Synthesis and Reactions of Haloazodienes. A New and General Synthesis of Substituted Pyridazines

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The reaction of dihalohydrazones with Hünig's base gives 1-carbethoxy-3-phenyl-4-haloazodienes *in-situ*, which were found to combine with a variety of electron rich olefins to yield halo-substituted tetrahydropyridazines (Scheme 2 and Table 1). These haloazodiene cyclizations are best characterized as inverse electron demand, 4 + 2 hetero Diels−Alder reactions that maintain a high degree of regio- and stereochemical control (Schemes 5 and 6). The chloro-substituted tetrahydropyridazines that are formed give high yields of substituted pyridazines upon treatment with base (Table 1). The sequence of a chloroazodiene cyclization to a tetrahydropyridazine followed by an aromatization constitutes a new and general synthesis of substituted pyridazines. In contrast to the haloazodiene cyclizations, the novel cyclization reactions of the *in-situ* generated 1-carbethoxy-3-phenyl-4,4-dichloroazodiene were found to give *N*-aminopyrroles and pyridazines when combined with acyclic enamines (Table 3). However, reactions with cyclic enamines gave the *N*-aminopyrroles, pyridazines, a dihydropyridazine as products as well as the noncyclized enamine intermediates (Table 4). The noncyclized enamines could be converted to the *N*-aminopyrroles simply upon heating to higher temperatures, indicating a stepwise mechanism (Schemes 8 and 9). The examples described here are the first reported cyclization reactions for dichloroazodienes.

Introduction

A number of reports have appeared describing the generation and reactions of nonhalogenated azodienes with electron rich olefins.[1−9] These reactions lead mainly to the six-membered tetrahydropyridazine products or to the five-membered *N*-aminopyrrole products and are formal 4 + 2 or 3 + 2 cyclizations of an azodiene with an olefin. Derivatives prepared in this fashion are not set up for conversion directly to the corresponding aromatized pyridazines unless an external oxidant or strong base is utilized which limits their utility for the preparation of these compounds. Previous attempts to introduce a labile group into the tetrahydropyridazine followed by an aromatization to give pyridazines are described, but these reactions are limited in scope.[1,10,11] Also, extensively studied is the addition of active methylene compounds to nonhalogenated azodienes followed by cyclization and elimination of water to give *N*-aminopyrroles.[12] However, this sequence is not useful for the synthesis of pyridazines. We have an interest in 3-substituted pyridazines due to their unique biological activity[13] and sought to develop a new and general synthesis of these molecules. We envisioned introducing a labile group into the tetrahydropyridazine from a 4-haloazodiene.[14,15] This labile halogen could then be eliminated to produce the aromatized pyridazine providing that the other groups on the tetrahydropyridazine were stable to the reaction conditions.

We wish to report here a new and general procedure for the preparation of pyridazines that relies on the cyclization of a 1-carbethoxy-3-phenyl-4-haloazodiene with an electron rich olefin and subsequent aromatization with base.[16] These haloazodiene cyclizations are best characterized as inverse electron demand, 4 + 2 hetero Diels−Alder reactions that maintain a high degree of regio- and stereochemical control. Unlike the precedented syntheses of the pyridazine ring,[17] the azodiene route allows for the incorporation of many different types of functional groups. The sequence of a haloazodiene cyclization to a halotetrahydropyridazine followed by an aromatization reaction constitutes a new and general synthesis of substituted pyridazines.

Also reported, and in contrast to the 4-haloazodiene cyclizations described above, are the novel cyclization reactions of 1-carbethoxy-3-phenyl-4,4-dichloroazodienes

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(14) Two reports of a cycloaddition reaction involving a chloroazodiene have appeared, but these products were not elaborated to pyridazines (see also reference 15). Gilchrist, T. L.; Sanchez Romero, O. A.; Wasson, R. C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 353−359.

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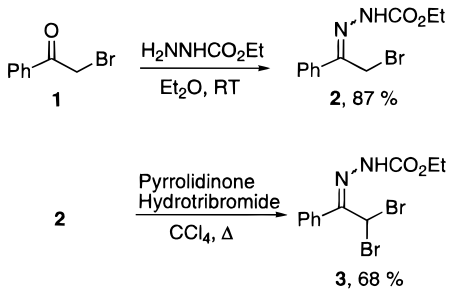
Scheme 1



which yield mixtures of products.[18] *N*-Aminopyrroles, pyridazines, a dihydropyridazine and noncyclized enamine intermediate are obtained from these dichloroazodiene cyclizations depending on the electron rich olefin that is used. These results suggest a stepwise addition of the electron rich olefin to the dichloroazodiene. No reports of successful cyclization reactions with dichloroazodienes have appeared; however, several authors mention the preparation and addition elimination reactions of these compounds.[19]

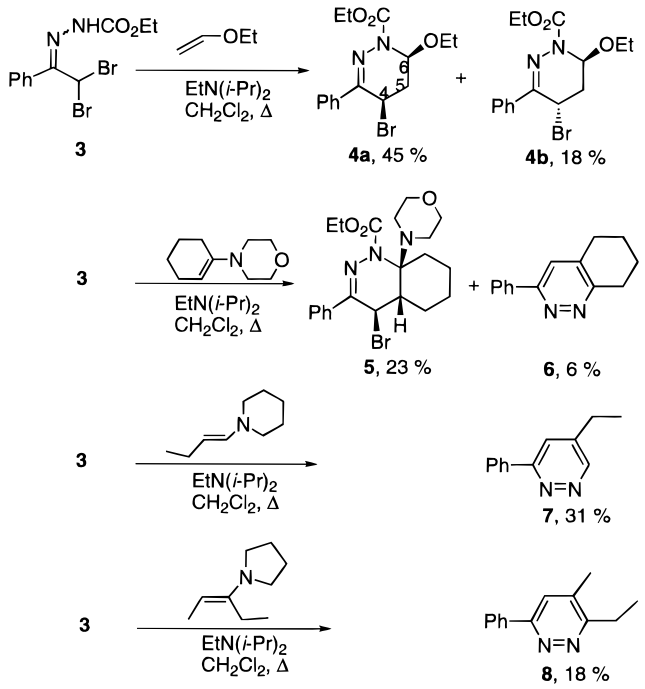
Results and Discussion

Synthesis and Reactions of Monohaloazodienes. The first step in developing a viable route to pyridazines required the preparation of a dihalohydrazone. Our initial attempts centered around the preparation of dibromohydrazone **3** (Scheme 1). Treatment of 2-bromoacetophenone with ethyl carbazate gave **2** in 87% yield. Further bromination of **2** with pyrrolidinone hydrotribromide gave the dibromohydrazone **3** in 68% yield.

This material served as the precursor to a bromo-substituted azodiene upon treatment with base.

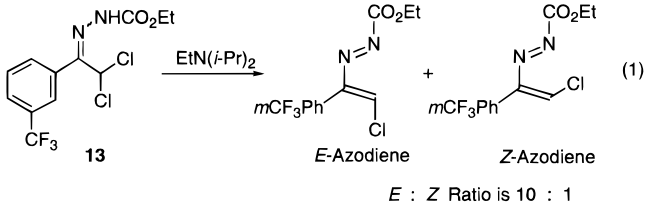
The azodiene was usually generated *in-situ* from the dibromohydrazone by treatment with a hindered base such as Hünig's base. Treatment of **3** with Hünig's base in refluxing CH_2Cl_2 produced a deep red color (presumed to be the bromoazodiene) which was discharged in the presence of the electron rich olefin,[20] indicating that a reaction had taken place. Combination of the azodiene derived from **3** with ethyl vinyl ether gave *cis*-tetrahydropyridazine **4a** in 45% yield and *trans*-tetrahydropyridazine **4b** in 18% yield (Scheme 2). Reaction of the morpholine enamine of cyclohexanone with the azodiene generated from **3** gave a mixture of diastereomers that was not stable at rt after isolation. One compound crystallized from this mixture in 23% yield which was the *cis*-isomer **5**. The pyridazine **6** was also isolated from this reaction in 6% yield. Treatment of **3** with Hünig's base followed by the enamines of either butanal or 3-pentanone gave the pyridazine products **7** in 31% yield and **8** in 18% yield. No tetrahydropyridazine products were isolated from these reactions. Apparently the bromotetrahydropyridazines were not stable under the reaction conditions in some cases and were aromatized directly to the pyridazine products.

