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Lewis Acid Activated Aza-Diels–Alder Reaction of *N*-(3-Pyridyl)aldimines: An Experimental and Computational Study

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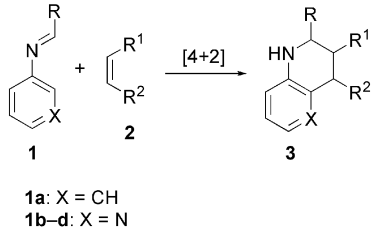
A combined theoretical and experimental study of a Povarov-type cycloaddition reaction suggests an asynchronous concerted process that is favored by double Lewis acid activation with $BF_3{\cdot}Et_2O$; *endo* selectivity was observed in the reactions between *N*-(3-pyridyl)aldimines and styrene, cyclopentadiene, or indene, and substituted tetrahydro-1,5-naphthyridine derivatives were obtained in a regio- and stereoselective fashion.

Introduction

Nitrogen-containing heterocycles are important compounds widely employed in the fields of biochemistry, pharmaceutics, and materials science.[1] Consequently, reactions, including those of carbonyl compounds with amines, in which nitrogen-containing heterocycles can be prepared both chemo- and stereoselectively, have often attracted the attention of organic chemists. The Povarov reaction is such an example. Povarov initially described the participation of aldimines **1a** (X = CH; Scheme 1), derived from aniline and aromatic aldehydes, in a formal [4+2] cycloaddition reaction with electron-rich alkenes in the presence of a Lewis acid catalyst and the subsequent tautomerization of the initial adduct to give 1,2,3,4-tetrahydroquinoline derivatives.[2] Since Povarov's original report and for nearly three decades, this reaction did not attract very much attention until it was developed into a multicomponent reaction (MCR).[3] In fact, this development triggered an ongoing period of considerable interest in the Povarov reaction.[4] Moreover, the Povarov reaction has also found applications in total synthesis, for example, in the synthesis of (±)-martinelline, (±)-martinellic acid, luotonin A, and camptothecin.[5]



Scheme 1. Povarov reaction of imines and alkenes.

However, no attention has been paid to theoretical studies nor to the elucidation of the Povarov reaction mechanism. In previous studies[3e] a stepwise reaction mechanism was suggested for the lanthanide triflate catalyzed imino-Diels–Alder reaction of imines derived from anilines with alkenes. In addition, experimental evidence[4a] points towards a concerted asynchronous cycloaddition.

Taking into account the fact that we have been involved in the chemistry of 1-[6] and 2-azadienes[7] as well as in the development of new methods for the preparation of three-,[8] five-,[9] and six-membered[10] nitrogen-containing heterocycles, we envisaged that the application of the Povarov-type reaction to amines other than anilines would provide not only a new family of polycyclic azaheterocycles but also a substantial increase in molecular diversity. Thus, we report herein the first stereoselective preparation of tetrahydro-1,5-naphthyridine derivatives **3** (X = N; Scheme 1) with control of the relative configuration of the three stereocenters, and a combined theoretical and experimental study of the Povarov-type reaction between imines and alkenes as well as the effects of the use of a Lewis acid ($BF_3{\cdot}Et_2O$) in a modified Povarov reaction involving *N*-(3-pyridyl)aldimines **1b–d** (X = N; Scheme 1) and alkenes such as ethylene (**2a**), styrene (**2b**), cyclopentadiene (**2c**), and indene (**2d**).

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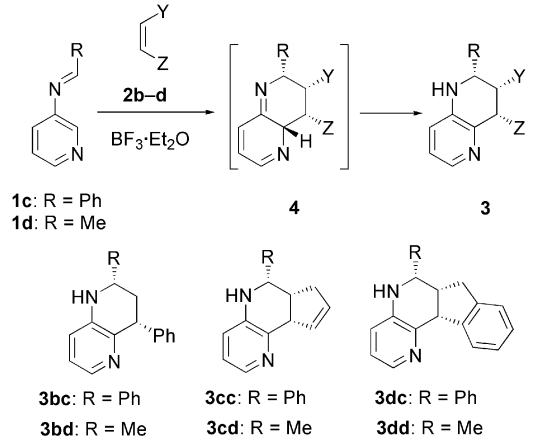
Results and Discussion

Experimental Study

First, the hetero-Diels–Alder reaction between *N*-(3-pyridyl)aldimine **1c** (R = Ph) and styrene (**2b**) was performed. No reaction was observed in the absence of a Lewis acid at room temperature or in chloroform at reflux. In contrast, when the reaction was performed at room temperature in the presence of 1 equiv. of $BF_3{\cdot}Et_2O$, bicyclic *endo* compound **3bc** was regioselectively obtained after 216 h (Scheme 2, Table 1, Entry 1), and when the same reaction was carried out in chloroform at reflux at 60 °C, the same compound **3bc** was obtained but in a shorter reaction time of 24 h (Table 1, Entry 2). In this context, it has been previously reported[11] that the pyridine nitrogen atom of azinylformamidines is the preferred site of protonation and for this reason we believed that the use of 2 equiv. of Lewis acid could accelerate the reaction rate. Thus, with 2 equiv. of $BF_3{\cdot}Et_2O$ at room temperature or in chloroform at reflux at 60 °C (Scheme 2, Table 1, Entries 3 and 4) the expected compound **3bc** was obtained in considerably shorter reaction times compared with the reactions in which 1 equiv. of $BF_3{\cdot}Et_2O$ was used (Scheme 2, Table 1, Entries 1 and 2). Note that almost quantitative conversion of the starting materials was observed when 2 equiv. of $BF_3{\cdot}Et_2O$ were used (Table 1, Entries 3 and 4) to give 1,2,3,4-tetrahydro-1,5-naphthyridine **3bc** with regio- and stereoselective control of the two stereocenters (Scheme 2). The use of 1.2 equiv. of $BF_3{\cdot}Et_2O$ was not sufficient to give optimal conditions; the required reaction time decreases, but not as much as with the use of 2 equiv. of $BF_3{\cdot}Et_2O$.



Scheme 2. Cycloaddition reactions of **1c**,**d** with **2b**–**d** in the presence of $BF_3{\cdot}Et_2O$.

