# Synthesis and Reactivity of Electron-Poor 2-Azadienes. [4 + 2] Cycloaddition Reactions with Alkenes and Enamines

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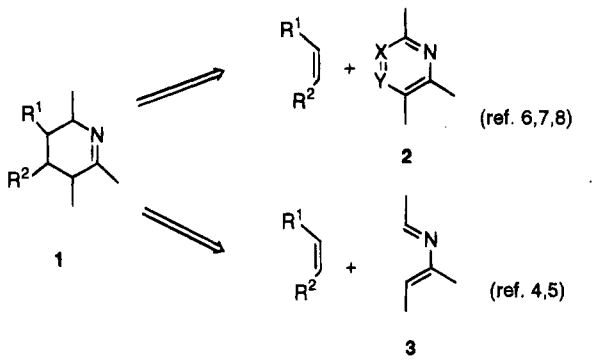
Electron deficient 2-azadienes derived from β-amino acids **3** are obtained by aza-Wittig reaction of *N*-vinylic phosphazenes **4** with carbonyl compounds. Inverse electron demand Diels–Alder reaction of azadienes **3** with *trans*-cyclooctene **7** and *cis,trans*-cyclooctadiene **8** leads to the formation of *trans*-cycloalkanotetrahydropyridines **10**. Heterodienes **3** also react with enamines **13**, **14**, and **18** affording pyridine derivatives **16**, **17**, and **20** in a regioselective fashion. Norbornadiene **11**, a less strained olefin than cycloalkenes **7** and **8**, requires the presence of lithium perchlorate as catalyst in a nonaqueous solvent like ether, to give cycloadducts **12**.

## Introduction

Alkaloids[1] and antitumor antibiotics,[2] containing six-membered nitrogen heterocycles such as piperidine and pyridine derivatives, are prevalent in nature, and many of these compounds display strong biological activity.[1–3] A convergent approach to the construction of the corresponding functionalized nitrogen-containing six-membered ring systems could be the [4 + 2] cycloaddition reaction of azadienes and alkenes[4,5] (Scheme 1). Heteroaromatic systems possessing reactive azadienes such as oxazoles[6] (**2**, X = Y: O), 1,3-oxazin-6-ones[7] (**2**, X = Y: COO) and substituted 1,3,4-triazenes[8] (**2**, X = Y: N=N) have been used with this aim. Acyclic 2-azadienes **3** such as electronically neutral azabutadienes[4b,5] and heterodienes with electron-donating substituents[4e] can be also used as precursors to pyridine derivatives. However, electron-poor 2-azadienes, in spite of being the most adequate 2-azadienes[9] for inverse demand Diels–Alder reaction,[10] have received much less attention, probably owing to the lack of general methods for the synthesis of these compounds.[4a] Azabutadienes of this type were limited, to the best of our knowledge, to 3-substituted electron-deficient heterodienes,[11] as well as to 4,4-[12] and to 3,4-electron-withdrawing substituted[13] 2-azadienes. The use of this kind of electron-poor 2-azadienes in the construction of heterocyclic systems was restricted to the intermolecular reaction of disubstituted compounds with enamines[13a] and to the intramolecular cycloaddition reaction with simple alkenes and alkynes. Whereas heterodiene, substituted with one electron-withdrawing group, undergoes dimerization[14] as well as cycloaddition reaction with both electron rich and electron deficient dienophiles.[15]

**Scheme 1. General Strategy for Formation of Six-Membered Nitrogen Heterocyclic Systems**

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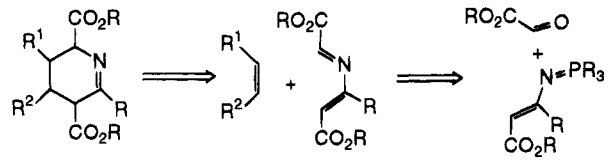
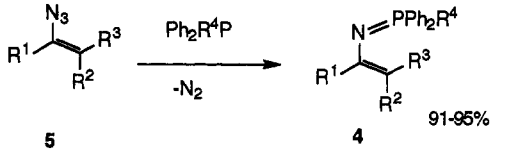
**Scheme 2. General Approach for Polysubstituted Pyridine Formation through [4 + 2] Cycloaddition Reaction of Azadienes 3**



1 3 4

Elsewhere, we have described the usefulness of phosphazenes in the preparation of acyclic[16] and heterocyclic compounds,[17] and recently we have reported the synthesis of α,β-unsaturated hydrazones[18] and secondary *E*-allylamines[19] through Wittig reaction of functionalized ylides. Phosphazenes,[20] nitrogen analogues to the isoelectronic phosphorus ylides, react with carbonyl compounds and lead to a very efficient and mild-condition method for construction of carbon-nitrogen double bonds. This strategy has recently been used in the preparation of acyclic imines[21] and in the synthesis of rigid bicyclic guanidines,[22] azulenes,[23] and alkaloids.[24] In this context, we have already used the aza-Wittig reaction[25] of *N*-vinylic phosphazenes derived from α-amino acids for the synthesis of 2-azadienes. Therefore, our approach to the construction of β-amino acid derivatives,[26] such as several polyfunctionalized pyridine compounds substituted with electron-withdrawing groups **1** (Scheme 2), utilizes the [4 + 2] cycloaddition reaction for efficient construction of nitrogen heterocycles from polysubstituted azadienes **3**. The complementary addition of electron-withdrawing groups to the acyclic azadiene could accelerate its 4π participation in LUMO diene-controlled Diels–Alder reactions, enhance, or control, the observed regioselectivity of the [4 + 2] cycloaddition reaction, and influence the mode of cycloaddition. The complementary and noncomplementary substitution of electron-withdrawing groups in heteroaromatic azadienes have been widely used in efficient and elegant synthesis of Steptonigrin[29] and Lavendomycin.[30]

**Scheme 3. Phosphazenes 4 Formation through Staudinger Reaction**



5 4 91-95%

| compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | m.p. °C [a] |
|---|---|---|---|---|---|
| **4a** | H | $CO_2C_2H_5$ | H | $CH_3$ | 117-118 |
| **4b** | $CO_2CH_3$ | H | $CO_2CH_3$ | Ph | 131-132 |
| **4c** | $CH_3$ | $CO_2CH_3$ | H | $CH_3$ | 154-155 |
| **4d** | $CH_3$ | $CO_2CH_3$ | H | Ph | 141-142 |

## Results and Discussion

Electron-deficient 2-azadienes **3** could be obtained by means of Aza-Wittig reaction of phosphazenes derived from β-amino acids **4** with carbonyl compounds (Scheme 2). The preparation of the required *N*-vinylic phosphazenes **4** was accomplished very easily through the classic Staudinger reaction[20a] of azides **5**[31] and phosphines (Scheme 3). Crystalline compounds **4** were characterized on the basis of their spectroscopic data. Thus, the $^{31}$P-NMR spectrum for **4a** showed an absorption at $\delta_P$ 8.8 ppm and in the $^1$H-NMR spectrum of **4a**, the vinylic proton adjacent to the nitrogen atom resonated at $\delta_H$ 7.84 ppm, as a well resolved double doublet with coupling constants of $^3J_{PH}$ = 30 Hz and $^3J_{HH}$ = 12 Hz, while the olefinic proton in position β to the nitrogen atom gave an upfield shift doublet ($\delta_H$ = 5.26; $^3J_{HH}$ = 12 Hz). The vicinal H-H coupling constant ($^3J_{HH}$ = 12 Hz) suggested that both proton atoms in compound **4a** were relatively *trans*.[19]