Scheme 2



In systems such as the disubstituted tetrahydropyridazines **4a** and **4b**, the group at the 6-position is in an axial position allowing the molecule to adopt a half-chair conformation.[2] The stereochemical assignments for **4a** and **4b** could then be made based on the differences in coupling constants for the H-4 proton. The equatorial proton H-4 of compound **4a** is a doublet which appears at δ 5.01 (400 MHz NMR spectrum) and has a 6.0 Hz coupling to the axial proton H-5. The axial proton H-4 of compound **4b** is a doublet of doublets which appears at δ 5.24 and has a 15.0 Hz coupling to the axial H-5 proton and a 8.0 Hz coupling to the equatorial H-5 proton. The large diaxial coupling constant of 15.0 Hz for compound **4b** is what distinguishes the *trans*-isomer **4b** from the *cis*-isomer **4a**. This phenomenon has proven to be general for all of the 4,6-disubstituted tetrahydropyridazines that we have prepared and is consistent with what is reported for related systems.[2]

At this point we elected to prepare dichlorohalohydrazones as starting materials for the azodiene reaction in hope of generating stable tetrahydropyridazine intermediates that could be isolated and studied. We found that high yields of dichlorohydrazones **12** and **13** were obtained from acetophenones **9** by treatment with ethyl carbazate followed by 2 equiv of NCS (Scheme 3). The dichlorohydrazones usually existed as a mixture of *E* and *Z* isomers. When hydrazone **13** was treated with Hünig's base in an NMR tube, the solution turned deep red and gave what was identified as a 10:1 mixture of the *E*-azodiene to the *Z*-azodiene as shown in eq 1. The 400 MHz NMR signal for the olefinic proton of the *E*-isomer



was at 7.60 ppm while the *Z*-isomer was at 6.84 ppm. One would expect the proton of the *Z*-isomer to be at

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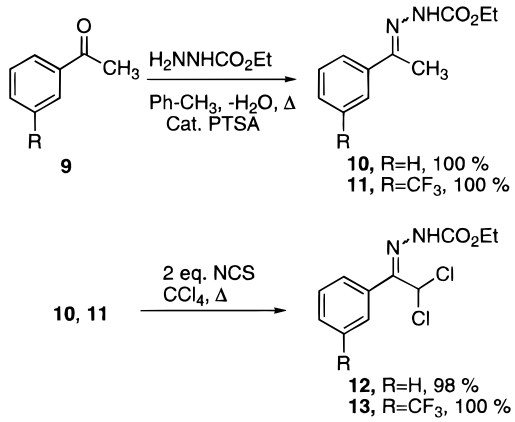
Scheme 3



higher field since it is in the shielding region of the phenyl ring.[14] The next step was to study the reaction of the 4-chloroazodienes with electron rich olefins.

The dichlorohydrazones **12** and **13** were treated with Hünig's base to generate the 4-chloroazodiene *in-situ*. Reaction of the 4-chloroazodiene with a variety of electron rich olefins[20] gave the tetrahydropyridazine adducts (Table 1). These sequences were found to usually give two diastereomers of the corresponding tetrahydropyridazine or in some cases the pyridazines directly from the reaction mixture. A subsequent aromatization of the tetrahydropyridazines with a base gave the corresponding pyridazines in high yields.

Combination of the chloroazodiene derived from **12** with ethyl vinyl ether gave two diastereomers of the corresponding tetrahydropyridazines in good yield (entry 1, Table 1). These diastereomers were assigned based on the vicinal coupling constants in the proton NMR as discussed above. Compounds **14a** and **15a** were converted to the 3-phenyl-substituted pyridazine **16** in 95% yield using KOH in EtOH. In an analogous fashion, the *m*-(trifluoromethyl)phenyl pyridazine **16b** was prepared without isolation of the corresponding tetrahydropyridazines in 50% overall yield from the dichlorohydrazone (entry 2, Table 1). This reaction was also successful with other enol ethers such as *trans*-3-ethoxy-2-propene (entries 7 and 8, Table 1) which gave two diastereomers of the corresponding trisubstituted pyridazines in good yields. An explanation of the structure determination relative to the NMR data for the 4,5,6-trisubstituted tetrahydropyridazines is given for Scheme 5 below. The diastereomers in entries 7 and 8 of Table 1 were aromatized in good yield to the corresponding 5-methyl-substituted pyridazines **16g** and **16h**. Combination of 2-methoxypropene with the chloroazodienes gave the 6-methyl substituted pyridazines **16p** and **16q** directly from the reaction mixture without further base treatment (entries 16 and 17, Table 1). The yields of the products derived from 1,1-disubstituted olefins were somewhat lower than the 1,2-disubstituted olefins. This phenomenon has proven to be general for the electron rich olefins that we have studied to date and may be related to steric hindrance in the transition state of the 4 + 2 reaction.

The chloroazodienes also combined smoothly with enamines to give the corresponding tetrahydropyridazines. The cyclic morpholine enamine of cyclohexanone gave **14c** (entry 3, Table 1) which had the all *cis* stereochemistry. Compound **14c** was aromatized to the bicyclic pyridazine **16c** with base in high yield. The cyclic enamine of cyclopentanone gave the pyridazine **16d** in moderate yield directly from the azodiene reaction (entry 4, Table 1). The *trans*-disubstituted enamines (entries 5, 6, and 9−13, Table 1) all gave two diastereomers of the corresponding tetrahydropyridazines in good yield. All were converted to the pyridazines in good yields by base treatment. In the cases of trisubstituted enamines (entries 14, 15, and 18) a significant amount of aromatized product was obtained directly from the azodiene reaction. However, in lieu of attempting to separate these mixtures, the crude materials were treated with base to complete any aromatizations followed by purification to give the pyridazines shown in moderate yields.

In general, the azodiene route to tetrahydropyridazines and subsequent aromatization to pyridazines is compatible with either enol ethers or enamines that are substituted with a variety of functional groups. The mono- and disubstituted olefins gave higher yields of cyclization products than the trisubstituted olefins. This may be due to steric hindrance in the 4 + 2 reaction. A number of olefins did not give any cyclization products in these reactions. These include *cis*-1-ethoxy-2-bromoethylene, 1-methoxy-1-butene-3-yne, ethyl *trans*-3-ethoxyacrylate, 1-methoxy-2-phenylethylene, ethyl 3-morpholino-4,4,4-trifluoroacrylate, and 3-((*tert*-butyldimethylsilyl)oxy)-2-pentene. In these cases, the olefin may not be electron rich enough to undergo cyclization with the chloroazodienes or sterics may also play a role.

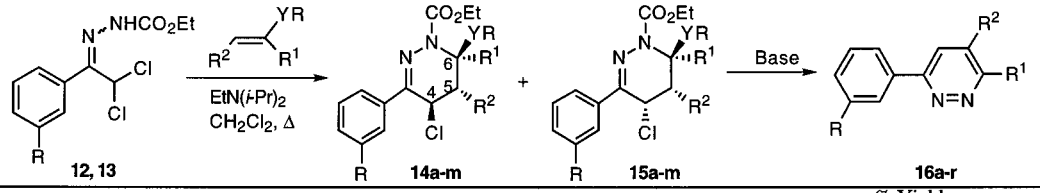
The reaction of the azodiene derived from **13** with a 1,2-disubstituted enamine where the 2-position was substituted with a carbonyl group resulted in the formation of yellow dihydropyridazine products **17** and **18** rather than the tetrahydropyridazine products described above (Scheme 4). These products result from the base-induced elimination of HCl from the molecule. The dihydropyridazine **17** could be aromatized with a base to give carboxylic acid **19**. The ester and ketone **20** and **21** were formed simply by heating in a high boiling solvent.

In the reactions of chloroazodienes described above all of the disubstituted olefins had the *trans* geometry about the double bond. One reaction was run where the olefin was a mixture of *cis* and *trans* isomers in an effort to understand the stereochemistry of the chloroazodiene cyclization reaction. There are four diastereomeric tetrahydropyridazines that are possible from the azodiene reaction (Scheme 5) if a regiospecific, concerted, 4 + 2 Diels−Alder reaction is in operation. Combination of the chloroazodiene **13** with the enamine of methoxyacetaldehyde (1.17:1.00 mixture of *cis* and *trans* isomers) gave three out of four possible diastereomeric tetrahydropyridazines (Scheme 5). Compound **22** was obtained in 25% yield, **23** was obtained in 20% yield, and **24** was obtained in 16% yield.