The structure of compound **3bc** was assigned on the basis of 1D and 2D NMR spectroscopy, including 1D-NOESY, HMQC, and HMBC experiments, and mass spectrometric data. The ^1H NMR spectrum of compound **3bc** showed one double doublet at δ = 4.59 ppm with coupling constants of $^3J_{HH}$ = 11.3 and 2.3 Hz corresponding to the proton 2-H, one double doublet at δ = 4.45 ppm with coupling constants of $^3J_{HH}$ = 12.2 and 6.1 Hz corresponding to the proton 4-H, one decoupled double doublet at δ = 2.41 ppm with coupling constants of $^2J_{HH}$ = 12.6 Hz and $^3J_{HH}$ = 6.1 and 2.3 Hz corresponding to one of the methylene protons 3-H, and a decoupled double doublet at δ = 2.26 ppm with coupling constants of $^2J_{HH}$ = 12.6 Hz and $^3J_{HH}$ = 12.2 and 11.3 Hz corresponding to the other methylene proton 3-H. An HMBC study of compound **3bc** showed, among others, cross-signals between NH and the methylene carbon atom C-3, which confirms the regiochemistry of the process. In the 1D-NOESY spectrum of compound **3bc**, the selective saturation of the multiplet at δ = 2.41 ppm (see Figure 1 and the Supporting Information) corresponding to one of the methylene protons 3-H afforded a positive NOESY with protons 2-H (2.54%) and 4-H at δ = 4.45 ppm (3.52%). This observation together with the coupling constants observed in the ^1H NMR spectrum of compound **3bc** is consistent with the relative *cis* configuration of all these protons.

Table 1. Experimental reaction conditions and compounds **3** obtained from the reactions of aldimines **1** with alkenes **2**.

Entry	Dienophile	R	Reaction conditions	Product obtained	Yield[a] (%)
1	 **2b**	Ph	216 h, 20 °C, 1 equiv. $BF_3{\cdot}Et_2O$	**3bc**	74
2			24 h, 60 °C, 1 equiv. $BF_3{\cdot}Et_2O$		76
3			41 h, 20 °C, 2 equiv. $BF_3{\cdot}Et_2O$[b]		98
4			4 h, 60 °C, 2 equiv. $BF_3{\cdot}Et_2O$		99
5		Me	2 h, 20 °C, 1 equiv. $BF_3{\cdot}Et_2O$	**3bd**	99
6			2 h, 20 °C, 2 equiv. $BF_3{\cdot}Et_2O$		99
7	 **2c**	Ph	96 h, 60 °C, 1 equiv. $BF_3{\cdot}Et_2O$[c]	**3cc**	70
8			30 h, 60 °C, 2 equiv. $BF_3{\cdot}Et_2O$[d]		90
9		Me	45 h, 20 °C, 1 equiv. $BF_3{\cdot}Et_2O$	**3cd**	55
10			23 h, 20 °C, 2 equiv. $BF_3{\cdot}Et_2O$		65
11	 **2d**	Ph	48 h, 60 °C, 2 equiv. $BF_3{\cdot}Et_2O$	**3dc**	99
12		Me	24 h, 20 °C, 1 equiv. $BF_3{\cdot}Et_2O$	**3dd**	99
13			12 h, 20 °C, 2 equiv. $BF_3{\cdot}Et_2O$		99

[a] Percentage of consumption of the starting material by NMR analysis of the crude reaction mixture. [b] By using 1.2 equiv. of $BF_3{\cdot}Et_2O$, a time of 53 h was required for complete reaction. [c] No reaction was observed at room temperature. [d] By using 1.2 equiv. of $BF_3{\cdot}Et_2O$, a time of 50 h was required for complete reaction.

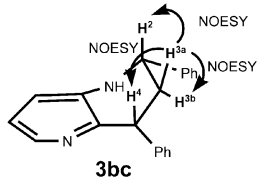


Figure 1. Relative configuration assigned by 1D-NOESY analysis of compound **3bc**.

The reaction was then performed with styrene (**2b**) and *N*-(3-pyridyl)aldimine **1d** derived from acetaldehyde (R = Me) in the presence of 1 or 2 equiv. of $BF_3{\cdot}Et_2O$ at room temperature (Scheme 2, Table 1, Entries 5 and 6) and compound **3bd** was obtained in a very high yield in a regio- and stereoselective manner. The reaction times were considerably shorter than the reactions of imine **1c** derived from benzaldehyde (R = Ph).

Next, the hetero-Diels–Alder reactions of *N*-(3-pyridyl)-aldimines **1c** (R = Ph) and **1d** (R = Me) with cyclic olefins cyclopentadiene (**2c**) and indene (**2d**) were studied. No reaction was observed between **2c**,**d** and *N*-(3-pyridyl)aldimines

1c,**d** in the absence of a Lewis acid. However, almost quantitative conversion of the starting materials was observed (with exception of compound **3cd**; Table 1, Entry 10) when 2 equiv. of $BF_3{\cdot}Et_2O$ were used (Table 1, Entries 7–9 and 11–13) with only one isomer obtained, the tricyclic *endo*-tetrahydro-1,5-naphthyridine derivatives **3cc**,**cd** or the tetracyclic *endo*-tetrahydro-1,5-naphthyridine derivatives **3dc**,**dd**, with regio- and stereoselective control of the three stereocenters (Scheme 2). As before, when using 2 equiv. of $BF_3{\cdot}Et_2O$ at room temperature or in chloroform at reflux at 60 °C (Scheme 2, Table 1, Entries 8, 10, 11, and 13), the reaction time was reduced considerably compared with the reactions in which 1 equiv. of $BF_3{\cdot}Et_2O$ was used (Scheme 2, Table 1, Entries 7, 9, and 12).

The structures of compounds **3cd**,**cc**,**dc**,**dd** were assigned on the basis of 1D and 2D NMR spectroscopy and mass spectrometric data. The structure of compound **3dc** was also confirmed unambiguously by X-ray analysis (Figure 2).

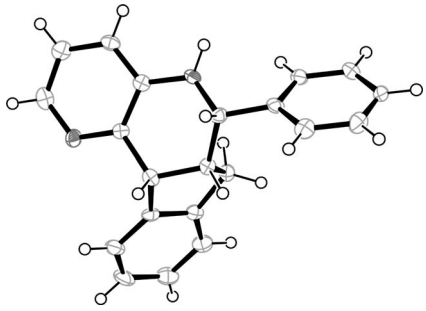
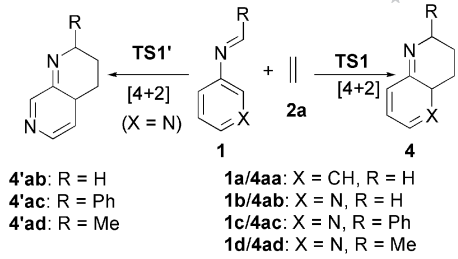


Figure 2. ORTEP view of molecular structure of the 1,2,3,4-tetrahydro-1,5-naphthyridine derivative **3dc**.