Reaction of compounds **4** with ethyl glyoxalate and diethyl ketomalonate in $CHCl_3$ at room temperature gave very high yields of di-, tri-, and tetrasubstituted 2-azadienes **3a–e** (Scheme 4). Heterodienes **3a,b** (Table 1, entries 1, 2), derived from ketomalonate are isolated as thick sticky oils which could be purified by column chromatography. Compounds **3a,b** were characterized on the basis of their spectroscopic data and mass spectrometry. For instance, the olefinic protons of **3a** gave $^1$H resonances at δ 7.76 and 6.02 ($^3J_{HH}$ = 13 Hz) as doublets; while mass spectrometry of **3a** showed the molecular ion peak (*m*/*z* 271, 10%). However, azadienes **3c–e** (Table 1, entries 3–5), which proved to be unstable to distillation or chromatography, were therefore not isolated, and crude reaction mixtures without purification were satisfactorily used for the following purposes. Likewise, when pyruvonitrile was used as carbonyl compound, the isolation of diene **3f** was cumbersome to carry out on a routine basis and tautomeric dienamine **6** was isolated instead. The presence of the azadiene **3f** in the crude reaction mixture was confirmed by $^1$H NMR

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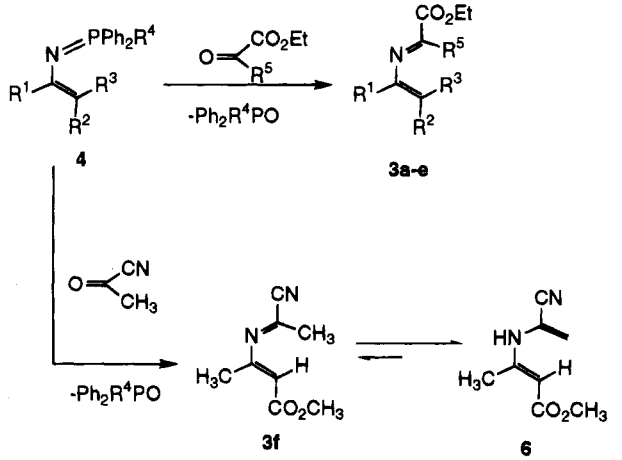
Table 1. 2-Azadienes 3a–e Obtained

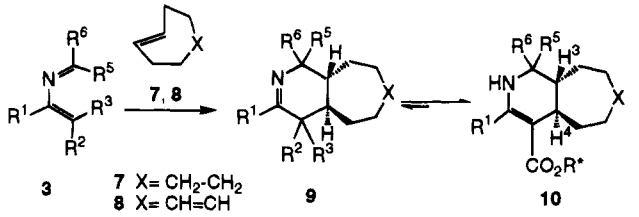
| entry | starting material | products | $R^1$ | $R^2$ | $R^3$ | $R^5$ | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | **3a** | H | $CO_2C_2H_5$ | H | $CO_2C_2H_5$ | 92[a] |
| 2 | **4c, 4d** | **3b** | $CH_3$ | $CO_2CH_3$ | H | $CO_2C_2H_5$ | 95[a] |
| 3 | **4b** | **3c** | $CO_2CH_3$ | H | $CO_2CH_3$ | H | *b* |
| 4 | **4a** | **3d** | H | $CO_2C_2H_5$ | H | H | *b* |
| 5 | **4c, 4d** | **3e** | $CH_3$ | $CO_2CH_3$ | H | H | *b* |

[a] Purified by flash chromatography. [b] Not isolated.

**Scheme 4. Electron Deficient 2-Azadiene 3 Formation through Aza-Wittig Reaction**



**Scheme 5. Diels–Alder Reaction of Azadienes 3 with Strained Olefins 7 and 8**



spectroscopy and diene **3f** was used "in situ" without isolation in [4 + 2] cycloaddition reactions.

The reactivity of polysubstituted 2-azadienes **3** as heterodienes in inverse electron demand Diels–Alder reaction was explored, since the presence of strong electron-withdrawing substituents in the acyclic dienes affects the rate of cycloaddition and could also serve to enhance the rate and the regioselectivity of the cycloaddition.[4,10] At first, strained olefins such as *trans*-cyclooctene[32] and *cis,trans*-cyclooctadiene were used as dienophile. These reagents gave excellent yields in 1,3-dipolar cycloaddition reactions with low-lying $\pi$ MO'S 1,3-dipoles such as azoxy compounds.[33] Likewise, several *trans*-cyclooctene derivatives were used in [4 + 2] cycloaddition processes with 1,3-butadiene and cyclopentadiene.[34]

*Trans*-cyclooctene (**7**) and *cis,trans*-cyclooctadiene (**8**) were allowed to react with azadienes **3** (see Scheme 5). The reactions were performed under conditions shown in Table 2 (entries 1–6), affording cycloadducts **10**. Spectral data were in agreement with the enamine structure of bicyclic tetrahydropyridines **10**. Vicinal coupling constants ($^3J_{H^3H^4}$) in the range of 10–12 Hz between the axial protons of cycloadducts were consistent[35] with the *trans*-ring juncture of the fused bicyclic compounds, maintaining the *E* configuration of the starting olefins **7** and **8**.

When azadienes **3d,c** were used, two stereoisomeric adducts **10b,c** and **10'b,c** (Table 2, entries 2, 3) were obtained. The relative proportion of these isomers (1:1) was determined by capillary GC analysis of the mixture obtained as a viscous oil, where mass spectrum and elemental analysis supported the expected structure. The vicinal coupling constant ($^3J_{H^2H^3}$) of 7.8 and 4.2 Hz were consistent with the *anti* and *syn* configurations of protons in compounds **10** and **10'** (Figure 1).

Diels–Alder reaction of azadiene **3** with a less strained olefin than **7** and **8** such as norbornadiene **11** was explored (Scheme 6). Thus, cycloaddition of **3a,b** with norbornadiene **11** was attempted at 120 °C using toluene as solvent, but no reaction took place. However, the expected adducts **12** were obtained when the reaction was performed in the presence of lithium perchlorate in a nonaqueous solvent such as diethyl ether (LP–$Et_2O$) (Table 2, entries 7, 8). No cycloadducts were oberved with another olefin such as norbornene, with or without the presence of LP–$Et_2O$ as catalyst. Vicinal coupling constants ($^3J_{H^3H^4}$) of compounds **12** in the range of 8.0–9.0 Hz and the absence of coupling between these protons ($H^3$, $H^4$) and adjacent protons ($H^A$, $H^B$) were consistent[35,36] with the "*exo*" structure.[36] Apparently, in this case, the catalytic effect due to the lithium perchlorate[37] seemed to be the rate-promoting factor of the reaction. To the best of our knowledge, this reaction shows the first example of rate-enhancement in Diels–Alder reaction of electron-poor azadienes by perchlorate salts in nonaqueous solvents.[37,38]