As described above, the morpholine prefers to be in an axial position which allows the tetrahydropyridazine to adopt a half-chair conformation.[2] Using this premise, the minimum energy conformations were calculated using the Sybil program for all four of the possible diastereomers shown in Scheme 5. These energy-minimized structures were then transferred to the Macromodel program, and values were calculated for the vicinal proton−proton NMR coupling constants (Table 2). The calculated vicinal coupling constants were then compared with the actual values that are shown in Table 2.

One of the four possible diastereomers was eliminated from consideration since it was calculated to have a large diaxial coupling of 7.3 Hz between the 4-H axial proton H^a and the 5-H axial proton H^b (Scheme 5, structure labeled "not observed"). None of the three diastereomers

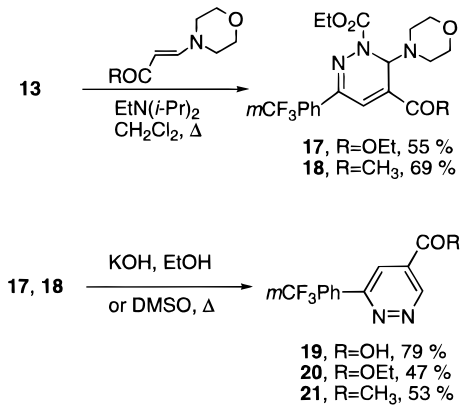
Table 1. Synthesis of Tetrahydropyridazines 14 and 15 and Pyridazines 16 *via* Chloroazodienes[a]



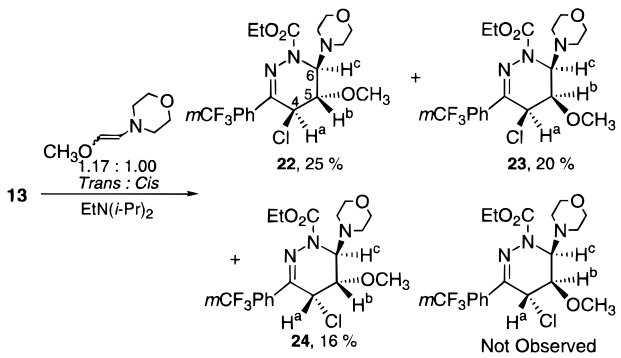
Entry	R	YR	R^1	R^2	% Yield 14	15	16
1	H	OEt	H	H	**a**, 69	**a**, 10	**a**, 95[b]
2	CF_3	OEt	H	H	-[c]	-[c]	**b**, 50[b]
3	H	Morpholino	$-(CH_2)_4-$	$R^1=R^2$	**c**, 34	-[e]	**c** (**6**), 92[d]
4	H	Morpholino	$-(CH_2)_3-$	$R^1=R^2$	-[e]	-[e]	**d**, 25[f]
5	H	Piperidino	H	Et	**e**, 45[g]	**e**, 22[g]	**e** (**7**), 34[d]
6	CF_3	Piperidino	H	Et	**f**, 35[g]	**f**, 17[g]	**f**, 33[h]
7	H	OEt	H	Me	**g**, 66	**g**, 26	**g**, 68[b]
8	CF_3	OEt	H	Me	**h**, 40	**h**, 14	**h**, 76[h]
9	CF_3	Morpholino	H	Ph	**i**, 46	**i**, 39	**i**, 82[b]
10	CF_3	Morpholino	H	*m*-CF_3Ph	-[c]	-[c]	**j**, 43[b]
11	CF_3	Morpholino	H	*i*-Pr	**k**, 65	**k**, 10	**k**, 38[b]
12	CF_3	Morpholino	H	CF_3	**l**, 25	**l**, 17	**l**, 85[b]
13	H	Morpholino	H	CF_3	**m**, 54	**m**, 15	**m**, 51[b]
14	H	Morpholino	Et	Me	-[c]	-[c]	**n** (**8**), 22[d]
15	CF_3	Morpholino	Me	Et	-[c]	-[c]	**o**, 12[b]
16	H	OMe	Me	H	-[e]	-[e]	**p**, 13[f]
17	CF_3	OMe	Me	H	-[e]	-[e]	**q**, 21[f]
18	CF_3	Morpholino	Me	CO_2Et	-[c]	-[c]	**r**, 22[b,i]

[a] The reactions were run with 5 equiv of enol ether or 1.1−2.5 equiv of eneamine in refluxing CH_2Cl_2 for 4−24 h with equal amounts of Hünig's base present in the reaction mixture. [b] KOH in EtOH was used for the aromatization reaction. [c] After workup, the tetrahydropyridazine intermediates were used directly in the aromatization reaction and were not isolated. [d] *t*-BuOK in *t*-BuOH was used for the aromatization reaction. [e] This isomer was not observed. [f] The pyridazine was isolated directly from the reaction of the azodiene with the electron rich olefin. [g] Isolated as a 2:1 mixture of diastereomers **14**:**15**. [h] NaOH in DMSO/H_2O was used for the aromatization reaction. [i] The pyridazine was isolated as the carboxylic acid after treatment of the reaction with base.

Scheme 4



Scheme 5



isolated from the azodiene reaction had a large diaxial coupling of this magnitude between the 4-H and 5-H protons. There were several distinguishing characteristics in the proton NMR's of the three remaining isomers that allowed for the assignment of the stereochemistry shown in Scheme 5.

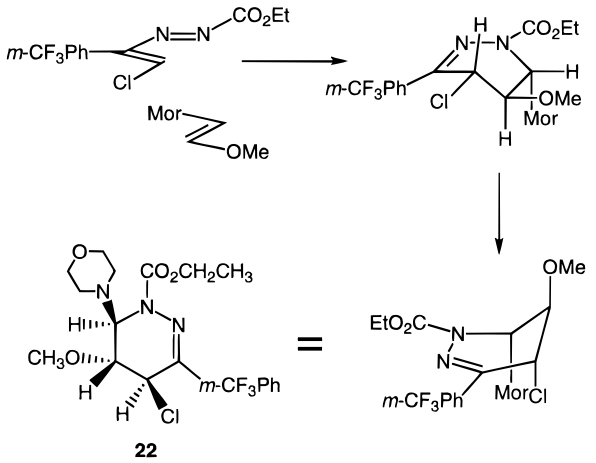
The 4-H equatorial proton of **22** (Scheme 5, Table 2) was a doublet of doublets with coupling constants of 1.44 and 1.36 Hz. The 1.44 Hz coupling is between the 4-H equatorial proton H^a and the 5-H equatorial proton H^b. The 1.36 Hz coupling is between the 4-H equatorial proton H^a and the 6-H equatorial proton H^c. This latter coupling is a W-coupling that is only possible when **22** adopts a half-chair conformation with the morpholine and chloro groups both in an axial position. Also, the methoxy group of this isomer must be in an axial position (*trans* to the morpholine) since the coupling between the

Table 2. 400 MHz ^{1}H NMR Coupling Constants for Compounds 22−24[a]

compd	$^3J_{a,b}$ obsd	$^3J_{a,b}$ calcd	$^3J_{b,c}$ obsd	$^3J_{b,c}$ calcd	$^4J_{a,c}$ obsd
22	1.44	2.2	2.64	2.7	1.36
23	5.42	4.0	3.28	3.3	1.00
24	4.58	3.5	4.58	3.5	0

[a] All NMR spectra were taken in $CDCl_3$ and coupling constants are shown in hertz. See Experimental Section for complete NMR data. Calculated three-bond coupling constants were derived using the Macromodel program. Four-bond couplings were not calculated.

Scheme 6



22

4-H and 5-H protons is small at 1.44 Hz which indicates a diequatorial relationship.

The 4-H equatorial proton H^a of **23** (Scheme 5, Table 2) is a doublet of doublets with a coupling of 5.42 Hz to the 5-H axial proton H^b and a W-coupling of 1.00 Hz to the 6-H equatorial proton H^c. As was shown above with **22** the presence of the W-coupling in **23** indicates that this isomer is also in a half-chair conformation with the morpholine and the chloro groups both in axial positions. Since the coupling between the 4-H and 5-H protons of **23** is 5.42 Hz (this is a larger coupling than the equatorial−equatorial coupling of 1.44 Hz between the 4-H and 5-H protons of **22**), this indicates an equatorial−axial relationship between H^a and H^b. This places the 5-methoxy group in an equatorial position *cis* to the axial morpholine.