As far as we know, this strategy represents the first synthesis of bicyclic *cis*-2,4- (**3bc**,**bd**) as well as tricyclic (**3cc**,**cd**) and tetracyclic (**3dc**,**dd**) *cis*-2,3,4-substituted tetrahydro-1,5-naphthyridine derivatives. All these results suggest that the formation of compounds **3** can be explained by a [4+2] cycloaddition reaction of imines **1** with dienophiles **2** (Scheme 2) via *endo*-A cycloadducts **4** followed by prototropic tautomerization under the reaction conditions. However, a nonconcerted stepwise reaction mechanism cannot be discarded. For this reason we performed a computational study of this process to confirm our experimental results and to try to predict a computational model consistent with the reaction.

Computational Studies

First, the simple parent reaction between imine **1a** (Scheme 3, R = H, X = CH) and ethene (**2a**) to give **4aa** (Scheme 3) was examined. All structures were optimized by density functional theory (DFT) using the B3LYP[12] and M06-2X[13] hybrid functionals as implemented in the Gaussian 03[14] and Jaguar[15] software packages. The standard split-valence 6-31G* basis set[16] was used in all cases.



Scheme 3. Cycloaddition reactions of imines **1a**–**d** and ethene (**2a**).

According to our results, the reaction is exothermic, but the transition-state structure **TS1aa** lies at 28.1 kcal/mol and is quite asynchronous (Figure 3, Table 2, Entry 1). This disfavored reaction may be a consequence of a significant decrease in the aromatic stabilization energy in the transition state. We therefore considered that the weaker aromatic character of *N*-(3-pyridyl)aldimines **1b**–**d** (X = N) could accelerate the reaction between the imines and alkenes. Thus, the [4+2] cycloaddition reaction between *N*-(3-pyridyl)aldimines **1b**–**d** (X = N) and ethylene (**2a**) was studied computationally (Scheme 3). The calculations indicate that the formation of the cycloadducts **4ab**–**ad** via transition-state structures **TS1** is more favorable (Table 2, Entries 2, 4, and 6) than the formation of the regioisomers **4′ab**–**ad**, respectively, via transition-state structures **TS1′** (Table 2, Entries 3, 5, and 7) under conditions of kinetic control (Fig-

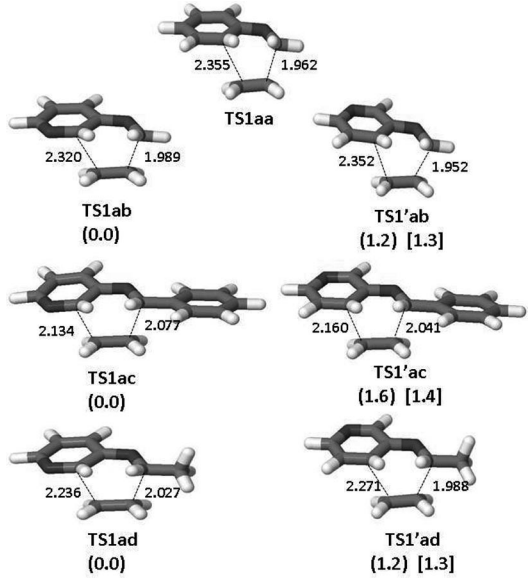


Figure 3. Fully optimized transition-state structures **TS1aa** from the reaction of **1a** with **2a**, and **TS1** and **TS1′** from the reactions of imines **1b**–**d** with **2a**. Selected bond lengths are given in Å. The numbers given in parentheses are the relative energy differences (in kcal/mol) between the transition state **TS1′** and the corresponding transition state **TS1** of the same starting imine, calculated at the B3LYP/6-31G*+ΔZPVE level of theory. Numbers in square brackets correspond to the same relative energy differences (in kcal/mol) calculated at the M06-2X/6-31G*//B3LYP/6-31G*+ΔZPVE level of theory.

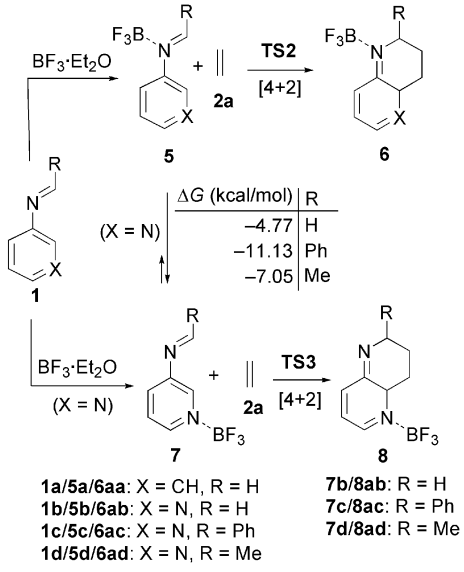
ure 3). In addition, the similar relative energies found for both the B3LYP and M06-2X functionals indicate that the former is accurate enough for the study of these reactions.

Table 2. Activation energies[a] (ΔE_a), reaction energies[a] (ΔE_{rxn}), and synchronicities[b] (Sy) associated with the formation of the [4+2] cycloadducts in Schemes 3, 4, and 5.

Entry	Reaction	TS	ΔE_a [kcal/mol]	ΔE_{rxn} [kcal/mol]	Sy[c]
1	**1a** + **2a** → **4aa**	**TS1aa**	28.1	–8.4	0.85
2	**1b** + **2a** → **4ab**	**TS1ab**	27.0	–10.8	0.85
3	**1b** + **2a** → **4′ab**	**TS1′ab**	28.2	–7.9	0.84
4	**1c** + **2a** → **4ac**	**TS1ac**	31.3	0.9	0.92
5	**1c** + **2a** → **4′ac**	**TS1′ac**	32.9	3.9	0.91
6	**1d** + **2a** → **4ad**	**TS1ad**	30.3	–4.5	0.88
7	**1d** + **2a** → **4′ad**	**TS1′ad**	31.5	–1.7	0.87
8	**5a** + **2a** → **6aa**	**TS2aa**	20.1	–14.1	0.78
9	**5b** + **2a** → **6ab**	**TS2ab**	18.8	–16.1	0.77
10	**5c** + **2a** → **6ac**	**TS2ac**	30.9	–4.0	0.84
11	**5d** + **2a** → **6ad**	**TS2ad**	25.5	–8.7	0.84
12	**7b** + **2a** → **8ab**	**TS3ab**	22.6	–12.5	0.86
13	**7c** + **2a** → **8ac**	**TS3ac**	27.3	–1.8	0.94
14	**7d** + **2a** → **8ad**	**TS3ad**	26.1	–6.8	0.91
15	**9b** + **2a** → **10ab**	**TS4ab**	14.3	–16.5	0.76
16	**9c** + **2a** → **10ac**	**TS4ac**	27.2	–3.7	0.83
17	**9d** + **2a** → **10ad**	**TS4ad**	21.5	–9.0	0.93

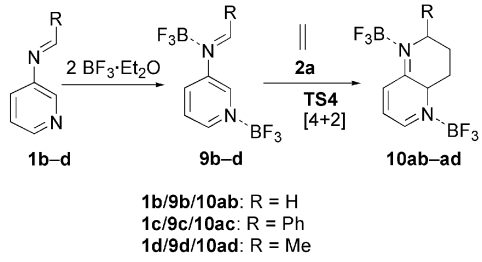
[a] Computed at the B3LYP/6-31G*+ΔZPVE level of theory. [b] Computed at the B3LYP/6-31G* level of theory according to the approach and equations described previously.[7a] [c] For a perfectly synchronous reaction, Sy = 1.