In order to enhance and generalize the synthetic use of these heterodienes **3**, the reaction of electron deficient 2-azadienes **3** with enamines was explored (Scheme 7). Pyrrolidine enamine **13** was allowed to react with azadiene **3b** at room temperature for 15 h in $CHCl_3$ affording dihydropyridine derivative **16a** in excellent yield (Table 3, entry 2). A less reactive electron-rich olefin such as morpholino enamine[39] **14** needed more time (24 h, 25 °C) to give the corresponding bicyclic compound **16b** (Table 3, entry 3). Formation of compounds **16** can be explained by [4 + 2] cycloaddition reaction of heterodiene **3** and enamine to give adduct **15** followed by $\beta$-elimination of amine. Cycloadduct **15a** was even isolated when azadiene **3c** reacted with enamine **13**. Heating bicyclic

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**Table 2. Cycloadducts 10–12 Obtained**

| entry | 2-azadiene | dienophile | adducts | $R^1$ | R* | $R^5$ | $R^6$ | reaction conditions: T (°C) | reaction conditions: time (h) | yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **3a** | **7** | **10a** | H | $C_2H_5$ | $CO_2C_2H_5$ | $CO_2C_2H_5$ | 50 | 72 | 88[a] |
| 2 | **3d** | **7** | **10b** | H | $C_2H_5$ | H | $CO_2C_2H_5$ | 25 | 2 | 87[a,b] |
| 3 | **3c** | **7** | **10c** | $CO_2CH_3$ | $CH_3$ | H | $CO_2C_2H_5$ | 50 | 72 | 78[a,b] |
| 4 | **3f** | **7** | **10d** | $CH_3$ | $CH_3$ | $CH_3$ | CN | 70 | 72 | 86[a] |
| 5 | **3a** | **8** | **10e** | H | $C_2H_5$ | $CO_2C_2H_5$ | $CO_2C_2H_5$ | 25 | 20 | 95[a] |
| 6 | **3f** | **8** | **10f** | $CH_3$ | $CH_3$ | $CH_3$ | CN | 25 | 20 | 70[a] |
| 7 | **3a** | **11** | **12a** | H | $C_2H_5$ | $CO_2C_2H_5$ | $CO_2C_2H_5$ | 25 | 72 | 68[a,c] |
| 8 | **3b** | **11** | **12b** | $CH_3$ | $CH_3$ | $CO_2C_2H_5$ | $CO_2C_2H_5$ | 25 | 100 | 75[a,c] |

[a] Purified by flash chromatography. [b] Diastereoisomeric ratio (1:1) of **10/10′**. [c] LP–$Et_2O$ was used as catalyst.

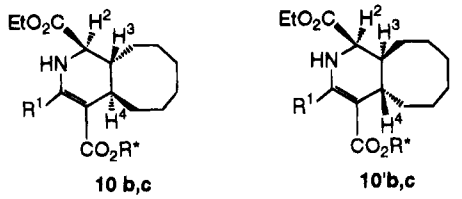
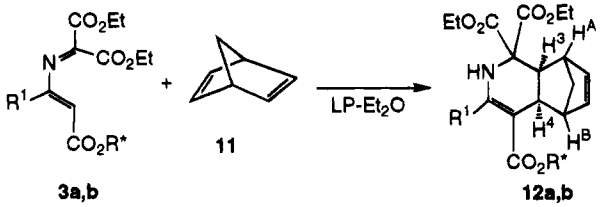
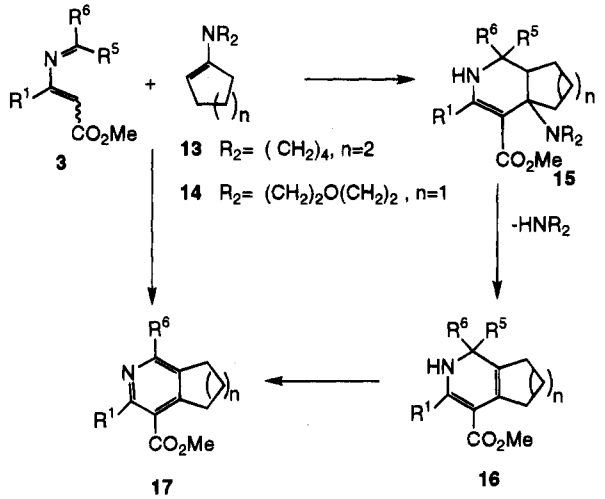



**Figure 1.** Stereisomeric *trans*-cyclooctanotetrahydropyridines **10** and **10′**.

**Scheme 6. Diels–Alder Reaction of Azadienes 3 with Norbornadiene 11**




**Scheme 7. [4 + 2] Cycloaddition Reaction of Azadienes 3 and Enamines 13 and 14**




compound **15a** in toluene (Table 3, entry 4) gave pyridine derivative **17a**. Formation of compounds **17** can be assumed by aromatization of derivatives **16** by the reaction conditions and can also be directly obtained by the reaction of azadienes **3f,e** with enamines **13** and **14** (Table 3, entries 5, 6).

Less nucleophilic enamines such as β-enamino ketones are not sufficiently reactive to participate in a [4 + 2] cycloaddition reaction with cyclic heterodienes such as 1,2,4-triazines.[40] However, acyclic 2-azadienes **3** reacted even with enamines containing an electron-withdrawing group such as β-enamino esters **18** (Scheme 8), leading to the formation of dihydropyridine derivatives **20** in a regioselective fashion. Compounds **20** were characterized on the basis of their spectroscopic data, which indicated that they were isolated as a single regioisomer. Thus, in the $^1H$ NMR spectrum of **20a** ($R^1 = R^2 = H$), 4-H resonated at $\delta_H$ 7.67 ppm as a singlet, while 2-H and 6-H showed absorptions at $\delta_H$ 5.24 and 7.70 ppm, as well resolved doublets, with coupling constants of 4.4 and 6.8 Hz, due to the influence of the proton bonded to the nitrogen atom. Both absorptions corresponding to the protons adjacent to the nitrogen atom changed to singlets when $D_2O$ was added (see Experimental Section). NOE difference experiments were combined with the information derived from $^1H$ NMR spectrum to confirm the structure of compound **20a**. At room temperature in $CDCl_3$, the selective saturation of the singlet at 5.24 ppm afforded positive NOE over the adjacent proton bonded to the nitrogen atom and absence of interaction with 4-H (Scheme 8). Both observations were compatible with structure **20a** toward the alternative regioisomer **21a** ($R^1 = R^2 = H$).

Observed selectivity of the [4 + 2] cycloaddition of azadiene **3** and enamine **18** is in full agreement with the observations obtained in prior investigations with cyclic azadienes such as 1,3-oxazin-6-ones[7,41] and 1,3,4-triazenes,[8,29,30] but is the opposite to that observed in the cycloaddition of 2-azadienes derived from cysteine methyl ester with enamines[15a] as well as in its dimerization, in which one molecule acts as the heterodiene and another as dienophile. To the best of our knowledge, we describe here the first example of this type of regioselectivity in the reaction of acyclic 2-azadienes with enamines, in which the nucleophilic carbon of the electron-rich olefin attaches to C-1 of the azadiene. Therefore, the observed results obtained in the reaction of electron poor 2-azadienes **3** with enamines, show that the complementary and noncomplementary substitution of acyclic 2-azadienes with electron-withdrawing groups (di-, tri-, and tetrasubstituted compounds), not only increase the cycloaddition rate but also enhance and control the regioselectivity of the [4 + 2] cycloaddition reaction to give only one regioisomer.

We conclude that electron deficient 2-azadienes **3** derived from β-amino acids are suitable 4π systems in [4 + 2] cycloaddition reactions with representative strained olefins such as *trans*-cyclooctene and *cis,trans*-cyclooctadiene as well as electron-rich olefins such as enamines. The reaction of azadienes **3** with norbornadiene requires, however, the presence of lithium perchlorate salts.

