1, 132.4, 128.9, 128.2, 127.8, 127.5, 126.8, 126.5, 123.8, 68.8, 56.9, 51.7, 50.3, 40.1, 29.1, 23.8; mass spectrum (m/z, %) 397 (< 1, M^+), 256 (100), 118 (42), 91 (33); HRMS calcd for $C_{22}H_{23}NO_4S$: 397.1348, found 397.1340. Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52; found C, 66.32; H, 5.75; N, 3.47.

The minor diastereomer **17a** could not be obtained completely free of **15a**; the following signals were assigned to **17a**: ^1H NMR (300 MHz) δ 5.69−5.58 (m, 1 H), 5.44−5.42 (m, 1 H), 5.05 (s, 1 H), 4.04 (dd, J = 11.6, 7.9 Hz, 1 H), 3.61 (s, 3 H), 3.26 (t, J = 11.5 Hz, 1 H), 2.76−2.70 (m, 1 H), 1.35−1.24 (m, 1 H), 0.86−0.79 (m, 1 H) ; ^{13}C NMR (75 MHz) δ 173.8, 137.6, 137.5, 133.0, 129.2, 129.1, 127.9, 127.6, 127.4, 127.3, 122.9, 71.1, 54.6, 54.3, 52.3, 41.6, 22.9, 22.8.

Typical Procedure for the BCl_3-Catalyzed IMDA Cycloaddition of 13 and 14 (see Table 3). Preparation of 16a and 18a. The aza-MBH adduct **12a** (Ar = phenyl; EWG = CN) was converted into the triene **14a** in 98% yield by the same procedure used for the preparation of **13a** from **11a**. *N*-(2-Cyano-1-phenylallyl)-*N*-(penta-2,4-dienyl)benzenesulfonamide (**14a**) was obtained as a colorless oil: IR (film) 2223, 1346, 1161, 1091 cm^{-1}; ^1H NMR (400 MHz) δ 7.86−7.82 (m, 2 H), 7.63−7.59 (m, 1 H), 7.54−7.50 (m, 2 H), 7.36−7.28 (m, 3 H), 7.14−7.11 (m, 2 H), 6.23 (d, J = 1.6 Hz, 1 H), 6.10−6.00 (m, 2 H), 5.86 (s, 1 H), 5.82 (dd, J = 15.2, 10.4 Hz, 1 H), 5.16−5.03 (m, 3 H), 3.87 (d, J = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz) δ 140.3, 135.7, 134.4, 134.1, 133.9, 133.0, 129.2, 129.1, 129.0, 128.9, 128.4, 127.5, 122.1, 118.2, 117.4, 63.4, 47.5; mass spectrum (m/z, %) 364 (17, M^+), 118 (100), 91(44); HRMS calcd for $C_{21}H_{20}N_2O_2S$: 364.1245; found: 364.1233.

Boron trichloride (0.064 mL of a 1.0 M solution in dichloromethane, 0.064 mmol) was added dropwise to a stirred solution of **14a** (23.2 mg, 0.0636 mmol) in 1,2-dichloroethane (1 mL) under nitrogen at 0 °C. This was slowly warmed to room temperature and stirred for 14 h. The reaction was poured into water and extracted with dichloromethane. The combined organic fractions were dried and concentrated in vacuo. The crude product was chromatographed over silica gel (toluene/ethyl acetate, 16:1) to afford 22.7 mg (98%) of a 90:10 mixture of diastereomers of *N*-benzenesulfonyl-3-phenyl-3a-cyano-1,2,3,4,5,7a-hexahydroisoindole (**16a** and **18a**). Further chromatography produced **16a** as a colorless oil: IR (film) 2243, 1348, 1167 cm^{-1}; ^1H NMR (300 MHz) major isomer **16a**: δ 7.89 (d, J = 7.2 Hz, 2 H), 7.68−7.49 (m, 3 H), 7.37−7.22 (m, 5 H), 5.64 (s, 2 H), 5.10 (s, 1 H), 4.04 (dd, J = 8.2, 7.5 Hz, 1 H), 3.19 (dd, J = 12.3, 8.5 Hz, 1 H), 2.88−2.78 (m, 1 H), 2.37−2.24 (m, 1 H), 2.15−2.02 (m, 1 H), 1.85 (dd, J = 13.2, 6.9 Hz, 1 H), 0.83 (ddd, J = 13.1, 11.1, 7.1 Hz, 1 H); ^{13}C NMR (75 MHz) δ 136.6, 136.6, 133.3, 129.3, 129.2, 128.6, 128.5, 127.6, 127.0, 121.5, 120.1, 68.9, 50.0, 48.6, 40.3, 27.4, 23.6; mass spectrum (m/z, %) 364 (1, M^+), 118 (100), 91 (32); HRMS: calcd for $C_{21}H_{20}N_2O_2S$, calcd 364.1245, found 364.1228.