In the case of **24** (Scheme 5, Table 2) the 4-H proton H^a is a doublet with a 4.58 Hz coupling to the 5-H equatorial proton H^b. No W-coupling was observed for this compound. These coupling constants indicate that **24** is in a half-chair conformation with the chlorine in an equatorial position. The methoxy is in an axial position *trans* to the axial morpholine. The absence of the W-coupling confirms this.

The calculated values for the vicinal coupling constants (Table 2) of the diastereomers shown in Scheme 5 are close to the values that were observed experimentally. These data further corroborate the structural assignments as discussed above.

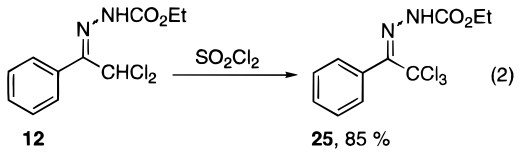
In all of the reactions of the chloroazodienes reported in Table 1 above with *trans*-olefins, only two diastereomers were observed from the reaction. In every case, the NMR data for the diastereomers in Table 1 was consistent with what was observed for **22** and **24** in Scheme 5. All of the stereochemical assignments in Table 1 are corroborated based on this analogy.

One of the preferred modes of reaction is shown in Scheme 6. Here the *trans* olefin is reacting *via* an *endo* transition state with respect to the morpholine with the *E*-azodiene to give, after a ring flip, compound **22** (Scheme 6). This mode of reaction would also lead to the major diasteromers **14** shown in Table 1. Reaction of the *trans* olefin *via* an *exo* transition state (not shown) with respect to the morpholine group with the *E*-azodiene would give compound **24** (Scheme 5) and the minor diastereomers **15** shown in Table 1. When a *cis* olefin is also present as in Scheme 5, the preferred mode of reaction is an *endo* transition state (not shown) with respect to the morpholine with the *E*-azodiene to give compound **23**. It is not clear why the product that would arrise from reaction of a *cis*-olefin with the *E*-azodiene *via* an *exo* attack was not observed.

The results of the chloroazodiene cyclizations in Table 1 and Scheme 5 are best explained based on a regiospecific, concerted, 4 + 2 Diels−Alder reaction with a high degree of *endo* character. The pure tetrahydropyridazine isomers were found to be stable under the reaction conditions used for the azodiene cyclization and were not interconvertible. The stereochemistry of the diene and dienophile is retained in the products. As mentioned above, the chloroazodiene is a 10:1 mixture of *E* and *Z* isomers. Therefore, 90% of the product mixture is derived from the *E*-azodiene and the *Z*-azodiene does not influence the product mixture to any great extent. Theoretically, exclusive *endo* attack of the *trans*-dienophile on the 10:1 mixture of the *E* and *Z* dienes would give a 10:1 ratio of products **14:15** (Table 1) or **22:23** (Scheme 5). Exclusive *exo* attack of a *trans* dienophile on the same diene mixture would give the opposite 10:1 ratio of **15:14** or **23:22**. In practice this ratio of **14:15** or **22:23** has ranged from 6.9:1 to 1.5:1 (Table 1 and Scheme 5) which indicates that *endo* attack of the dienophile is preferred in these azodiene cyclizations, while some product is derived from *exo* attack.

Synthesis and Reactions of Dichloroazodienes. The methodology described above for the synthesis of pyridazines from chloroazodienes was extended to include the synthesis and reactions of the *in-situ* generated 1-carbethoxy-3-phenyl-4,4-dichloroazodiene. Cyclization reactions of this dichloroazodiene are not only in the correct oxidation state for aromatization directly to pyridazines, but also allow for the introduction of a chloro group into the molecule. In contrast to the reactions described above, the dichloroazodiene cyclizations yield mixtures of products. *N*-Aminopyrroles, pyridazines, a dihydropyridazine and/or noncyclized enamine intermediates are isolated from the cyclization reactions depending on the electron rich olefin that is used. These results suggest that a stepwise mechanism may be preferred in the cyclization reactions of the dichloroazodiene rather than a concerted 4 + 2 Diels−Alder; however, no experimental evidence was gathered to prove any proposed mechanisms.

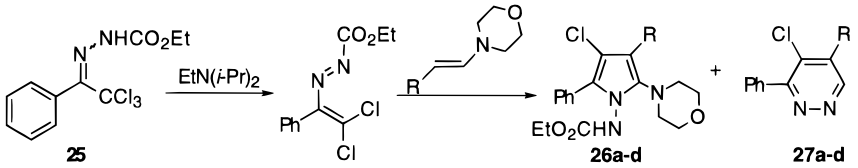
The preparation of the trichlorohydrazone precursor necessary for the dichloroazodiene formation is shown in eq 2. The trichlorohydrazone is prepared from dichlorohydrazone **12** by using neat SO_2Cl_2 to give trichlorohydrazone **25** in 85% yield. The highly colored dichloroazodiene is generated *in-situ* in the presence of the electron rich olefin[20] from the trichlorohydrazone **25** by treatment with Hünig's base in CH_2Cl_2 at rt to reflux or in CCl_4 at reflux to give the products shown in Tables 3 and 4.



12 **25**, 85 %

When the enamine contains a monosubstituted alkyl group as in Table 3 the products obtained from the dichloroazodiene cyclization are *N*-aminopyrroles **26a** and **26c** and pyridazines **27a** and **27c** in roughly equal amounts. When the enamine was substituted with a phenyl group, the main product (75%) was *N*-aminopyrrole **26d** and the minor product was pyridazine **27d**. The

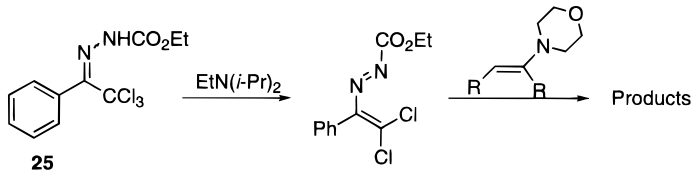
Table 3. Synthesis of Chloro-Substituted *N*-Aminopyrroles 26 and Pyridazines 27

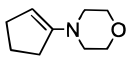
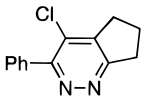
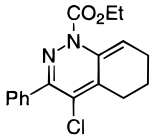
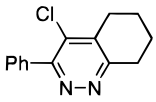
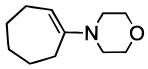
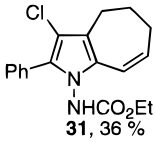
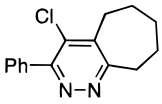
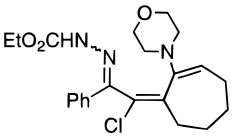
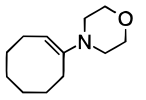
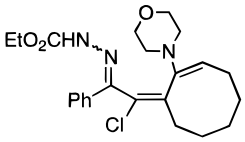


Entry	R	% Yield **26**	% Yield **27**
1[a]	Et	**a**, 15	**a**, 16
2[a]	OCH_3	**b**, 11	-
3[b]	*i*-Pr	**c**, 23	**c**, 36
4[b]	Ph	**d**, 75	**d**, 7

[a] Reaction was performed at room temperature in CH_2Cl_2 with 2.0 equiv of Hünig's base and 1.6−3.3 equiv of the olefin for 2.5−6 h. [b] Reaction was performed in CH_2Cl_2 at reflux with 2.0 equiv of Hünig's base and 2.5−3.3 equiv of olefin for 18−24 h.

Table 4. Reactions of Cyclic Enamines with Dichloroazodienes



Entry	Enamine	Products		
1[a]		-	 **28**, 48 %	-
2[a]		 **29**, 44 %	 **30**, 9 %	-
3[a]		 **31**, 36 %	 **32**, 12 %	 **33**, 31 %
4[b]		 **34**, 3 %	-	 **35**, 31 %

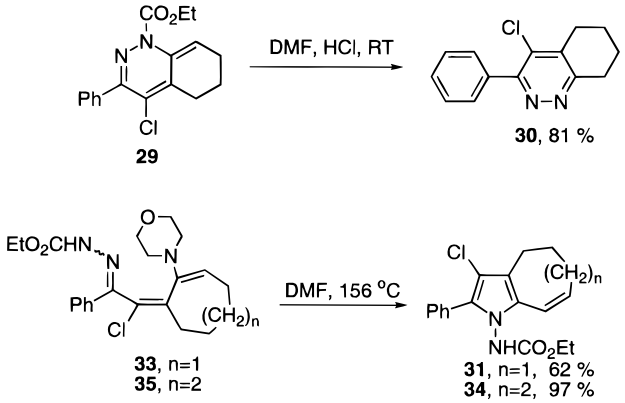
[a] Reaction was performed at room temperature in CH_2Cl_2 with 2.0 equiv of Hünig's base and 1.3−1.8 equiv of the olefin for 1.5−4 h. [b] Reaction was performed in CH_2Cl_2 at reflux with 2.0 equiv of Hünig's base and 2.6 equiv of olefin for 24 h.

methoxy-substituted enamine gave only *N*-aminopyrrole product **26b**.