The use of Lewis acids in these reactions minimizes competitive side-reactions, thereby allowing good to excellent yields and high regio- and diastereoselectivities. For this reason, to determine the influence of the Lewis acid (BF_3·Et_2O), we first examined whether 1 equiv. of BF_3 coordinates preferentially with either the imine or the pyridine ring[11] nitrogen atom in compounds **1b**–**d** to give **5b**–**d** or **7b**–**d**, respectively (Scheme 4).



Scheme 4. Cycloaddition reactions with 1 equiv. of BF_3·Et_2O.

The computational results indicate that the coordination of BF_3 to the pyridine nitrogen atom results in compounds **7**, which are more stable (see the table in Scheme 4) than compounds **5** in which BF_3 is coordinated to the imine nitrogen atom. The activation barriers for the [4+2] cycloaddition reactions of **2a** with **7b**–**d** via transition states **TS3ab**–**ad**, in which the Lewis acid is coordinated to the pyridinic nitrogen atom, are consistently lower (Table 2, Entries 12–14) than in the noncoordinated case through transition states **TS1ab**–**ad** (Scheme 4, Table 2, Entries 2, 4, and 6). Nevertheless, in these theoretical studies we could observe that if BF_3 coordinates preferentially to the imine nitrogen atom in the [4+2] cycloaddition reactions of **5a**–**d** with **2a** via transition states **TS2**, the activation barriers could be even lower (Table 2, Entries 8–11). This led us to believe that a second equivalent of BF_3 could accelerate even more the reaction by the coordination of this second molecule of BF_3 to the imine nitrogen atom. In accord with what we had thought, the computational studies showed that when compounds **9b**–**d**, in which one Lewis acid molecule is coordinated to the imine nitrogen atom and the other to the pyridine nitrogen atom, reacted with **2a** to give cycloadducts **10** via transition structures **TS4** (Scheme 5), the relative activation energies (Table 2, Entries 15–17) decreased considerably compared with the reactions between **7** and **2a** via transition states **TS3**.



Scheme 5. Cycloaddition reactions of **1b**–**d** in the presence of 2 equiv. of BF_3·Et_2O.

The molecular DFT-based parameters reported in Table 3 indicate that the double-coordinated compounds **9** (Scheme 4, Table 3, Entries 4, 8, and 12) are more electrophilic than the noncoordinated compounds **1** (Table 3, Entries 1, 5, and 9), as well as the single-coordinated compounds **5** (Scheme 4, Table 3, Entries 2, 6, and 10) and **7** (Scheme 4, Table 3, Entries 3, 7, and 11). Thus, the chemical potentials are lower for compounds **9**, the computed electrophilicities of compounds **9** are larger than those computed for **1**, **5**, and **7**, and the ΔN_{max} values for **5** and **9** are the largest. This data reflects the enhanced electron-withdrawing effect of BF_3 bonded to both the imine and pyridine nitrogen atoms.

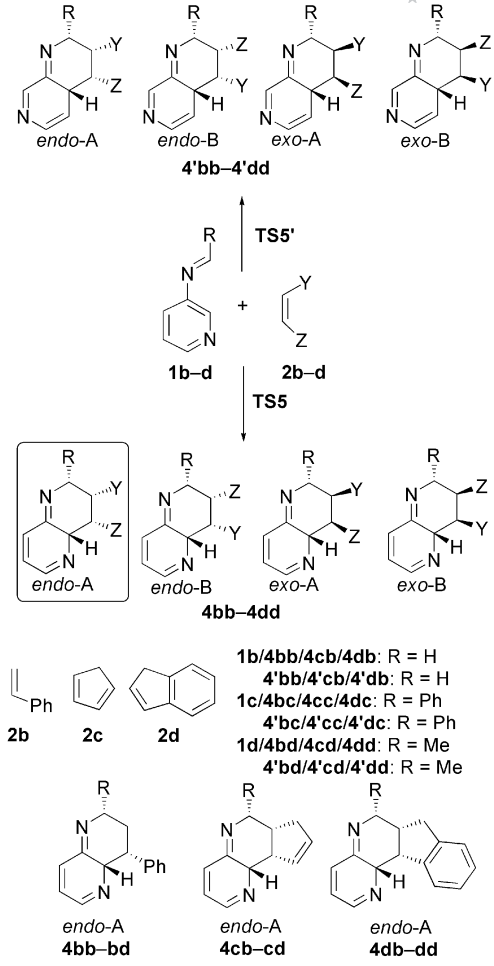
Next, we extended the computational calculations to the study of the regio- and diastereoselectivities of the [4+2] cycloaddition reactions of imines **1b** (R = H), **1c** (R = Ph), and **1d** (R = Me) with the nonsymmetrical dienes styrene (**2b**), cyclopentadiene (**2c**), and indene (**2d**), because it had been observed that the reaction of olefins **2b**–**d** with imines **1c**,**d** gave only the cycloadducts **3bc**–**3dd** regio- and diastereoselectively (see above) with control of the two or three stereocenters. The diverse approach of the dienophiles **2b**–**d** to the heterodienes **1b**–**d** may lead to eight different cy-

Table 3. Hardnesses[a] (η), chemical potentials[a] (μ), global electrophilicities[a] (ω), and maximun number of accepted electrons[a] (ΔN_{max}) of compounds **1b–d** and products **5b–d**, **7b–d**, and **9b–d** coordinated to BF_3.