The minor product **18a** could not be obtained completely free of **16a**; the following signals were assigned to **18a**: ^1H NMR (300 MHz) δ 5.82−5.78 (m, 1 H), 5.51−5.47 (m, 1 H), 4.68 (s, 1 H), 4.16 (dd, J = 10.8, 7.1, 1 H), 3.55 (t, J = 15.2 Hz, 1 H), 2.56−2.46 (m, 1 H), 1.78−1.67 (m, 1 H), 1.06−1.00 (m, 1 H).

Typical Procedure for the Rearrangement and IMDA Cycloaddition of 14 (see Table 4). Preparation of 20a. Triene **14a** (138 mg, 0.378 mmol) was stirred in DMF (4 mL) with two crystals (ca. 2−3 mg) of DABCO for 3 h. The mixture was then poured into water and extracted with ethyl acetate. The combined organic fractions were washed with brine, dried and concentrated to afford 133 mg (96%) of the rearranged product *N*-[(*Z*)-2-cyano-3-phenyl-allyl]-*N*-[(*E*)-penta-2,4-dienyl)]benzenesulfonamide (**19a**) as a colorless oil; IR (film) 2214, 1348, 1167 cm^{-1}; ^1H NMR (400 MHz) δ 7.91−7.87 (m, 2 H), 7.72 (d, J = 2.2 Hz, 1 H), 7.70 (d, J = 3.4 Hz, 1 H), 7.63−7.59 (m, 1 H), 7.55−7.51 (m, 2 H), 7.46−7.42 (m, 3 H), 7.13 (s, 1 H), 6.33−6.14 (m, 2 H), 5.54 (dt, J = 15.1, 6.9 Hz, 1 H), 5.23 (d, J = 16.1 Hz, 1 H), 5.15 (d, J = 9.3 Hz, 1 H), 4.16 (s, 2 H), 4.02 (d, J = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz) δ 146.4, 139.9, 136.1, 135.5, 133.0, 132.7, 130.9, 129.2, 129.0, 128.9, 127.4, 126.7, 126.1, 118.9, 106.2, 50.2, 49.9; mass spectrum (m/z, %) 364 (4, M^+), 142 (65), 118 (100), 91 (57), 77 (78); HRMS calcd for $C_{21}H_{20}N_2O_2S$: 364.1245; found 364.1228.