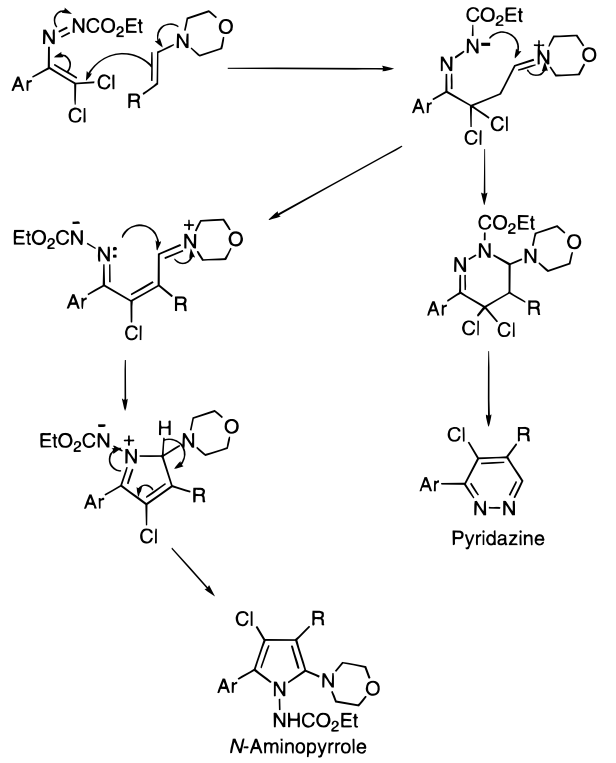
A similar set of products were obtained under the same reaction conditions when cyclic or disubstituted enamines were utilized in the reaction with the dichloroazodiene, Table 4.

Combination of the morpholinocyclopentene with the dichloroazodiene gave only the chloropyridazine product **28** in 48% yield. The reaction with morpholinocyclohexene gave a small amount (9 %) of chloropyridazine **30** as well as an unusual bicyclic *N*-carboxyl-substituted pyridazine (44%) derivative **29** that appears to have been formed by a ring closure reaction followed by a morpholine elimination. Morpholine elimination products were also obtained in the reactions of morpholinocycloheptene and morpholinocyclooctene. However, in these cases the *N*-aminopyrroles were formed, and the double bond migrated away from the bridge head to give products **31** and **34**. The chloropyridazine **32** was present in the reaction with the morpholinocycloheptene, but not with morpholinocyclooctene. In addition to the cyclic products that were isolated from these reactions, acyclic enamine intermediates were also isolated in the case of compounds **33** and **35**. The structural assignments in Tables 3 and

Scheme 7



Scheme 8

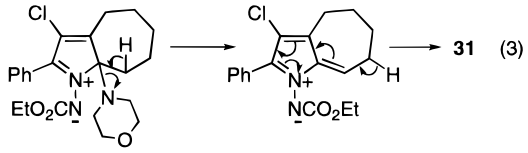


4 were made primarily on the basis of ^{1}H NMR and APT NMR data.

It appeared that in entries 2−4 (Table 4) that there were compounds isolated which were precursors to other products isolated. In an effort to test this hypothesis these compounds were subjected to more stringent reaction conditions (Scheme 7). When compound **29** was treated with acid in DMF at rt pyridazine **30** was formed in 81% yield. Simply heating the open chain compounds **33** and **35** in DMF at 156 °C resulted in the formation of cyclic *N*-aminopyrroles **31** (62% yield) and **34** (97% yield), respectively. These experiments suggest that **29** was an intermediate in the formation of **30** and that **33** and **35** were precursors to **31** and **34**.

A stepwise mechanism that explains the results obtained in Tables 3 and 4 is shown in Scheme 8. Stepwise addition of the enamine to the dichloroazodiene leads to a zwitterionic intermediate. Cyclization of the anion on the N_2 α to the carboxylate would lead to the six-membered tetrahydropyridazine, which upon aromatization yields a chloropyridazine.[21] Alternatively, cyclization using the lone pair on the N_2 β to the carboxylate would lead to a five-membered zwitterion which upon rearrangement would yield the *N*-aminopyrrole.

When cyclic enamines are used the reaction probably proceeds through the intermediate shown in eq 3. Here the cyclic five-membered ring intermediate cannot lose a proton to give the aromatized *N*-aminopyrrole directly. Morpholine elimination would give a double bond at the bridgehead which then rearranges by loss of a proton to give the *N*-aminopyrrole **31** where the double bond is in the saturated ring. Since no attempts were made to prove the mechanistic details of this reaction, the mechanism proposed above is purely speculative. It is possible that some of these products could have been formed by a 3 + 2 cycloaddition reaction.



In summary, the reactions of 1-carbethoxy-3-phenyl-4-chloroazodienes with a variety of electron rich olefins produces tetrahydropyridazines with a high degree of stereochemical and regiochemical control. This indicates that these cyclizations are concerted, 4 + 2 hetero Diels−Alder reactions with a high degree of *endo* character. The chloro-substituted tetrahydropyridazines were aromatized in moderate to high yields to pyridazines. This sequence constitutes a new and general synthesis of substituted pyridazines that is superior to the methodology currently available for the preparation of these molecules. In contrast to the chloroazodiene cyclizations the synthesis and reaction chemistry of 1-carbethoxy-3-phenyl-4,4-dichloroazodienes gives *N*-aminopyrroles, pyridazines, a dihydropyridazine, and/or noncyclized enamine intermediates, depending on the substitution pattern of the electron rich olefin. It is most likely that the compounds derived from dichloroazodienes are derived by a stepwise addition of the enamine to the dichloroazodiene since such a variety of products have been isolated and shown to be interconvertable. The reactions described here are the first reported cyclization reactions for dichloroazodienes.

Experimental Section

General Methods. Melting points are uncorrected. Absorptions are expressed in parts per million (δ) with tetramethylsilane, the deuterated solvent, or 1,1,1-benzotrifluoride as internal reference. Infrared spectral absorptions are reported in wavenumbers (cm^{-1}). Low-resolution electron impact mass spectra and chemical ionization mass spectra were obtained by a direct probe insertion at 70 eV. All mass spectra are electron impact unless noted otherwise. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. All solvents were reagent grade and were obtained from Fisher Scientific. All commercially available chemicals were obtained from Aldrich Chemical Co., Milwaukee, WI, or Fairfield Chemical Co., Blythwood, South Carolina.

Ethyl 2-(2-Bromo-1-phenylethylidene)hydrazinecarboxylate (2). 2-Bromoacetophenone (27.1 g, 0.136 mol) and ethyl carbazate (16.0 g, 0.149 mol) were stirred in ether (500 mL) at rt under N_2 for 24 h. After this time the product had precipitated as a white solid which was collected and dried (31.3 g, 87% yield) and was a 4:1 mixture of isomers: mp 116−

(21) It is also possible that the pyridazines may also be formed by a concerted mechanism.

117 °C; major isomer ^{1}H NMR (400 MHz, acetone-d_6) δ 7.90−7.85 (m, 2-H), 7.49−7.40 (m, 3-H), 4.71 (s, 2-H), 4.25 (q, J = 10.9 Hz, 2-H), 1.30 (t, J = 10.9 Hz, 3-H); minor isomer ^{1}H NMR (400 MHz, acetone-d_6) δ 7.90−7.85 (m, 2-H), 7.60−7.50 (m, 3-H), 4.45 (s, 2-H), 4.17−4.10 (q, J = 10.9 Hz, 2-H), 1.20 (t, J = 10.9 Hz, 3-H). Anal. Calcd for $C_{11}H_{13}N_2O_2Br$: C, 46.33; H, 4.60; N, 9.82. Found: C, 46.12; H, 4.66; N, 9.81.