(40) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179.

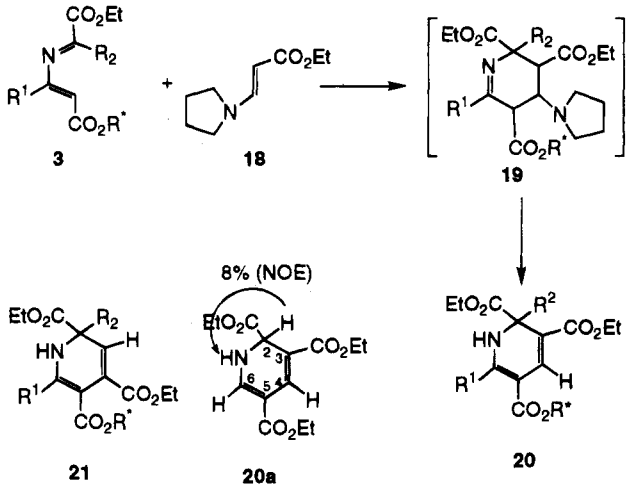
(41) Steglich, W.; Buschmann, E.; Hollitzer, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 533.

**Table 3. Pyridine Derivatives 15–17 Obtained**

| entry | 2-azadiene | dienophile | adducts | $R^1$ | $R^5$ | $R^6$ | reaction conditions: $T$ (°C) | reaction conditions: time (h) | yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **3c** | **13** | **15a** | $CO_2CH_3$ | H | $CO_2C_2H_5$ | 25 | 2 | 68 |
| 2 | **3b** | **13** | **16a** | $CH_3$ | $CO_2C_2H_5$ | $CO_2C_2H_5$ | 25 | 15 | 83 |
| 3 | **3b** | **14** | **16b** | $CH_3$ | $CO_2C_2H_5$ | $CO_2C_2H_5$ | 25 | 24 | 76 |
| 4 | **3c** | **13** | **17a** | $CO_2CH_3$ | – | $CO_2C_2H_5$ | 80 | 48 | 98[a] |
| 5 | **3f** | **13** | **17b** | $CH_3$ | – | $CH_3$ | 25 | 27 | 74 |
| 6 | **3e** | **14** | **17d** | $CH_3$ | – | $CO_2C_2H_5$ | 25 | 9 | 73 |

[a] Obtained from **15a**.

**Scheme 8. [4 + 2] Cycloaddition Reaction of Azadienes 3 and Enamine 18**




## Experimental Section

**General.**[42] Melting points are uncorrected. Standard experimental parameters for the acquisition of NOE difference were used.

**4-(Ethoxycarbonyl)-1,1-diphenyl-1-methyl-2-aza-1λ⁵-phosphabuta-1,3-diene (4a).** A solution of 0.705 g (5 mmol) of ethyl 3-azidoacrylate[31] in anhydrous $CH_2Cl_2$ (3 mL) was added dropwise to a solution of 1.001 g (5 mmol) of methyldiphenylphosphine in anhydrous $CH_2Cl_2$ (8 mL) under $N_2$, and the mixture was stirred for 2 h at rt. Evaporation of solvent under reduced pressure afforded an oil which was recrystallized from hexane/$CH_2Cl_2$ to give 1.456 g (93%) of **4a** as a white solid: mp 117–118 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.84 (dd, $^3J_{PH}$ = 30 Hz, $^3J_{HH}$ = 12 Hz, 1H), 7.65–7.47 (m, 10H), 5.26 (d, $^3J_{HH}$ = 12 Hz, 1H), 4.06 (q, 2H), 2.11 (d, $^2J_{PH}$ = 13 Hz, 3H), 1.20 (t, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 170.0 (d, $^4J_{PC}$ = 3.5 Hz), 156.8 (s), 132.8–127.0 (m), 99.4 (d, $^3J_{PC}$ = 28 Hz), 58.8 (s), 14.8 (s), 13.7 (d, $^1J_{PC}$ = 74 Hz); IR (KBr) 1680, 1267; $^{31}$P NMR ($CDCl_3$, 120 MHz) $\delta$ 8.87; MS (EI) $m/z$ 313 ($M^+$, 5). Anal. Calcd for $C_{18}H_{20}NO_2P$: C, 68.98; H, 6.44; N, 4.47. Found: C, 69.10; H, 6.46; N, 4.46.

**1,1,1-Triphenyl-3,4-bis(methoxycarbonyl)-2-aza-1λ⁵-phosphabuta-1,3-diene (4b).** Reaction of 0.925 g (5 mmol) of dimethyl azidoethylendicarboxylate[31] with 1.312 g (5 mmol) of triphenylphosphine (as described above for compound **4a**) led to the isolation of 1.991 g (95%) of **4b**, after recrystallization from hexane/$CH_2Cl_2$; mp 131–132 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.87–7.40 (m, 15H), 5.82 (d,1H, $^4J_{PH}$ = 6.5 Hz), 3.73 (s, 3H), 3.36 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.5 (s), 168.0 (s), 149.43 (s), 132.8–126.9 (m), 100.7 (d, $J_{PC}$ = 17.5 Hz), 52.1 (s), 50.5 (s). $^{31}$P NMR ($CDCl_3$, 120 MHz) $\delta$ 12.20; IR (KBr) 1723), 1720, 1250; MS (EI) $m/z$ 419 ($M^+$, 5). Anal. Calcd for $C_{24}H_{22}NO_4P$: C, 68.71; H, 5.29; N, 3.34. Found: C, 68.76; H, 5.30; N, 3.35.

**1,1-Diphenyl-1,3-dimethyl-4-(methoxycarbonyl)-2-aza-1λ⁵-phosphabuta-1,3-diene (4c).** Reaction of 0.705 g (5 mmol) of methyl 3-azidocrotonate[31] with 1.001 g (5 mmol) of diphenymethylphosphine (as described above for compound **4a**) led to the isolation of 1.425 g (91%) of **4c** after recrystallization from hexane/$CH_2Cl_2$; mp 154–155 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.72–7.36 (m, 10H), 4.46 (s, 1H), 3.40 (s, 3H), 2.38 (d, $^4J_{PH}$ = 2 Hz, 3H), 2.03 (d, $^2J_{PH}$ = 13 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.9 (d, $^4J_{PH}$ = 6 Hz), 169.0 (s), 132.0–128.4 (m), 94.7 (d, $^3J_{PC}$ = 16.6 Hz), 49.6 (s), 25.2(d, $^3J_{PC}$ = 24 Hz), 13.5 (d, $^1J_{PC}$ = 70 Hz); $^{31}$P NMR $\delta$ 8.46 ppm; IR (KBr) 1703, 1350; MS (EI) $m/z$ 313 ($M^+$, 4). Anal. Calcd for $C_{18}H_{20}NO_2P$: C, 68.98; H, 6.44; N, 4.47. Found: C, 69.11; H, 6.45; N, 4.45.