Entry	Compound	η [a.u.]	μ [a.u.]	ω [eV]	ΔN_{max} [a.u.]
1	**1b**	0.19301	–0.14308	0.053	0.741
2	**5b**	0.18531	–0.18679	0.094	1.008
3	**7b**	0.19445	–0.17986	0.083	0.925
4	**9b**	0.20065	–0.22056	0.121	1.099
5	**1c**	0.16414	–0.14607	0.065	0.890
6	**5c**	0.16410	–0.17755	0.096	1.082
7	**7c**	0.16707	–0.17075	0.087	1.022
8	**9c**	0.16762	–0.19819	0.117	1.182
9	**1d**	0.19717	–0.13497	0.046	0.683
10	**5d**	0.19474	–0.17549	0.079	0.898
11	**7d**	0.19400	–0.17250	0.077	0.889
12	**9d**	0.20864	–0.20791	0.104	0.997

[a] Computed at the B3LYP/6-31G* level of theory according to the approach and equations described previously.[17]

cloadducts (Scheme 6). These cycloadducts are identified as *endo*/*exo* on the basis of the orientation of the phenyl group in styrene (**2b**), the double bond of cyclopentadiene (**2c**), and the benzene moiety of indene (**2d**) and as A/B with respect to the regiochemistry of the reaction. Moreover, the imines **1b–d** could react with the dienophiles **2b–d** via transition-state structures **TS5** to give the corresponding *endo*/*exo*-A and *endo*/*exo*-B cycloadducts **4bb–4dd** or via transition-state structures **TS5′** to give the corresponding *endo*/*exo*-A and *endo*/*exo*-B cycloadducts **4′bb–4′dd** (Scheme 6). However, we found that the pathways involving *endo* transition-state structures **TS5bb–dd**-*endo*-A, which give the corresponding *endo*-A adducts **4bb–4dd**, exhibit the lowest activation barriers (details of the relative activation barriers for *endo*/*exo* selectivity and A/B regiochemistry are presented in Table 1 of the Supporting Information).[18] All the reactions occur in a concerted manner, but the bond formation is quite asynchronous with the C(dienophile)–C(imine) bond being more advanced in all cases (Scheme 6, Table 4, Entries 1–9, noncoordinated pathway, and Table 1 of the Supporting Information).



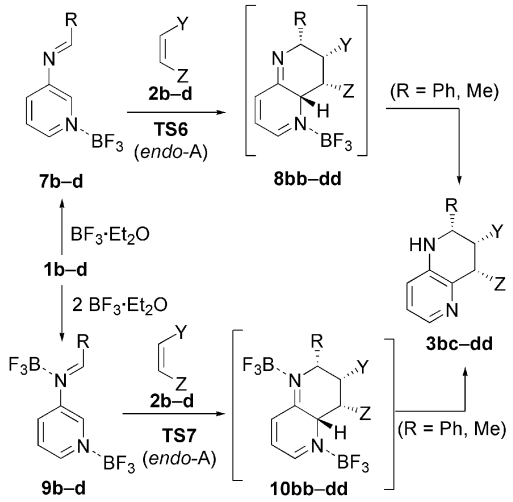
Scheme 6. Possible [4+2] cycloadducts from the reactions of **1b–d** with the nonsymmetric alkenes **2b–d**.

The influence of the Lewis acid on the reactions of the activated imines **7** and **9** with the dienes **2b–d** (Scheme 7) was similar to that observed in their reactions with ethylene (**2a**). Thus, the computational data indicate that the reactions of double-coordinated compounds **9** with **2b–d** to give the *endo*-A adducts **10bb–dd** via **TS7** have lower activation barriers (Scheme 7, Figure 4, Table 4, double-coordinated

Table 4. Activation energies[a] (ΔE_a [kcal/mol]), reaction energies[a] (ΔE_{rxn} [kcal/mol]), and synchronicities[a] (Sy) associated with the formation of the [4+2] *endo*-A cycloadducts **4**, **8**, and **10**.

Entry	Dienophile	R	Non coordinated pathway					Single coordinated pathway					Double coordinated pathway				
			Reaction	TS	ΔE_a	ΔE_{rxn}	Sy	Reaction	TS	ΔE_a	ΔE_{rxn}	Sy	Reaction	TS	ΔE_a	ΔE_{rxn}	Sy
1	Ph	H	**1b** + **2b** → **4bb**	**TS5bb**	24.05	–2.0	0.75	**7b** + **2b** → **8bb**	**TS6bb**	17.4	–5.2	0.75	**9b** + **2b** → **10bb**	**TS7bb**	4.0	–12.4	0.61
2	Ph	Ph	**1c** + **2b** → **4bc**	**TS5bc**	31.1	12.1	0.80	**7c** + **2b** → **8bc**	**TS6bc**	25.1	5.4	0.81	**9c** + **2b** → **10bc**	**TS7bc**	17.5	1.6	0.68
3	**2b**	Me	**1d** + **2b** → **4bd**	**TS5bd**	28.7	5.7	0.77	**7d** + **2b** → **8bd**	**TS6bd**	22.1	0.3	0.71	**9d** + **2b** → **10bd**	**TS7bd**	11.2	–3.9	0.67
4		H	**1b** + **2c** → **4cb**	**TS5cb**	21.7	–3.8	0.60	**7b** + **2c** → **8cb**	**TS6cb**	16.3	–6.7	0.69	**9b** + **2c** → **10cb**	**TS7cb**	2.3	–13.4	0.61
5		Ph	**1c** + **2c** → **4cc**	**TS5cc**	31.1	6.2	0.78	**7c** + **2c** → **8cc**	**TS6cc**	25.6	4.4	0.78	**9c** + **2c** → **10cc**	**TS7cc**	20.2	3.1	0.68
6	**2c**	Me	**1d** + **2c** → **4cd**	**TS5cd**	28.7	2.0	0.74	**7d** + **2c** → **8cd**	**TS6cd**	22.7	–0.3	0.73	**9d** + **2c** → **10cd**	**TS7cd**	11.8	–2.6	0.63
7		H	**1b** + **2d** → **4db**	**TS5db**	25.1	–2.3	0.74	**7b** + **2d** → **8db**	**TS6db**	17.4	–5.1	0.74	**9b** + **2d** → **10db**	**TS7db**	3.7	–12.0	0.62
8		Ph	**1c** + **2d** → **4dc**	**TS5dc**	32.5	7.8	0.81	**7c** + **2d** → **8dc**	**TS6dc**	26.7	6.0	0.80	**9c** + **2d** → **10dc**	**TS7dc**	21.0	4.5	0.70
9	**2d**	Me	**1d** + **2d** → **4dd**	**TS5dd**	30.2	3.5	0.77	**7d** + **2d** → **8dd**	**TS6dd**	24.0	1.5	0.77	**9d** + **2d** → **10dd**	**TS7dd**	13.3	–2.9	0.65

[a] Computed at the B3LYP/6-31G*+ΔZPVE level of theory.