Ethyl (2,2-Dibromo-1-phenylethylidene)hydrazinecarboxylate (3). Compound **2** (5.0 g, 0.0175 mol) and pyrrolidinone hydrotribromide (13.1 g, 0.0263 mol) were heated at reflux in CCl_4 (180 mL) for 4 h. The solids were filtered off and washed with CCl_4. The filtrate was diluted with EtOAc and extracted 3 × 100 mL with 1.2 N HCl and then once with 0.5 M $Na_2S_2O_4$. The solution was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The residue was recrystallized from cyclohexane to give 4.3 g of a white solid (68% yield): mp 93−95 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.58 (bs, 1-H), 7.65−7.50 (m, 5-H), 6.90 (s, 1-H), 4.13 (q, J = 10.9 Hz, 2-H), 1.18 (t, J = 10.9 Hz, 3-H); ^{13}C NMR (100 MHz, acetone-d_6) δ 153.4, 148.5, 131.1, 130.5, 129.9, 129.6, 62.1, 43.6, 14.6. Anal. Calcd for $C_{11}H_{12}N_2O_2Br_2$: C, 36.29; H, 3.32; N, 7.70. Found: C 36.08; H, 3.35; N, 7.65.

General Procedure for the Reactions of Dibromohydrazone (3) with Electron rich Olefins (Scheme 2). The appropriate enamine or enol ether (1.5−5.0 equiv) and EtN(*i*-Pr)$_2$ (1.1 equiv) were stirred in CH_2Cl_2 (0.1 M with respect to the dibromohydrazone) under N_2 while the dibromohydrazone **3** (0.008−0.011 mol) was added dropwise as a solution in CH_2Cl_2 over 30 min. After the addition was complete, the mixture was heated at reflux for 1−4 h. Loss of the azodiene was monitored by TLC. The mixture was then partitioned between EtOAc/H_2O, the organic layer was dried ($MgSO_4$) and filtered through SiO_2, and the solvent was removed *in-vacuo*. The residue was chromatographed on the Prep-500 and/or recrystallized.

Ethyl 4-Bromo-6-ethoxy-5,6-dihydro-3-phenyl-1(4*H*)-pyridazinecarboxylates (4a,b). These compounds were prepared according to the general procedure given above for Scheme 2. Compound **4a** was isolated (1.76 g, 45% yield) as a white solid by chromatography on the Prep-500: mp 87−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.80 (m, 2-H), 7.45−7.35 (m, 3-H), 5.77 (s, 1-H), 5.01 (d, J = 6.0 Hz, 1-H), 4.40−4.30 (m, 2-H), 3.75−3.65 (m, 2-H), 2.86 (d, J = 16.1 Hz), 2.37 (ddd, J = 16.1, 5.8, 3.6 Hz), 1.39 (t, J = 8.0 Hz, 3-H), 1.23 (t, J = 8.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 144.5, 134.8, 129.5, 128.3, 126.2, 75.5, 63.7, 63.0, 31.7, 28.6, 15.0, 14.4. Anal. Calcd for $C_{15}H_{19}N_2O_3Br$: C, 50.72; H, 5.39; N, 7.89. Found: C, 50.81; H, 5.41; N, 7.87.

Compound **4b** was obtained (0.70 g, 18% yield) as an orange oil by chromatography on the Prep-500: RI 1.5666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 2-H), 7.45−7.35 (m, 3-H), 5.69 (dd, J = 3.0, 2.0 Hz), 5.24 (dd, J = 15.0, 8.0 Hz), 4.45−4.25 (m, 2-H), 3.65−3.55 (m, 2-H), 2.89 (ddd, J = 18.0, 8.0, 3.0 Hz), 2.51 (ddd, J = 18.0, 15.0, 2.0 Hz, 1-H), 1.40 (t, J = 11.0 Hz, 3-H), 1.15 (t, J = 11.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 148.5, 136.4, 129.1, 128.0, 126.9, 78.2, 63.8, 62.9, 36.8, 35.3, 14.9, 14.4. Anal. Calcd for $C_{15}H_{19}N_2O_3Br$: C, 50.72; H, 5.39; N, 7.89. Found: C, 50.82; H, 5.41; N, 7.85.

Ethyl 4-Bromo-4a,5,6,7,8,8a-hexahydro-8a-(4-morpholinyl)-3-phenyl-1(4*H*)-cinnolinecarboxylate (5) and 5,6,7,8-tetrahydro-3-phenylcinnoline (6). These compounds were prepared according to the general procedure given above for Scheme 2. Compound **5** was isolated (1.42 g, 23% yield) as a mixture of diastereomers by chromatography on the Prep-500. One diastereomer crystallized on standing and was collected as a brown solid: mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.75 (m, 2-H), 7.45−7.35 (m, 3-H), 4.55 (s, 1-H), 4.35−4.25 (m, 2-H), 3.85-3.75 (m, 2-H), 3.65−3.55 (m, 2-H), 3.25 (d, J = 18.5 Hz, 1-H), 2.90−2.80 (m, 2-H), 2.75 (dd, J = 18.5, 4.0 Hz, 1-H), 2.60−2.50 (m, 2-H), 1.85−1.70 (m, 3-H), 1.35 (t, J = 7.5 Hz, 3-H), 1.6−1.2 (m, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 144.3, 135.6, 129.3, 128.2, 126.5, 66.7, 62.7, 46.5, 42.2, 37.7, 31.3, 27.8, 26.9, 25.5, 23.0, 14.5. Anal. Calcd for $C_{21}H_{28}N_3O_3Br$: C, 56.00; H, 6.27; N, 9.33. Found: C, 55.93; H, 6.28; N, 9.29.

Compound **6** was isolated (0.17 g, 6% yield) by Prep-500 chromatography as a brown solid: mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.00 (m, 2-H), 7.65 (s, 1-H), 7.50−7.35 (m, 3-H), 3.00 (t, J = 6.0 Hz, 2-H), 2.80 (t, J = 6.0 Hz, 2-H), 1.90−1.70 (m, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 156.9, 137.4, 136.8, 129.4, 128.8, 126.8, 123.6, 29.8, 28.2, 22.5, 21.9. Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.89; H, 6.76; N, 13.29.

5-Ethyl-3-phenylpyridazine (7). This compound was prepared according to the general procedure given above for Scheme 2. Compound **7** was isolated (0.47 g, 31% yield) by chromatography on the Prep-500 as a white solid: mp 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, J = 2.5 Hz, 1-H), 8.10−8.05 (m, 2-H), 7.65 (d, J = 2.5 Hz, 1-H), 7.55−7.45 (m, 3-H), 2.75 (q, J = 8.0 Hz, 2-H), 1.35 (t, J = 8.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 150.9, 143.3, 136.6, 129.9, 128.9, 127.2, 122.8, 25.8, 13.8. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20. Found: C, 78.27; H, 6.57; N, 15.14.

3-Ethyl-4-methyl-6-phenylpyridazine (8). This compound was prepared according to the general procedure given above for Scheme 2. Compound **8** was isolated (0.30 g, 18% yield) by chromatography on a Prep-500 as a white solid: mp 51−53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−8.00 (m, 2-H), 7.50 (s, 1-H), 7.48−7.40 (m, 3-H), 2.97 (q, J = 8.0 Hz, 2-H), 2.33 (s, 3-H), 1.40 (t, J = 8.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 157.2, 136.5, 136.2, 129.5, 128.8, 126.7, 124.6, 26.5, 18.3, 12.3. Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.58; H, 7.15; N, 14.05.

Ethyl 3-(α-Methylbenzylidene)carbazate (10) or Ethyl 2-(1-(3-(trifluoromethyl)phenyl)ethylidene)-hydrazinecarboxylate (11). Acetophenone (100 g, 0.830 mol) or *m*-(trifluoromethyl)acetophenone (50 g, 0.266 mol), ethyl carbazate (1.05 equiv), and catalytic PTSA (40 mg) were heated at reflux under N_2 in benzene (1 L and 0.5 L, respectively) over a Dean-Stark trap until the theoretical amount of water was removed (4 h). The solvent was removed and the solid was recrystallized from cyclohexane/EtOAc to give compound **10** (171 g, 100% yield) or **11** (74 g, 100% yield) both as white solids.