**1,1,1-Triphenyl-3-methyl-4-(methoxycarbonyl)-2-aza-1λ⁵-phosphabuta-1,3-diene (4d).** Reaction of 0.705 g (5 mmol) of methyl 3-azidocrotonoate[31] with 1.312 g (5 mmol) of triphenylphosphine (as described above for compound **4a**) led to the isolation of 1.782 g (95%) of **4d** after recrystallization from hexane/$CH_2Cl_2$: mp 141–142 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.75–7.32 (m, 15H), 4.72 (s, 1H), 3.49 (s, 3H), 2.49 (d, $^4J_{PH}$ = 2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 169.5 (d, $^4J_{PC}$ = 4 Hz), 169.0 (s), 132.7–128.1 (m), 95.9 (d, $^3J_{PC}$ = 15 Hz), 49.8 (s), 25.5 (d,$^3J_{PC}$ = 23 Hz); $^{31}$P NMR ($CDCl_3$, 120 MHz) $\delta$ 5.98; IR (KBr) 1679, 1359; MS (EI) $m/z$ 375 ($M^+$, 5). Anal. Calcd for $C_{23}H_{22}NO_2P$: C, 73.57; H, 5.91; N, 3,73. Found: C, 73.86; H, 5.90; N, 3.71.

**1,1,4-Tris(ethoxycarbonyl)-2-azabuta-1,3-diene (3a).** 0.870 g (5 mmol) of ethyl ketomalonate was added to a 0–10 °C solution of 1.566 g (5 mmol) of phosphazene **4a** in $CHCl_3$ (10 mL) under $N_2$, and the mixture was stirred at rt, until TLC indicated the disappearance of phosphazene (0.5 h). Evaporation of solvent under reduced pressure afford an oil which was chromatographed on silica gel ($Et_2O$/hexane: 1/3) to give 1.247 g (92%) of a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.76 (d, $^3J_{HH}$ = 13 Hz, 1H), 6.02 (d, $^3J_{HH}$ = 13 Hz, 1H), 4.18 (q, 4H), 4.01 (q, 2H), 1.15 (t, 6H), 1.07 (t, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 165.2, 160.7, 154.4, 146.8, 123.1, 62.7, 60.7, 14.0, 13.8; IR (film) 1746, 1750, 1685; M/S (EI) $m/z$ 271.1 ($M^+$, 10). Anal. Calcd for $C_{12}H_{17}NO_6$: C,53.12; H, 6.32; N, 5.17. Found: C, 53.21; H, 6.34; N, 5.18.

**1,1-Bis(ethoxycarbonyl)-3-methyl-4-(methoxycarbonyl)-2-azabuta-1,3-diene (3b).** Reaction of 1.566 g (5 mmol) of **4c** or 1.876 g (5 mmol) of **4d** with 0.870 g (5 mmol) of ethyl ketomalonate (as described for compound **3a**) for 0.5 h (for **4c**) or 20 h (for **4d**) led to the formation of compound **3b**. Evaporation of solvent under reduced pressure afford an oil wich was chromatographed on silica gel ($Et_2O$/hexane: 1/3) to give 1.288 g (95%) of a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.06 (s, 1H), 4.31 (q, 4H), 3.63 (s, 3H), 2.32 (s, 3H), 1.29 (t, 6H); $^{13}$ C NMR (75 MHz, $CDCl_3$) $\delta$ 166.1, 162.6, 160.2, 149.5, 100.2, 62.9, 62.3, 50,9, 16.9, 13.70; IR (film) 1780, 1750, 1682; M/S (EI) $m/z$ 271 ($M^+$, 5). Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.12; H, 6.32; N, 5.17. Found: C, 53.02; H, 6.31; N, 5.19.

**1-(Ethoxycarbonyl)-3,4-bis(methoxycarbonyl)-2-azabuta-1,3-diene (3c).** Reaction of 2.095 g (5 mmol) of phosphazene **4b** with 0.510 g (5 mmol) of freshly distilled ethyl glyoxalate (as described for compound **3a**) for 4 h led to the formation of compound **3c**. The reaction product is unstable to distillation or chromatography and therefore was not isolated and used for the following reactions: $^1$H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3c** + $Ph_3PO$) $\delta$ 7.78–7.40 (m, 16 H), 6.16 (s, 1H), 4.25 (q, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 1.22 (t, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3c** + $Ph_3PO$) $\delta$ 174.5, 169.3, 167.8, 163.6, 147.3, 133.2–128.4 (m), 94.3, 62.4, 52.8, 51.1, 13.9.

(42) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron* **1994**, *50*, 12727.

**1,4-Bis(ethoxycarbonyl)-2-azabuta-1,3-diene (3d).** Reaction of 1.566 g (5 mmol) of **4a** with 0.510 g (5 mmol) of freshly distilled ethyl glyoxalate (as described for compound **3a**) for 0.5 h led to the formation of compound **3d**. The crude reaction product was used for the following reactions: $^1$H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3d** + $Ph_2CH_3PO$) $\delta$ 8.17−7.28 (m, 12H), 6.12 (d, $^3J_{HH}$ = 13 Hz, 1H), 4.31−3.80 (m, 4H), 1.83 (d, $^2J_{PH}$ = 13 Hz, 3H), 1.29−0.92 (dt, 6H); $^{13}$ C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3d** + $Ph_2CH_3PO$) $\delta$ 170,6, 157.5, 148.3, 133.8−127.0 (m), 107.5, 61.2, 59.3, 14.5, 14.4, 13.6 (d, $^1J_{PC}$ = 74 Hz).

**1-(Ethoxycarbonyl)-3-methyl-4-(methoxycarbonyl)-2-azabuta-1,3-diene (3e).** Reaction of 1.556 g (5 mmol) of **4c** or 1.876 g (5mmol) of **4d** with 0.510 g (5 mmol) of freshly distilled ethyl glyoxalate (as described for compound **3a**) for 2 h (for **4c**) or 6 h (for **4d**) led to formation of compound **3e**. The crude reaction product was used for the following reactions: $^1$H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3e** + $Ph_3PO$) $\delta$ 7.97−7.29 (m, 16H), 5.69 (s, 1H), 4.07−3.44 (q, 2H), 3.64 (s, 3H), 2.16 (s, 3H), 1.17 (t, 3H); $^{13}$ C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3e** + $Ph_3PO$) $\delta$ 175.2, 168.5, 165.1, 132.0−127.8 (m), 108.9, 60.3, 50.2, 24.7, 14.0.

**1-Cyano-1,3-dimethyl-4-(methoxycarbonyl)-2-azabuta-1,3-diene (3f).** Reaction of 1.566 g (5 mmol) of **4c** or 1.870 g (5 mmol) of **4d** with 0.345 (5 mmol) of pyruvonitrile (as described for compound **3a**) for 0.5 h (for **4c**) or 20 h (for **4d**) led to the formation of compound **3f**. Azadiene **3f** was detected in the crude of reaction mixture by $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.39 (s, 1H), 3.63 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H) and by $^{13}$C NMR(75 MHz, $CDCl_3$) $\delta$ 166.5, 163.2, 138.1, 118.2, 102.9, 51.0, 25.5, 17.2. The reaction product was not isolated and was used for the following reactions. Evaporation of solvent under reduced pressure affords an oil which was chromatographed on silica gel ($Et_2O$/hexane: 1/3) to give 0.747 (90%) of a oil, identified as **4-cyano-2-methyl-1-(methoxycarbonyl)-3-azapenta-1,4-diene (6)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.30 (s, 1H), 5.44 (s, 1H), 5.42 (s, 1H); 4.74 (s, 1H); 3.58 (s, 3H), 2.12 (s, 3H); $^{13}$C NMR(75 MHz, $CDCl_3$) $\delta$ 170.2, 156.1, 118.3, 117.6, 115.9, 89.8, 50.7, 19.9; IR (film) 3385, 2220, 1729; M/S (EI) $m/z$ 166 ($M^+$, 13). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.81; H, 6.07; N, 16.86. Found: C, 57.76; H, 6.08; N, 16.88.