Scheme 7. Cycloaddition reactions of **1b**–**d** with **2b**–**d** in the presence of BF_3·Et_2O.

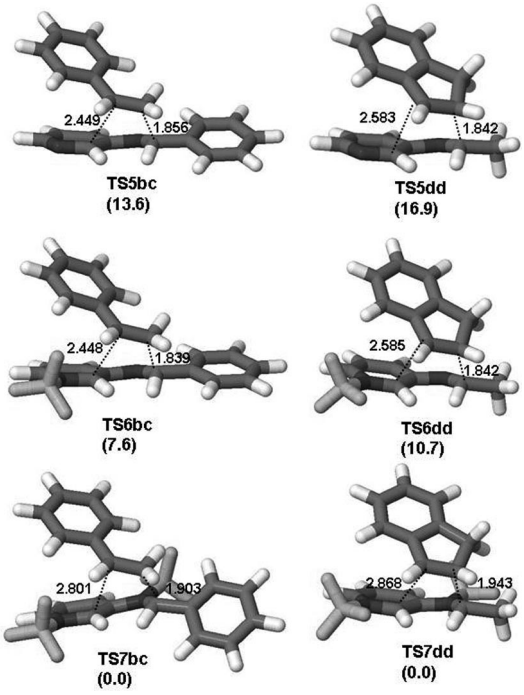


Figure 4. Fully optimized transition-state structures **TS5**, **TS6**, and **TS7** from the reactions of imines **1c**, **7c**, and **9c** with **2b** and imines **1d**, **7d** and **9d** with **2d** as examples. Selected bond lengths are given in Å. The numbers given in parentheses correspond to the relative energy differences (in kcal/mol) of **TS5** and **TS6** with respect to double-coordinated transition-state structures **TS7** calculated at the B3LYP/6-31G*+ΔZPVE level of theory.

pathway) not only when imines **1b**–**d** react through the transition states **TS5**-*endo*-A to give *endo*-A adducts **4bb**–**dd** (Scheme 6, Figure 4, Table 4, noncoordinated pathway), but also when single-coordinated imines **7** react via transition states **TS6** to give *endo*-A adducts **8bb**–**dd** (Scheme 7, Figure 4, Table 4, single-coordinated pathway). As in the preceding cases, all the reactions occur in a concerted asynchronous manner with the C(dienophile)–C(imine) bond being more advanced in all cases (see Table 4 and Figure 4). These computational predictions are consistent with our experimental results, given that in our hands the reactions of imines **1c**,**d** with olefins **2b**–**d** gave only the *endo* cycloadducts **3bc**–**dd**.

Conclusions

The computational studies performed on imines **1a** (X = CH) and the computational and experimental studies on imines **1b**–**d** (X = N) suggest that the Povarov reactions with olefins **2** take place in an asynchronous concerted process. In addition, the Povarov reactions between imines **1b**–**d** (X = N) and olefins **2b**–**d** take place via *endo* transition states to give tetrahydro-1,5-naphthyridine derivatives **3** with regio- and stereoselective control of the three stereocenters. Moreover, the use of 2 equiv. of BF_3·Et_2O activates the azadiene system, accelerating the reaction more than when only 1 equiv. is used.

Experimental Section

General Experimental: Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were distilled as necessary. All reactions were performed under dry nitrogen. Visualization was accomplished by UV light or $KMnO_4$. ^1H, ^{13}C, and 2D NMR spectra were recorded with a Varian Unity Plus 300 and Bruker Avance 400 spectrometer by using $CDCl_3$. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) with a Hewlett–Packard 5971 or 5973 spectrometer. Data are reported in the form *m*/*z* (intensity relative to base × 100). High-resolution mass spectra (HRMS) were obtained by chemical ionization (CI) with an Agilent GC–MS spectrometer model 6890N with a TOF (Micromass) analyzer. Infrared spectra (IR) were recorded with a Nicolet iS10 spectrometer. CCDC-737355 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of Imine 1c: A solution of 3-aminopiridine (2 mmol, 0.19 g) and freshly distilled benzaldehyde (2 mmol, 0.20 mL) in $CHCl_3$ (15 mL) with molecular sieves was stirred at room temperature until TLC indicated the disappearance of the starting materials (48 h). The resulting solution was filtered. The solvent was evaporated under reduced pressure to give compound **1c** as an oil. The reaction product is unstable during distillation and/or chromatography and was used without purification in the following reactions.

Preparation of Imine 1d: A solution of 3-aminopyridine (2 mmol, 0.19 g) and freshly distilled acetaldehyde (2 mmol, 0.28 mL) in $CHCl_3$ (15 mL) with molecular sieves was stirred at room tempera-

ture until TLC indicated the disappearance of the starting materials (3 h). The molecular sieves were removed by filtration under dry nitrogen, and the resulting solution was used without purification in the following reactions, because the reaction product is unstable during distillation and/or chromatography.

General Procedure for the Preparation of Compounds 3: Diene **2** (3 mmol) and one or more equivalents of $BF_3{\cdot}Et_2O$ were added to a solution of the previously prepared imine **1** (2 mmol) in $CHCl_3$ (15 mL). The mixture was stirred at the appropriate temperature until TLC and ^1H NMR spectroscopy indicated the disappearance of imine **1**. The reaction mixture was diluted with dichloromethane (20 mL), washed with a 2 M NaOH aqueous solution (20 mL) and water (20 mL), extracted with dichloromethane (2 × 20 mL), and dried ($MgSO_4$). Removal of the solvent under vacuum afforded an oil that was purified by silica gel flash column chromatography (eluent: hexane/Et_2O) to afford compounds **3**.