Data for **10**: mp 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (bs, 1-H), 7.80−7.70 (m, 2-H), 7.40−7.30 (m, 3-H), 4.30 (q, J = 8.0 Hz, 2-H), 2.20 (s, 3-H), 1.35 (t, J = 8.0 Hz, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 138.1, 129.7, 129.2, 128.4, 126.3, 62.0, 14.6, 13.0. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.97; H, 6.89; N, 13.66.

Data for **11**: mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (bs, 1-H), 7.97 (s, 1-H), 7.93 (d, J = 8.0 Hz, 1-H), 7.58 (d, J = 8.0 Hz, 1-H), 7.45 (t, J = 8.0 Hz, 1-H), 4.32 (q, J = 8.0 Hz, 2-H), 2.25 (s, 3-H), 1.35 (t, J = 8.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 146.8, 138.9, 130.7 (q, J = 33.1 Hz), 129.5, 128.8, 125.6 (q, J = 4.5 Hz), 124.0 (q, J = 271.9 Hz), 123.0 (q, 3.8 Hz), 62.1, 14.5, 12.8. Anal. Calcd for $C_{12}H_{13}N_2O_2F_3$: C, 52.56; H, 4.78; N, 10.21. Found: C, 52.50; H, 4.82; N, 10.18.

Ethyl (2,2-Dichloro-1-phenylethylidene)hydrazinecarboxylate (12) or Ethyl [2,2-Dichloro-1-[3-(trifluoromethyl)phenyl]ethylidene]hydrazinecarboxylate (13). Compound **10** (52.6 g, 0.260 mol) or **11** (74.0 g, 0.394 mol), NCS (2.1−2.2 equiv), and benzoyl peroxide (20 mg) were heated carefully to 50 °C in CCl_4 (1 L and 1.5 L, respectively) with a heat gun. At this temperature an exotherm occurred which caused the CCl_4 to reflux on its own. This exotherm was controlled with an ice bath. After the exotherm subsided, the mixture was heated at reflux for 2 h. The mixture was allowed to cool and the succinimide was filtered. The solvent was evaporated *in-vacuo* to give an oil which crystallized on standing. The solids were then recrystallized from cyclohexane to give **12** (70.0 g, 98% yield) or **13** (135 g, 100% yield) both as white solids.

Data for **12**: mp 105−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (bs, 1-H), 7.60−7.55 (m, 3-H), 7.43−7.35 (m, 2-H), 6.65 (s, 1-H), 4.24 (bq, J = 11.0 Hz, 2-H), 1.35−1.20 (m, 3-H). Anal. Calcd for $C_{11}H_{12}N_2O_2Cl_2$: C, 48.02; H, 4.40; N, 10.18. Found: C, 48.06; H, 4.42; N, 10.17.

Data for **13**: mp 81−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 1-H), 7.80 (t, J = 8.0 Hz, 1-H), 7.77 (s, 1-H), 7.66 (d, J = 8.0 Hz, 1-H), 7.58 (s, 1-H), 6.75 (s, 1-H), 4.35 (q, J = 7.0 Hz, 2-H), 1.40 (t, J = 7.0 Hz, 3-H). Anal. Calcd

for $C_{12}H_{11}N_2O_2Cl_2F_3$: C, 42.01; H, 3.23; N, 8.16. Found: C, 42.03; H, 3.24; N, 8.12.

Preparation of Enamines in Tables 1, 3, 4 and Schemes 2, 4, 5. The electron rich olefins in entries 1−3, 4, 7, and 8 of Table 1 were purchased from commercial sources. The other enamines in Tables 1, 3, 4 and Scheme 2, 4, 5 were prepared *via* published procedures[20] that involved heating to reflux 1 equiv of the appropriate aldehyde or ketone with an excess of the secondary amine in toluene or benzene over a Dean−Stark trap until the theoretical amount of water was collected. The products were then distilled or recrystallized where appropriate. The enamines in entries 12, 13 of Table 1 and those shown in Scheme 4 were prepared by stirring 1 equiv of the appropriate alkyne precursor with 1 equiv of morpholine in CH_2Cl_2 for 30 min to 1 h at rt followed by reflux for a short period of time. These enamines were used without isolation or purification. All of the above enamines had the *trans* geometry as shown in Table 1 as evidenced by the large coupling constant of the vinyl protons of 10−16 Hz.

General Procedure for the Preparation of the Tetrahydropyridazines and Pyridazines in Table 1, Schemes 4 and 5. The appropriate enol ether (5.0 equiv) or enamine (1.1−1.5 equiv) and Hünig's base (*N,N*-diisopropylethylamine, 1.1−2.5 equiv) were stirred in CH_2Cl_2 (0.1 molar with respect to the dichlorohydrazone) at rt under N_2 while the appropriate dichlorohydrazone (0.015-.036 mol of either **12** or **13**) was added dropwise as a solution in CH_2Cl_2 (usually 25% of the total solvent volume was used to dissolve the hydrazone) over 30 min. A transient deep red or orange color was noted. The mixture was then allowed to reflux for 4−24 h while monitoring the loss of the colored azodiene by TLC. The mixture was then cooled and poured into an extraction funnel containing EtOAc and water. The organic layer was washed 2−3 times with water, dried ($MgSO_4$), filtered through a pad of SiO_2, and the solvent was removed *in-vacuo* to give the crude tetrahydropyridazines as an oil. In entries 1, 3, 5−9, 11, 12, and 13 of Table 1 the tetrahydropyridazines were separated and isolated by chromatography on a Prep-500 followed by recrystallization from an appropriate solvent mixture. In entries 2, 14, 15, and 18 the crude tetrahydropyridazine mixtures were not separated, but were converted directly to the pyridazine products by treatment with base. In entries 4, 16, and 17 the pyridazine products were isolated by chromatography directly from the azodiene reaction after workup.

The tetrahydropyridazine products were converted to the pyridazine products by treatment with 5 equiv of KOH in EtOH at reflux for 1−4 h, 5 equiv of KO*t*-Bu in *t*-BuOH at rt for 4−24 h, 5 equiv of NaOH in DMSO at 100 °C for 2−4 h, or heating in DMF at reflux for 0.5−2 h or DMSO at 175 °C for 0.5 h. This operation was followed by pouring the mixtures into water, followed by extraction several times with EtOAc. The organic layer was dried ($MgSO_4$), filtered through a pad of SiO_2, and evaporated *in-vacuo* to give the crude pyridazines. The pyridazines were chromatographed on the Prep-500 and/or recrystallized where appropriate.

Ethyl 4-Chloro-6-ethoxy-5,6-dihydro-3-phenyl-1(4*H*)-pyridazinecarboxylates (14a and 15a). These compounds were prepared according to the general procedure given for Table 1 above and were isolated from the azodiene reaction by Prep-500 chromatography. Compound **14a** was obtained as a white solid (7.79 g, 69% yield), and **15a** was also obtained as a white solid (1.15 g, 10% yield).

Data for **14a**: mp 80−82 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.85 (m, 2-H), 7.45−7.38 (m, 3-H), 5.80 (bs, 1-H), 4.93 (d, J = 10.0 Hz, 1-H), 4.38 (q, J = 11.0 Hz, 2-H), 3.68 (q, J = 11.0 Hz, 2-H), 2.84 (d, J = 19.0 Hz, 1-H), 2.31 (ddd, J = 19.0, 10.0, 3.0 Hz, 1-H), 1.41 (t, J = 11.0 Hz, 3-H), 1.22 (t, J = 11.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 144.5, 134.8, 129.5, 128.4, 126.3, 75.4, 63.8, 63.0, 40.5, 32.1, 15.0, 14.5. Anal. Calcd for $C_{15}H_{19}N_2O_3Cl$: C, 57.97; H, 6.16; N, 9.01. Found: C, 57.75; H, 6.21; N, 8.97.

Data for **15a**: mp 50−53 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 2-H), 7.42−7.35 (m, 3-H), 5.75 (dd, J = 3.0, 3.0 Hz, 1-H), 5.20 (dd, J = 12.0, 8.0 Hz, 1-H), 4.45−4.25 (m, 2-H), 3.68−3.56 (m, 2-H), 2.81 (ddd, J = 16.0, 8.0, 3.0 Hz, 1-H), 2.30 (ddd, J = 16.0, 12.0, 3.0 Hz, 1-H), 1.41 (t, J = 11.0 Hz, 3-H), 1.27 (t, J = 11.0 Hz, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 148.3, 135.6, 129.2, 128.0, 127.2, 78.1, 64.0, 63.0, 45.9, 35.5, 15.0, 14.4. Anal. Calcd for $C_{15}H_{19}N_2O_3Cl$: C, 57.97; H, 6.16; N, 9.01. Found: C, 58.24; H, 6.31; N, 8.98.