**Triethyl *trans*-3,4-Hexamethylene-1,2,3,4-tetrahydro-2,2,5-pyridinetricarboxylate (10a).** To a solution of 1.356 g (5 mmol) of 2-azadiene **3a** in dry $CHCl_3$ (10 mL) was added 0.550 g (5 mmol) of *trans*-cyclooctene (**7**), and the mixture was warmed at 50 °C for 72 h under $N_2$. Evaporation of solvent under reduced pressure and chromatographed on silica gel ($Et_2O$/hexane: 1/4) gave 1.677 g (88%) of **10a** as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38 (d, $^3J_{HH}$ = 6 Hz, 1H),[43] 5.23 (d, $^3J_{HH}$ = 6 Hz, 1H), 4.26−3.98 (m, 6H), 2.74 (m, 1H), 2.52 (m, 1H), 2.18−1.09 (m, 21H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.9,168.2, 167.9, 140.5, 102.6, 68.1, 61.9, 61.8, 58.7, 37.4, 32.0, 29.6−25.8 (m, 6C), 14.2, 13.8, 13.7; IR (film) 3343, 1736, 1701, 1676; M/S (EI) $m/z$ 381 ($M^+$, 14). Anal. Calcd for $C_{20}H_{31}NO_6$: C, 62.96; H, 8.20; N,3.67. Found: C, 62.94; H, 8.18; N, 3.65.

**Diethyl *trans*-3,4-Hexamethylene-1,2,3,4-tetrahydro-2,5-pyridinedicarboxylate (10b).** To a solution of 2-azadiene **3d** (5 mmol) in dry $CHCl_3$ (10 mL) was added 0.550 g (5 mmol) of *trans*-cyclooctene (**7**), and the mixture was stirred at rt for 2 h under $N_2$. Evaporation of solvent under reduced pressure and chromatography on silica gel ($Et_2O$/hexane: 1/5) gave 1.345 g (87%) of a 1:1 diastereomeric mixture of **10b/10'b** as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.46 (d, $^3J_{HH}$ = 5.3 Hz, 1H)[43] and 4.97 (d, $^3J_{HH}$ = 5.3 Hz, 1H) for **10b**, 7.44 (d,$^3J_{HH}$ = 5.7 Hz, 1H)[43] and 4.64 (d, $^3J_{HH}$ = 5.7 Hz, 1H) for **10'b**, 4.22−4.03 (m, 8H), 3.73 (d, $^3J_{HH}$ = 4.2 Hz, 1H) for **10b**, 3.36 (d, $^3J_{HH}$ = 7.8 Hz, 1H) for **10'b**, 2.65−2.49 (m, 2H), 2.28−2.22 (m, 2H), 2,19−1.28 (m, 36 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.3, 171.4, 168.6, 168.2, 142.4, 141.5, 104.6, 102.1, 61.2, 61.0, 59.3, 58.9, 55.4, 39.1, 36.6, 33.5, 33.4, 31.8, 31.4, 31.3, 27.8−25.3 (m, 9C), 14.4, 14.2, 14.1; IR (film) 3360, 1740; M/S (CI) $m/z$ 310.2 (M + 1, 44). Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.98; H, 8.80; N, 4.53. Found: C, 66.00; H, 8.78; N, 4.52.

(43) The absorption became a singlet after $D_2O$ addition.

**Dimethyl 6-(Ethoxycarbonyl)-*trans*-4,5-hexamethylene-1,4,5,6-tetrahydro-2,3-pyridinedicarboxylate (10c).** To a solution of 2-azadiene **3c** (5 mmol) in dry $CHCl_3$ (10 mL) was added 0.550 g (5 mmol) of *trans*-cyclooctene (**7**) and the mixture was stirred at rt for 36 h under $N_2$. Evaporation of solvent under reduced pressure and chromatography on silica gel ($Et_2O$/hexane: 1/3) gave 1.377 g (78%) of a 1:1 distereomeric mixture of **10c/10'c** as a pale yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.87 and 4.51 (s, 1H), 4.27−4.18 (m, 4H), 3.81 and 3.77 (s, 3H), 3.73 (d, $^3J_{HH}$ = 4.2 Hz, 1H) for **10c**, 3.71 and 3.68 (s, 3H), 3.43 (d, $^3J_{HH}$ = 7.6 Hz, 1 H) for **10'c**, 2.67−2.51 (m, 2H), 2.41−2.21 (m, 2 H), 2.03−1.27(m, 30 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.4, 171.9, 168.8, 167.5, 161.2, 165.4, 139.0, 136.6, 112.2, 111.9, 61.5, 61.3, 59.9, 55.9, 52.7, 52.6, 52.2, 51.6, 39.2, 38.9, 35.8, 33.2, 31.8, 31.4, 31.3, 27.4−25.2 (m, 9C), 14.2, 14.1; IR (film) 3281, 1742, 1740, 1720, 1718; M/S (EI) $m/z$ 353 ($M^+$, 13). Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.16; H, 7.71; N, 3.97. Found: C, 61.22; H, 7.73; N, 3.96.

**Methyl 2-Cyano-*trans*-3,4-hexamethylene-1,2,3,4-tetrahydro-2,6-dimethyl-5-pyridinecarboxylate (10d).** To a solution of 2-azadiene **3f** (5 mmol) in dry $CHCl_3$ (10 mL) was added 0.550 g (5 mmol) of *trans*-cyclootene (**7**), and the mixture was warmed at 70 °C for 72 h under $N_2$. Evaporation of solvent under reduced pressure and chromatography on silica gel ($Et_2O$/hexane: 1/4) gave 1.188 g (86%) of **10d** as a white crystalline solid: mp 86−87 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.08 (s, 1H), 3.66 (s, 3H), 2,68 (m, 1H), 2.15 (s, 3H), 2.10−1.19 (m, 16 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.7, 150.2, 120.8, 107.1, 55.0, 50.6, 49.7, 37.0, 36.8, 30.4, 26.9, 26.2, 25.1, 24.9, 24.1, 20.5; IR (KBr): 3315, 1731; M/S (EI) $m/z$ 276 ($M^+$, 10). Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.52; H, 8.76; N, 10.14. Found: C, 69.63; H, 8.74; N, 10.12.

**Triethyl *trans*-3,4-(*cis*-3-Hexenylene)-1,2,3,4-tetrahydro-2,2,5-pyridinetricarboxylate (10e).** To a solution of 1.356 g (5 mmol) of 2-azadiene **3a** in $CHCl_3$ (10 mL) was added 0.540 g of *cis,trans*-cyclooctadiene (**8**), and the mixture was stirred a rt for 20 h under $N_2$. Evaporation of solvent under reduced pressure and chromatography on silica gel (hexane) gave 1.801 g (95%) of **10e** as a white crystalline solid: mp 79−81 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.41 (d, $^3J_{HH}$ = 6 Hz, 1H),[43] 5.84−5.58 (m, 2H), 4.95 (d, $^3J_{HH}$ = 6 Hz, 1H), 4.29−4.03 (m, 6H), 2.86−2.79 (m, 1H), 2.62−2.53 (m, 1H), 2.50−2.01 (m, 6H), 1.72−1.12 (m, 11H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 169.0, 168.7, 168.2, 140.5, 131.2, 129.1, 107.9, 68.6, 62.3, 61.9, 50.3, 42.6, 35.6, 32.4, 29.6, 26.0, 25.2, 14.4, 13.9; IR (KBr) 3335,1739, 1699, 1698; M/S (EI) $m/z$ 379 ($M^+$, 5). Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.29, H, 7.71, N, 3.70. Found: C, 63.20; H, 7.72, N, 3.69.