2,4-Diphenyl-1,2,3,4-tetrahydronaphthyridine (3bc): The procedure was carried out by using freshly distilled styrene (**2b**; 3 mmol, 0.31 mL) and imine **1c**. When 2 mmol (0.36 mL) of $BF_3{\cdot}Et_2O$ was used and the mixture was stirred at room temperature for 216 h (74% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.350 g of compound **3bc** (61%) was obtained. If the mixture was stirred at reflux temperature for 24 h (76% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.355 g of compound **3bc** (62%) was obtained. When 4 mmol (0.72 mL) of $BF_3{\cdot}Et_2O$ was used and the mixture was stirred at room temperature for 41 h (98% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.412 g of compound **3bc** (71%) was obtained. If the same mixture was stirred at reflux temperature for 4 h (99% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.435 g of compound **3bc** (76%) was obtained as a yellow solid. M.p. 136–138 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.26 (ddd, $^2J_{HH}$ = 12.6, $^3J_{HH}$ = 12.2, $^3J_{HH}$ = 11.3 Hz,1 H, CH_2), 2.41 (ddd, $^2J_{HH}$ = 12.6, $^3J_{HH}$ = 6.1, $^3J_{HH}$ = 2.3 Hz, 1 H, CH_2), 3.99 (s, 1 H, NH), 4.45 (dd, $^3J_{HH}$ = 12.2, $^3J_{HH}$ = 6.1 Hz, 1 H, Ph-C*H*), 4.59 (dd, $^3J_{HH}$ = 11.3, $^3J_{HH}$ = 2.3 Hz, 1 H, HN-C*H*-Ph), 6.86 (dd, $^3J_{HH}$ = 8.06, $^3J_{HH}$ = 1.48 Hz, 1 H, CH_{Ar}), 6.94 (dd, $^3J_{HH}$ = 8.04, $^3J_{HH}$ = 4.55 Hz, 1 H, CH_{Ar}), 7.18–7.46 (m, 10 H, CH_{Ar}), 7.94 (d, $^3J_{HH}$ = 4.55 Hz, 1 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.8 (CH_2), 47.5 (*C*H-Ph), 56.9 (N-CH), 121.0, 122.1, 126.3, 126.6, 127.9, 128.5, 128.7, 139.4 (CH_{Ar}), 141.8, 143.0, 144.7, 144.8 (C_{Ar}) ppm. IR: $\tilde{\nu}$ = 3192, 3154, 2980, 1584, 1451, 1286 cm^{-1}. MS (EI): *m*/*z* (%) = 286 (10) $[M]^+$. HRMS (CI): calcd. for $C_{20}H_{18}N_2$ $[M]^+$ 286.1470; found 286.1474.

2-Methyl-4-phenyl-1,2,3,4-tetrahydronaphthyridine (3bd): The procedure was carried out by using freshly distilled styrene (**2b**; 3 mmol, 0.31 mL) and imine **1d**. When 2 mmol (0.36 mL) of $BF_3{\cdot}Et_2O$ was used and the mixture was stirred at room temperature for 2 h (99% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.233 g of compound **3bd** (52%) was obtained. When 4 mmol (0.72 mL) of $BF_3{\cdot}Et_2O$ was used and the mixture was stirred at room temperature for 2 h (99% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.322 g of compound **3bd** (72%) was obtained as a brown solid. M.p. 130–132 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, $^3J_{HH}$ = 6.2 Hz, 3 H, CH_3), 1.89 (ddd, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 12.4, $^3J_{HH}$ = 12.0 Hz, 1 H, 1 H, CH_2), 2.20 (ddd, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 6.4, $^3J_{HH}$ = 2.3 Hz, 1 H, CH_2), 3.50–3.56 (m, 1 H, HN-C*H*-Me), 3.6 (s, 1 H, NH), 4.20 (dd, $^3J_{HH}$ = 12.0, $^3J_{HH}$ = 6.4 Hz, 1 H, C*H*-Ph), 6.73 (dd, $^3J_{HH}$ = 8.1, $^2J_{HH}$ = 1.3 Hz, 1 H, CH_{Ar}), 6.83 (dd, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 4.6 Hz, 1 H, CH_{Ar}), 7.08–7.26 (m, 5 H, CH_{Ar}), 7.80 (d, $^3J_{HH}$ = 4.5 Hz, 1 H, CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (CH_3), 42.2 (CH_2), 47.3 (*C*H-Ph), 47.6 (HN-CH), 120.9, 122.2, 126.1, 128.8, 139.2 (CH_{Ar}), 141.9, 145.2, 145.3 (C_{Ar}) ppm. IR: $\tilde{\nu}$ = 3228.69, 2958.84, 2938.54, 1588.72, 1451.24, 1335.02 cm^{-1}. HRMS (CI): calcd. for $C_{20}H_{18}N_2$ $[M]^+$ 224.1313; found $[M]^+$ 224.1307.

6-Phenyl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,5]naphthyridine (3cc): The procedure was carried out as described in the main text by using freshly distilled cyclopentadiene (**2c**; 3 mmol, 0.20 mL) and imine **1c**. When 2 mmol (0.36 mL) of $BF_3{\cdot}Et_2O$ was used and the mixture was stirred at reflux temperature for 96 h (70% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.328 g of compound **3cc** (66%) was obtained. When 4 mmol (0.72 mL) of $BF_3{\cdot}Et_2O$ was used and the mixture was stirred at reflux temperature for 30 h (90% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.407 g of compound **3cc** (82%) was obtained as a brown solid. M.p. 156–158 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.89 (ddd, $^2J_{HH}$ = 16.4, $^3J_{HH}$ = 8.8, $^3J_{HH}$ = 1.5 Hz, 1 H, CH_2), 2.64 (ddd, $^2J_{HH}$ = 16.4, $^3J_{HH}$ = 9.4, $^3J_{HH}$ = 2.4 Hz, 1 H, CH_2), 3.12 (ddd, $^2J_{HH}$ = 8.8, $^3J_{HH}$ = 3.1, $^3J_{HH}$ = 2.4 Hz, 1 H, CH_2-C*H*), 3.75 (s, 1 H, NH), 4.24 (dd, $^3J_{HH}$ = 8.8, $^3J_{HH}$ = 2.4 Hz, 1 H, =CH-C*H*), 4.71 (d, $^3J_{HH}$ = 3.1 Hz, 1 H, Ph-C*H*), 5.73 (dd, $^3J_{HH}$ = 4.3, $^3J_{HH}$ = 1.5 Hz, 1 H, =CH), 6.03–6.06 (m, 1 H, =CH), 6.89–6.95 (m, 2 H, CH_{Ar}), 7.28–7.47 (m, 5 H, CH_{Ar}), 8.05 (d, $^3J_{HH}$ = 4.4 Hz, 1 H, CH_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.7 (CH_2), 46.1 (CH_2-*C*H), 49.4 (=CH-*C*H), 57.6 (Ph-*C*H), 121.4, 122.3, 126.4, 127.5, 128.6 (CH_{Ar}), 131.0 (=*C*H-CH_2), 133.5 (=*C*H-CH), 140.3 (CH_{Ar}), 141.6, 142.1, 147.1 (C_{Ar}) ppm. IR: $\tilde{\nu}$ = 3366, 3049, 2923, 1584, 1448 cm^{-1}. MS (EI): *m*/*z* (%) = 248 (100) $[M]^+$. HRMS (CI): calcd. for $C_{17}H_{16}N_2$ $[M]^+$ 248.1313; found 248.1319.