The above rearranged product **19a** was refluxed in anisole (6 mL) for 2 d, the reaction mixture was concentrated in vacuo and chromatographed on silica gel (toluene/ethyl acetate, 16:1) to afford 81.2 mg (59% overall yield from **14a**) of *N*-benzenesulfonyl-4-phenyl-1,2,3,4,5,7a-hexahydro-isoindole-3a-carbonitrile (**20a**) as colorless needles: mp 192−195 °C (from ethyl acetate); IR (film) 2238, 1352, 1176 cm^{-1}; ^1H NMR (400 MHz) δ 7.83−7.81 (m, 2 H), 7.69 (ddd, J = 8.8, 2.6, 1.3 Hz, 1 H), 7.63−7.57 (m, 2 H), 7.37−7.32 (m, 3 H), 7.24−7.19 (m, 2 H), 6.03 (ddt, J = 10.1, 5.6, 1.7 Hz, 1 H), 5.73−5.66 (m, 1 H), 3.73 (t, J = 9.3 Hz, 1 H), 3.52 (d, J = 10.4, 1 H), 3.32−3.20 (m, 2 H), 3.11−3.05 (m, 1 H), 2.83−2.65 (m, 2 H), 2.36 (dt, J = 17.8, 4.3 Hz, 1 H); ^{13}C NMR (100 MHz) δ 138.3, 136.4, 133.3, 129.6, 129.4, 128.9, 128.7, 128.2, 127.5, 122.2, 119.8, 53.5, 51.8, 45.0, 44.4, 40.9, 29.5; mass spectrum (m/z, %) 364 (22, M^+), 223 (100); HRMS calcd for $C_{21}H_{20}N_2O_2S$: 364.1245; found 364.1234. Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.20; H, 5.53; N, 7.69. Found: C, 68.80; H, 5.55; N, 7.47.

Typical Procedure for the DABCO-Catalyzed Rearrangement of 22 (Method A in Table 5). Preparation of *N*-[(*2E,4Z*)-4-cyano-5-phenyl-penta-2,4-dienyl]-*N*-(2-propynyl)benzenesulfonamide (23a). Dienyne **22a** was prepared from **21a** and propargyl bromide as described previously.[8]

Dienyne **22a** (121 mg, 0.335 mmol) was stirred in DMF (3 mL) at room temperature with 2−3 mg of DABCO for 6 h. The product was poured into water and extracted with ethyl acetate. The combined organic fractions were washed with brine, dried, and concentrated under reduced pressure to afford 105 mg (87%) of the rearranged product **23a** as a colorless oil: IR (film) 3294, 2217, 2121, 1349, 1168, 1096 cm^{-1}; ^1H NMR (400 MHz) (major 2*E*,4*Z* isomer) δ 7.89−7.85 (m, 4 H), 7.79−7.78 (m, 1 H), 7.62−7.49 (m, 3 H), 7.44−7.41 (m, 2 H), 7.05 (s, 1 H), 6.41 (d, J = 15.4 Hz, 1 H), 6.12 (dt, J = 15.4, 6.2, Hz, 1 H), 4.19 (d, J = 2.4 Hz, 2 H), 4.04 (d, J = 6.1 Hz, 2 H), 2.15 (t, J = 2.3 Hz, 1 H); ^{13}C NMR (100 MHz) (major *2E,4Z* isomer) δ 144.5, 138.8, 133.3, 133.0, 131.3, 130.8, 129.2, 129.1, 129.0, 128.1, 127.7, 116.1, 109.7, 76.2, 74.3, 47.7, 36.5; mass spectrum (m/z, %) 362 (8, M^+), 141 (39), 125 (63), 77 (100); HRMS calcd for $C_{21}H_{18}N_2O_2S$: 362.1089, found 362.1073.

Typical Procedure for the Reaction of 21 with *N*-(Propargyl)-benzenesulfonamide (Method B in Table 5). Preparation of 23a. A solution of **21a** (55.6 mg, 0.172 mmol), *N*-(propargyl)benzenesulfonamide (36.9 mg, 0.189 mmol), and potassium carbonate (28.2 mg, 0.204 mmol) in DMF (1.5 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into water, extracted with ethyl acetate, dried, and concentrated under reduced pressure. The product was chromatographed on silica gel (toluene/ethyl acetate, 16:1) to afford 60.0 mg (96%) of **23a** with the same properties as the product obtained via method A.