**Dimethyl 2-Cyano-*trans*-3,4-(*cis*-3-hexenylene)-1,2,3,4-tetrahydro-2,6-dimethyl-5-pyridinedicarboxylate (10f).** To a solution of 2-azadiene **3f** (5 mmol) in dry $CHCl_3$ (10 mL) was added 0.550 g (5 mmol) of *cis,trans* cyclooctadiene (**8**), and the mixture was stirred a rt for 20 h under $N_2$. Evaporation of solvent under reduced pressure and chromatography on silica gel (hexane) gave 0.960 g (70%) of **10f** as a white crystalline solid: mp 122−123 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.75−5.59 (m, 2H), 3.81 (s, 1H), 3.69 (s, 3H), 2.71−2.66 (m, 1H), 2.59−2.39 (m, 1H), 2.23 (s, 3H), 2.25−1.60 (m, 7H), 1.58 (s, 3H), 1.02−1.00 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.4, 152.3, 130.7,129.3, 120.9, 108.9, 55.5, 50.9, 50.1, 36.8, 36.2, 30.1, 25.8, 25.4, 23.6, 21.23; IR (KBr) 3321, 2220, 1700; M/S (EI) $m/z$ 274 ($M^+$, 5). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.03; H, 8.09; N, 10.22. Found: C, 69.98; H, 8.10; N, 10.23.

**Triethyl 3,4-(4-Cyclopenten-1,3-ylene)-1,2,3,4-tetrahydro-2,2,5-pyridinetricarboxylate (12a).** To a solution of 1.356 g (5 mmol) of 2-azadiene **3a** in $Et_2O$ (10 mL) was added 0.450 g (5 mmol) of norbornadiene (**11**) and 5.32 g (0.050 mol) of $LiClO_4$, and the mixture was stirred at rt for 72 h under $N_2$. The reaction mixture was poured on $CH_2Cl_2$ (20 mL), washed with a saturated solution of $NaHCO_3$, and dried ($MgSO_4$). Evaporation of solvent under reduced pressure and chromatography on silica gel (hexane) gave 1.235 g (68%) of **12a** as a white crystalline solid: mp 79−80 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 7.45 (d, $^3J_{HH}$ = 6.5 Hz, 1 H),[43] 6.20 (s, 2H), 5.05 (d, $^3J_{HH}$ = 6.5 Hz), 4.31 (q, 2H), 4.16−4.06 (m, 4H) 2.87 (s, 1H), 2.74 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 2.58 (d, $^3J_{HH}$ = 8.5 Hz,

1H), 2.33 (s, 1H), 1.56 (d, $^2J_{HH}$ = 8.8 Hz, 1H), 1.31–1.14 (m, 10 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.7, 168.4, 167.4, 141.9, 138.4, 138.0, 107.6, 68.8, 62.1, 59.2, 50.8, 45.4, 44.6, 43.9, 34.7, 14.36, 13.9, 13.8; IR (KBr) 3414, 1749, 1689; M/S (EI) *m/z* 363 ($M^+$, 5). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.78; H, 6.94; N, 3.86. Found: C, 62.74; H, 6.93; N, 3.87.

**Diethyl 3,4-(4-Cyclopenten-1,3-ylene)-1,2,3,4-tetrahydro-6-methyl-5-(methoxycarbonyl)-2,2-pyridinedicarboxylate (12b).** To a solution of 1.356 g (5 mmol) of 2-azadiene **3b** in $Et_2O$ (10 mL) were added 0.450 g (5 mmol) of norbornadiene (**11**) and 5.32 g (0.050 mol) of $LiClO_4$, and the mixture was stirred at rt for 100 h under $N_2$. The reaction mixture is poured on $CH_2Cl_2$ (20 mL), washed with a satured solution of $NaHCO_3$, and dried ($MgSO_4$). Evaporation of solvent under reduced pressure and chromatographed on silica gel (hexane) gave 1.816 g (75%) of **12b** as a yellow oil: $^1$H NMR (250 MHz, $CDCl_3$) δ 6.21 (s, 2H), 4.76 (s, 1H), 4.31 (q, 2H), 4.12 (q, 2H), 3.65 (s, 3H), 2.80 (s, 1H), 2.77 (d, $^3J_{HH}$ = 9 Hz, 1H), 2.64 (d, $^3J_{HH}$ = 9 Hz, 1H), 2.34 (s, 1H), 2.24 (s, 3H) 1.64 (d, $^2J_{HH}$ = 9 Hz, 1H), 1.32–1.26 (m, 4H), 1.16 (t, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.6, 168.5, 153.4, 138.6, 138.0, 104.1, 69.2, 62.4, 62.2, 52.1, 50.6, 45.8, 44.8, 43.9, 36.7, 21.3, 14.07, 13.8; IR (KBr) 3421, 3381, 1749,1703; M/S (EI) *m/z* 363 ($M^+$, 5). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.78; H, 6.94; N, 3.86. Found: C, 62.79; H, 6.95; N, 3.85.

**Dimethyl 6-(Ethoxycarbonyl)-4,5-tetramethylene-4-pyrrolidinyl-1,4,5,6-tetrahydro-2,3-pyridinedicarboxylate (15a).** To a solution of azadiene **3c** (5 mmol) in $CHCl_3$ (10 mL) was added 0.835 g (5 mmol) of enamine **13**, and the mixture was stirred at rt for 2 h under $N_2$. The solvent was evaporated under reduced pressure, and the resulting brown oil was purified by silica gel column chomatography eluting with hexane to give 1.340 g (68%) of **15a** as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 6.23 (s, 1H), 4.24 (q, 2 H), 3.83 (s, 3 H), 3.67 (s, 3 H), 3.44 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 2.60–2.34 (m, 5H), 1.93–1.81 (m, 4H), 1.74–1.54 (m, 8 H), 1.31 (t, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.5, 165.5, 162.8, 146.6, 98.75, 91.2, 70.9, 61.5, 52.8, 51.3, 44.3, 41.9, 41.1,36.8–26.7 (m, 6C), 14.1; IR (film) 3348, 1755, 1742, 1698; MS (EI) *m/z* 394 ($M^+$, 10), 323 ($M^+$ – 71, 60). Anal. Calcd for $C_{20}H_{30}N_2O_6$: C, 60.88; H, 7.67; N, 7.10. Found: C, 60.81; H, 7.65; N, 7.11.