6-Methyl-6,6a,7,9a-tetrahydro-5*H*-cyclopenta[*c*][1,5]naphthyridine (3cd): The procedure was carried out by using freshly distilled cyclopentadiene (**2c**; 3 mmol, 0.20 mL) and imine **1d**. When 2 mmol (0.36 mL) of $BF_3{\cdot}Et_2O$ was used and the mixture was stirred at room temperature for 46 h (55% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.120 g of compound **3cd** (30%) was obtained as a brown solid. When 4 mmol (0.72 mL) of $BF_3{\cdot}Et_2O$ was used and the mixture was stirred at room temperature for 23 h (65% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.192 g of compound **3cd** (48%) was obtained as a brown solid. M.p. 115–117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.23 (m, 3 H, CH_3), 2.31 (ddd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 9.3, $^3J_{HH}$ = 2.4 Hz, 1 H, CH_2), 2.53 (ddd, $^2J_{HH}$ = 16.2, $^3J_{HH}$ = 9.0, $^3J_{HH}$ = 2.3 Hz, 1 H, CH_2), 2.86 (dd, $^3J_{HH}$ = 9.0, $^3J_{HH}$ = 3.2 Hz, 1 H, C*H*-CH_2), 3.36 (s, 1 H, NH), 3.60–3.62 (m, 1 H, HN-C*H*-CH_3), 4.08 (d, $^3J_{HH}$ = 9.1 Hz, 1 H, =CH-C*H*) 5.75–5.77 (m, 1 H, =CH), 5.97–5.99 (m, 1 H, =CH), 6.75–6.88 (m, 2 H, CH_{Ar}) 7.94–7.96 (m, 1 H, CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 (CH_3), 31.1 (CH_2), 44.0 (*C*H-CH_2), 48.3 (HN-CH), 49.0 (=CH-*C*H), 121.0, 121.4 (CH_{Ar}), 130.5 (=*C*H-CH_2), 133.6 (=*C*H-CH), 139.2 (CH_{Ar}), 141.6, 147.0 (C_{Ar}) ppm. IR: $\tilde{\nu}$ = 3254.47, 2985.07, 2908.91, 1577.59, 1448.12 cm^{-1}. HRMS (CI): calcd. for $C_{17}H_{16}N_2$ $[M]^+$ 186.1157; found 186.1159.

6-Phenyl-6,6a,7,11b-tetrahydro-5*H*-indeno[2,1-*c*][1,5]naphthyridine (3dc): The procedure was carried out as described in the main text by using freshly distilled indene (**2d**; 3 mmol, 0.35 mL), imine **2c**, and 4 mmol (0.72 mL) of $BF_3{\cdot}Et_2O$. The mixture was stirred at reflux temperature for 48 h (99% consumption of the starting materials by NMR analysis of the crude reaction mixture), and 0.77 g of compound **3dc** (72%) was obtained as a yellow solid. M.p. 158–160 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.46 (dd, $^2J_{HH}$ = 20.2,

$^3J_{HH}$ = 12.6 Hz, 1 H, CH_2), 3.27–3.34 (m, 2 H, CH_2-C*H*, CH_2), 3.84 (s, 1 H, NH), 4.70 (d, $^3J_{HH}$ = 7.4 Hz, 1 H, Ar-C*H*), 4.80 (s, 1 H, HN-C*H*-Ph), 6.84–6.93 (m, 3 H, CH_{Ar}), 7.08–7.79 (m, 8 H, CH_{Ar}), 8.06 (d, $^3J_{HH}$ = 4.40 Hz, 1 H, CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.4 (CH_2), 47.8 (CH_2-*C*H), 49.1 (C_{Ar}-*C*H), 57.6 (*C*H-Ph), 121.7, 122.1, 124.3, 126.3, 126.5, 126.7, 127.1, 127.6, 128.7, 140.6 (CH_{Ar}), 141.4, 141.9, 142.5, 144.6, 145.1 (C_{Ar}) ppm. IR: $\tilde{\nu}$ = 3356.31, 3021.79, 2912.61, 1574.28, 1457.12 cm^{-1}. HRMS (CI): calcd. for $C_{17}H_{16}N_2$ [M]$^+$ 298.1470; found 298.1466.

6-Methyl-6,6a,7,11b-tetrahydro-5*H*-indeno[2,1-*c*][1,5]naphthyridine (3dd): The procedure was carried out by using freshly distilled indene (**2d**; 3 mmol, 0.35 mL) and imine **1d**. When 2 mmol (0.36 mL) of BF_3·Et_2O was used and the mixture was stirred at room temperature for 24 h (99% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.335 g of compound **3dd** (70%) was obtained. When 4 mmol (0.72 mL) of BF_3·Et_2O was used and the mixture was stirred at room temperature for 12 h (99% consumption of the starting materials by NMR analysis of the crude reaction mixture), 0.411 g of compound **3dd** (84%) was obtained as a yellow solid. M.p. 143–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (d, $^3J_{HH}$ = 6.5 Hz, 3 H, CH_3), 2.90 (dd, $^2J_{HH}$ = 14.0, $^3J_{HH}$ = 7.1 Hz, 1 H, CH_2), 3.09–3.16 (m, 2 H, CH_2-C*H*, CH_2), 3.5 (s, 1 H, NH), 3.66–3.72 (m, 1 H, CH_3-C*H*), 4.54 (d, $^3J_{HH}$ = 8.0 Hz, 1 H, Ar-C*H*), 6.74–7.30 (m, 5 H, CH_{Ar}), 7.75–7.77 (m, 1 H, CH_{Ar}), 7.99 (d, $^3J_{HH}$ = 4.6 Hz, 1 H, CH_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (CH_3), 30.9 (CH_2), 45.8 (CH_2-*C*H), 48.3 (*C*H-CH_3), 48.8 (C_{Ar}-*C*H), 121.36, 121.46, 124.30, 126.21, 126.56, 126.91, 139.84 (CH_{Ar}), 141.45, 142.52, 144.78, 145.21 (C_{Ar}) ppm. IR: $\tilde{\nu}$ = 3228.67, 3064.16, 2973.91, 1577.04, 1450.32 cm^{-1}. HRMS (CI): calcd. for $C_{17}H_{16}N_2$ [M]$^+$ 236.1313; found 236.1308.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **3bc**,**bd**,**cc**,**cd**,**dc**,**dd**. 1D NOESY, HMBC, and HMQC experiments for compounds **3bc** and **3cc**; details of all possible [4+2] cycloadducts **4bb**–**dd**; full computational characterization of all the reported reactions and stationary points.

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[18] For details on activation energies, reaction energies and synchronicities associated with the formation of all the possible [4+2] cycloadducts **4bb–dd** see the Supporting Information.

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