Typical Procedure for the Further Reaction of 21 to 24 (Method C in Table 5). Preparation of *N*-[(1*E*)-4-Cyano-5-phenyl-penta-1,3-dienyl]-*N*-(2-propynyl)benzenesulfonamide (24a). The above experiment was repeated with compound **21a** (168 mg, 0.519 mmol), *N*-(propargyl)benzenesulfonamide (111 mg, 0.569 mmol), and potassium carbonate (143 mg, 1.04 mmol) in DMF (3 mL) at room temperature for 4 d. The product was isolated as in the preceding procedure to afford 127 mg (68%) of **24a** as a colorless oil: IR (film) 3289, 2203, 2127, 1366, 1280, 1164, 1087 cm^{-1}; ^1H NMR (400 MHz) δ 7.86−7.82 (m, 2 H), 7.67−7.61 (m, 1 H), 7.57−7.51 (m, 2 H), 7.38−7.32 (m, 2 H), 7.31−7.21 (m, 4 H), 6.59 (d, J = 11.1 Hz, 1 H), 6.06 (dd, J = 13.8, 11.1 Hz, 1 H), 4.37 (d, J = 2.5 Hz, 2 H), 3.58 (s, 2 H), 2.06 (t, J = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz) δ 142.9, 138.1, 136.8, 134.4, 133.8, 129.4, 128.9, 127.4, 127.2, 118.1, 109.3, 107.9, 74.8, 74.6, 40.1, 35.4; mass spectrum (m/z, %) 362 (< 1, M^+), 77 (100); HRMS calcd for $C_{21}H_{18}N_2O_2S$: 362.1089, found 362.1106.

Typical Procedure for the IMDA Cycloaddition of Dienynes 23 in the Presence of Air (Table 6). Preparation of 25a, 26a, and 27a. Dienyne **23a** (338 mg, 0.931 mmol) was refluxed in anisole for 17 h. The reaction mixture was then concentrated to afford a crude mixture of **25a**, **26a**, and **27a** in the ratio of 2:1:0.9 (NMR integration). This was chromatographed over silica gel (toluene/ethyl acetate, 16:1) to afford 125 mg (37%) of **25a** and 128 mg of a mixture of **26a** and **27a**. Products **25a** and **27a** were identical to pure samples prepared by the procedures described below. The minor isomer **26a** could not be isolated free from **27a**, but the following signals from the mixture were assigned to **26a**: ^1H NMR (300 MHz) δ 6.63 (d, J = 1.8 Hz, 1 H), 5.77 (d, J = 2.0 Hz, 1 H), 4.17 (d, J = 13.8 Hz, 1 H), 4.00 (t, J = 8.5 Hz, 1 H), 4.08 (t, J = 5.7 Hz, 1 H), 3.41−3.33 (m, 1 H), 2.81 (dd, J = 11.1, 9.0 Hz, 1 H).

Typical Procedure for the Lewis Acid Catalyzed IMDA Cycloaddition of Dienynes 23 (Table 6). Preparation of *N*-Benzenesulfonyl-5-cyano-6-phenyl-2,3,3a,6-tetrahydro-1*H*-isoindole-5-carbonitrile (25a). Methylaluminum dichloride (0.059 mL, 0.059 mmol, 1 M solution in hexanes) was added to a stirred solution of **23a** (21.3 mg, 0.059 mmol) in 1,2-dichloroethane (1.5 mL) under nitrogen, and the solution was refluxed for 14 h. The reaction was then poured into water and extracted with dichloromethane. The combined organic layers were washed with brine, dried, and concentrated in vacuo. The crude product was chromatographed over silica gel (toluene/ethyl acetate, 16:1) to afford 19.8 mg (93%) of **25a** as colorless crystals: mp 166−168 °C (from ethyl acetate); IR (film) 2224, 1352, 1167, 1090 cm^{-1}; ^1H NMR (400 MHz) δ 7.88−7.87 (m, 1 H), 7.87−7.86 (m, 1 H), 7.69−7.65 (m, 1 H), 7.61−7.57 (m, 2 H), 7.36−7.30 (m, 3 H), 7.02 (dd, J = 7.7, 1.7 Hz, 2 H), 6.63 (t, J = 2.6 Hz, 1 H), 5.54 (s, 1 H), 4.13−4.08 (m, 1 H), 4.06−3.99 (m, 2 H), 3.87 (dd, J = 13.5, 1.3 Hz, 1 H), 3.29−3.19 (m, 1 H), 2.88 (dd, J = 11.2, 9.2 Hz, 1 H); ^{13}C NMR (100 MHz) δ 140.0, 138.2, 136.7, 133.1, 132.6, 129.3, 129.1, 128.3, 128.0, 127.5, 120.6, 117.8, 117.4, 51.6, 50.4, 43.9, 38.6; mass spectrum (m/z, %) 362 (< 1, M^+), 77 (100); HRMS calcd for $C_{21}H_{18}N_2O_2S$: 362.1089, found 362.1089. Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.36; H, 4.78; N, 7.64. See Supporting Information for the X-ray structure of **25a**.