**Diethyl 6-Methyl-5-(methoxycarbonyl)-1,2,5,6,7,8-hexahydro-1,1-isoquinolinedicarboxylate (16a).** To a solution of 1.365 g (5 mmol) of azadiene **3b** in $CHCl_3$ (10 mL) was added 0.835 g (5 mmol) of enamine **13**, and the mixture was stirred at rt for 15 h under $N_2$. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chomatography eluting with $Et_2O$/hexane (1/5) to give 1.457 g (83%) of **16a** as a white solid: mp 107–108 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 1 H), 4.29–4.16 (dq, 4 H), 3.67 (s, 3 H), 2.38–2.35 (m, 2 H), 2.23 (s, 3 H), 2.18–2.15 (m, 2 H), 1.67–1.57 (m, 4 H), 1.27 (t, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.0, 167.9, 147.9, 129.5, 115.1, 103.1, 69.7, 62.2, 50.43, 27.8, 26.5, 22.7, 22.3, 20.3, 14.0; IR (KBr) 3316, 1745, 1672; MS (EI) *m/z* 351 ($M^+$, 16). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.51; H, 7.18; N, 3.99. Found: C, 61.66; H, 7.19; N, 3.98.

**Diethyl 6-Methyl-5-(methoxycarbonyl)-3,4-trimethylene-1,2-dihydro-2,2-pyridinedicarboxylate (16b).** To a solution of 1.365 g (5 mmol) of azadiene **3b** in $CHCl_3$ (10 mL) was added 0.845 g (5 mmol) of enamine **14**, and the mixture was stirred at rt for 24 h under $N_2$. The solvent was evaporated under reduced pressure, and the resulting brown oil was purified by silica gel column chomatography eluting with hexane to give 1.281 g (76%) of **16b** as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1 H), 4.22–4.13 (dq, 4 H), 3.60 (s, 3 H), 2.70 (dt, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 7.1 Hz, 2 H), 2.50 (t, $^3J_{HH}$ = 7.1 Hz, 2 H), 2.30 (s, 3 H), 1.83 (t, $^3J_{HH}$ = 7.4 Hz, 2 H), 1.26–1.19 (dt, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.1, 168.8, 167.4, 151.2, 136.6, 117.2, 96.25, 69.1, 62.1, 50.0, 35.1, 32.9, 22.8, 20.7, 13.8; IR (film) 3362, 1749, 1686; MS (EI) m/z 337 ($M^+$, 30). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.51; H, 6.88; N, 4.15. Found: C, 60.83; H, 6.86; N, 4.17.

**Dimethyl 1-(Ethoxycarbonyl)-5,6,7,8-tetrahydro-5,6-isoquinolinedicarboxylate (17a).** A solution of 1.183 g of **15a** (3 mmol) in $CHCl_3$ (10 mL) was heated at 80 °C for 48 h under $N_2$. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chomatography eluting with hexane to give 0.944 g (98%) of **17a** as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 4.38 (q, 2 H), 3.91(s, 3H), 3.90 (s, 3H), 2.95 (t, $^3J_{HH}$ = 6 Hz, 2 H), 2.75 (t, $^3J_{HH}$ = 6 Hz, 2H), 1.79–1.75 (m, 4 H), 1.36 (t, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.4, 165.5, 164.7, 149.5, 146.6, 142.0, 136.7, 133.3, 62.1, 53.2, 52.8, 26.5, 26.3, 21.5, 21.1, 14.1; IR (film) 1739, 1733; MS (EI) *m/z* 321 ($M^+$, 13). Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.79; H, 5.96; N, 4.36. Found: C, 59.81; H, 5.93; N, 4.37.

**Methyl 1,3-Dimethyl-5,6,7,8-tetrahydro-4-isoquinolinecarboxylate (17b).** To a solution of azadiene **3f** (5 mmol) in $CHCl_3$ (10 mL) was added 0.835 g (5 mmol) of enamine **13**, and the mixture was stirred at rt for 67 h under $N_2$. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chomatography eluting with $Et_2O$/hexane (1/3) to give 0.811 g (74%) of **17b** as a white solid: mp 56–57 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3 H), 2.58 (t, $^3J_{HH}$ = 6 Hz, 2 H), 2.50 (t, $^3J_{HH}$ = 6 Hz, 2 H), 2.35 (s, 3 H), 2.33 (s, 3 H), 1.72–1.63 (m, 4 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ.169.4, 157.1, 150.0, 142.9, 127.7, 126.6, 51.8, 26.8, 25.7, 22.2, 22.1, 21.7; IR (KBr) 1729; MS (EI) *m/z* 219 ($M^+$, 60). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.19; H, 7.82; N, 6.39. Found: C, 71.22; H, 7.85; N, 6.38.

**Ethyl 6-Methyl-5-(methoxycarbonyl)-3,4-trimethylene-2-pyridinecarboxylate (17c).** To a solution of azadiene **3e** (5 mmol) in $CHCl_3$ (10 mL) was added 0.845 g (5 mmol) of enamine **14**, and the mixture was stirred at rt for 9 h under $N_2$. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chomatography eluting with hexane to give 0.960 g (73%) of **17c** as a white solid: mp 53–53 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 4.44 (q, 2 H), 3.92 (s, 3 H), 3.26 (t, $^3J_{HH}$ = 7.6 Hz, 2 H), 3.04 (t, $^3J_{HH}$ = 7.6 Hz, 2 H), 2.69 (s, 3 H), 2.12–2.03 (m, 2 H), 1.42 (t, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.7, 165.4, 156.8, 155.1, 143.8, 140.8, 126.8, 61.7, 52.2, 32.9, 32.3, 24.5, 23.6, 14.3; IR (KBr) 1723; MS (EI) *m/z* 263 ($M^+$, 30). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.77; H, 6.51; N, 5.33.

**Triethyl 1,2-Dihydro-2,3,5-pyridinetricarboxylate (20a).** To a solution of azadiene **3d** (5 mmol) in $CHCl_3$ (10 mL) was added 0.925 g (5 mmol) of enamine **18**, and the mixture was stirred at rt for 88 h under $N_2$. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chomatography eluting with $Et_2O$/hexane (1/1) to give 0.951 g (64%) of **20a** as a yellow solid: mp 77–78 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, $^3J_{HH}$ = 6.8 Hz, 1H),[43] 7.67 (s, 1H), 6.02 (m, 1H), 5.24 (d, $^3J_{HH}$ = 4.4 Hz, 1H),[43] 4.28–4.11 (m, 6H), 1.34–1.20 (m, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.9, 165.9, 165.7, 147.6, 133.4, 108.1, 98.7, 61.5, 60.3, 59.6, 52.7, 14.3, 14.2, 13.9; IR (KBr) 3268, 1747, 1689; MS (EI) *m/z* 297 ($M^+$, 5). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.54; H, 6.45; N, 4.71. Found: C, 56.39; H, 6.46; N, 4.69.

**Triethyl 6-Methyl-5-(methoxycarbonyl)-1,2-dihydro-2,2,3-pyridinetricarboxylate (20b).** To a solution of 1.365 g (5 mmol) of azadiene **3b** in $CHCl_3$ (10 mL) was added 0.925 g (5 mmol) of enamine **18**, and the mixture was stirred at 80 °C for 74 h under $N_2$. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chomatography eluting with hexane to give 1.310 g (71%) of **20b** as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 6.20 (s, 1 H), 4.31–4.16 (m, 6H), 3.71 (s, 3H), 2.44 (s, 3H), 1.30–1.21 (m, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.5, 165.9, 165.1, 157.6, 135.2, 108.8, 96.7, 67.3, 62.7, 60.4, 50.9, 20.7, 14.27, 13.8; IR (film) 3302, 1743, 1695; MS (EI) *m/z* 369 ($M^+$, 5). Anal. Calcd for $C_{17}H_{23}NO_8$: C, 55.26; H, 6.28; N, 3.79. Found: C, 55.31; H, 6.29; N, 3.78.

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