Typical One-Pot Procedure for the IMDA Cycloaddition and Aromatization of Dienynes 23 in the Presence of DDQ (Table 6). Preparation of *N*-Benzenesulfonyl-5-cyano-6-phenyl-2,3-dihydro-1*H*-isoindole (27a). Dienyne **23a** (48.7 mg, 0.133 mmol) and DDQ (30.1 mg, 0.133 mmol) were refluxed in anisole for 20 h. The reaction was concentrated in vacuo and chromatographed over silica gel (toluene/ethyl acetate, 16:1), affording 43.9 mg (91%) of **27a**: white solid; mp 164−166 °C (from ethyl acetate); IR (film) 2219, 1348, 1167, 1095 cm^{-1}; ^1H NMR (400 MHz) δ 7.93−7.91 (m, 2 H), 7.64−7.56 (m, 4 H), 7.49−7.46 (m, 5 H), 7.32 (s, 1 H), 4.73 (broad s, 2 H), 4,71 (broad s, 2 H); ^{13}C NMR (100 MHz) δ 145.7, 141.7, 137.5, 136.5, 135.8, 133.2, 129.4, 129.0, 128.8, 128.7, 127.8, 127.5, 124.5, 118.2, 111.1, 53.6, 53.0; mass spectrum (CI, m/z, %) 378 (100, $M^+ + NH_4$); HRMS calcd for $C_{21}H_{16}N_2O_2S$: 360.0932, found 360.0916.

Typical Procedure for the Friedel−Crafts Reactions of aza-MBH Adducts (Table 7). Preparation of 1,5-Diphenylpenta-1,3-diene-2-nitrile (28). A solution of **21a** (79.4 mg, 0.245 mmol) and aluminum trichloride (36.0 mg, 0.271 mmol) in benzene (2 mL) was refluxed for 1 h. The reaction was cooled to room temperature, poured into water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated in vacuo. The crude product was chromatographed over silica gel (hexanes/ethyl acetate, 8:1) to afford 33.9 mg (56%) of the product **28** as a colorless oil: IR (film) 2214, 1500, 1448 cm^{-1}; ^1H NMR (400 MHz) δ 7.78 (d, J = 6.6 Hz, 2 H), 7.49−7.32 (m, 5 H), 7.31−7.16 (m, 3 H), 6.96 (s, 1 H), 6.48

(dt, J = 15.4, 6.7 Hz, 1 H), 6.17 (d, J = 15.5 Hz, 1 H), 3.57 (d, J = 6.6 Hz, 2 H); ^{13}C NMR (75 MHz) δ 142.4, 138.9, 135.0, 133.7, 130.2, 129.0, 128.9, 128.8, 128.7, 128.4, 126.6, 116.6, 110.9, 38.8; mass spectrum (m/z, %) 245 (85, M^+), 244 (100), 154 (70); HRMS calcd for $C_{18}H_{15}N$: 245.1204, found 245.1202.

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Supporting Information Available: Characterization data and ^{1}H and ^{13}C NMR spectra of new compounds; X-ray crystallographic data for compounds **15b**, **16c**, **17c**, **20g**, and **25a** including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.