3-Phenylpyridazine (16a). This compound was prepared according to the general procedure given for Table 1 above and was obtained as a white solid (0.65 g, 95% yield) after aromatization from the corresponding tetrahydropyridazines by treatment with 5 equiv of KOH in refluxing EtOH for 4 h: mp 100−102 °C from cyclohexane/EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, J = 4.0 Hz, 1-H), 8.10−8.05 (m, 2-H), 7.85 (d, J = 12.0 Hz, 1-H), 7.60−7.35 (m, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 149.9, 136.3, 130.1, 129.0, 127.1, 126.8, 123.9. Anal. Calcd for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.96; H, 5.18; N, 17.85.

3-[3-(Trifluoromethyl)phenyl]pyridazine (16b). This compound was prepared according to the general procedure given for Table 1 above directly from the dichlorohydrazone without isolation of the tetrahydropyridazine intermediates. The azodiene cyclization was completed first followed by workup and aromatization with 5 equiv of KOH in refluxing EtOH for 4 h (white solid, 5.25 g, 50% overall yield: mp 74−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, J = 4.0 Hz, 1-H), 8.42 (s, 1-H), 8.31 (d, J = 7.0 Hz, 1-H), 7.96 (d, J = 7.0 Hz, 1-H), 7.80 (d, J = 7.0 Hz, 1-H), 7.80 (t, J = 7.0 Hz, 1-H), 7.75 (dd, J = 7.0, 4.0 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 150.3, 136.9, 131.3 (q, J = 32.5 Hz), 130.0, 129.4, 126.8, 126.5 (q, J = 3.6 Hz), 123.8 (q, J = 4.0 Hz), 123.7 (q, J = 271.0 Hz), 123.6. Anal. Calcd for $C_{11}H_7N_2F_3$: C, 58.93; H, 3.15; N, 12.50. Found: C, 58.83; H, 3.16; N, 12.40.

Ethyl 4-Chloro-4a,5,6,7,8,8a-hexahydro-8a-(4-morpholinyl)-3-phenyl-1(4*H*)-cinnolinecarboxylate (14c). This compound was prepared according to the general procedure given for Table 1 above. After workup of the azodiene reaction the diastereomer shown in Table 1 crystallized from the mixture and was isolated as a white solid (34% yield): mp 195 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.80 (m, 2-H), 7.45−7.35 (m, 3-H), 4.40 (s, 1-H), 4.38−4.24 (m, 2-H), 3.74-3.66 (m, 2-H), 3.59−3.52 (m, 2-H), 3.24 (d, J = 14.4 Hz, 1-H), 2.86−2.79 (m, 2-H), 2.68 (dd, J = 12.8, 3.0 Hz, 1-H), 2.56−2.48 (m, 2-H), 1.82−1.68 (m, 3-H), 1.51 (apparent dt, J = 13.2, 3.3 Hz, 1-H), 1.38 (t, J = 7.9 Hz, 3-H), 1.44−1.14 (m, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 144.1, 135.4, 129.3, 128.3, 126.6, 76.5, 66.8, 62.7, 49.2, 46.6, 42.5, 30.8, 27.7, 25.4, 22.9, 14.5. Anal. Calcd for $C_{21}H_{28}N_3O_3Cl$: C, 62.14; H, 6.95; N, 10.35. Found: C, 61.74; H, 6.98; N, 10.29.

5,6,7,8-Tetrahydro-3-phenylcinnoline (16c and 6). This compound was prepared according to the general procedure given for Table 1 above from the corresponding tetrahydropyridazine by treatment with 5 equiv of *t*-BuOK in *t*-BuOH at rt for 4 h, followed by chromatography and recrystallization from EtOAc/cyclohexane (92% yield). See **6** above for analytical data.

6,7-Dihydro-3-phenyl-5*H*-cyclopenta[*c*]pyridazine (16d). This compound was isolated directly from the azodiene reaction after workup by chromatography on the Prep-500, followed by recrystallization from EtOAc/cyclohexane to give a white solid (25% yield): mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.95 (m, 2-H), 7.62 (s, 1-H), 7.51−7.40 (m, 3-H), 3.22 (t, J = 11.0 Hz, 2-H), 3.00 (t, J = 11.0 Hz, 2-H), 2.18 (dt, J = 11.0 Hz, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 157.2, 142.9, 137.2, 129.4, 128.8, 127.1, 122.1, 32.0, 30.7, 22.9. Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.28; H, 6.22; N, 14.22.

Ethyl 4-Chloro-5-ethyl-5,6-dihydro-3-phenyl-6-(1-piperidinyl)-1(4*H*)-pyridazinecarboxylate (14e and 15e). These compounds were prepared according to the general procedure given for Table 1 above and were isolated as yellow oils (RI 1.5575) after workup and chromatography on a Prep-500 as a 2:1 mixture of diastereomers (5.2 g, 67% yield).

Data for **14e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.90 (m, 2-H), 7.45−7.40 (m, 3-H), 4.90 (bs, 1-H), 4.77 (bs, 1-H), 4.35−4.25 (m, 2-H), 2.99 (bt, J = 8.0 Hz, 1-H), 2.70−2.63 (m, 2-H), 2.48−2.41 (m, 2-H), 1.60−1.40 (m, 6-H), 1.34 (t, J = 8.0 Hz, 3-H), 1.30−1.20 (m, 2-H), 1.10 (t, J = 8.0 Hz, 3-H).

Data for **15e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.80 (m, 2-H), 7.48−7.44 (m, 3-H), 5.28 (d, J = 4.0 Hz, 1-H), 4.80 (d, J

= 6.0 Hz, 1-H), 4.3−4.2 (m, 2-H), 2.60−2.50 (m, 2-H), 2.40−2.30 (m, 1-H), 1.78−1.70 (m, 1-H), 1.75−1.65 (m, 1-H), 1.60−1.40 (m, 6-H), 1.32 (t, J = 8.0 Hz, 3-H), 1.40−1.20 (m, 2-H), 1.08 (t, J = 8.0 Hz, 3-H). Anal. Calcd for $C_{20}H_{28}N_3O_2Cl$: C, 63.56; H, 7.47; N, 11.12. Found: C, 63.69; H, 7.58; N, 10.97.

5-Ethyl-3-phenylpyridazine (16e and 7). This compound was prepared according to the general procedure given for Table 1 above and was isolated as a yellow solid (1.1 g, 34% yield) by Prep-500 chromatography after treatment of the corresponding tetrahydropyridazines with 5 equiv of *t*-BuOK in *t*-BuOH for 4 h at rt. See **7** above for analytical data.

Ethyl 4-Chloro-5-ethyl-5,6-dihydro-6-(1-piperidinyl)-3-[3-(trifluoromethyl)phenyl]-1(4*H*)-pyridazinecarboxylate (14f and 15f). These compounds were prepared according to the general procedure given for Table 1 above and were isolated as a yellow oil (6.67 g, 52% yield, RI 1.5256). After chromatography on the Prep-500, the oil was found to be a 2:1 mixture of diastereomers.

Data for **14f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1-H), 8.05 (d, J = 8.0 Hz, 1-H), 7.62 (d, J = 8.0 Hz, 1-H), 7.51 (t, J = 8.0 Hz, 1-H), 4.72 (bs, 1-H), 4.51 (s, 1-H), 4.40−4.30 (m, 2-H), 2.77 (bt, J = 8.0 Hz, 1-H), 2.63−2.55 (m, 2-H), 2.48−2.40 (m, 2-H), 1.60−1.40 (m, 6-H), 1.38 (t, J = 8.0 Hz, 3-H), 1.30−1.20 (m, 2-H), 1.05 (t, J = 8.0 Hz, 3-H).

Data for **15f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1-H), 7.89 (d, J = 8.0 Hz, 1-H), 7.63 (d, J = 8.0 Hz, 1-H), 7.52 (t, J = 8.0 Hz, 1-H), 5.09 (d, J = 4.0 Hz, 1-H), 4.79 (d, J = 6.0 Hz, 1-H), 4.40−4.30 (m, 2-H), 2.65−2.55 (m, 1-H), 2.45−2.40 (m, 2-H), 2.25−2.17 (m, 1-H), 1.90−1.80 (m, 1-H), 1.60−1.40 (m, 6-H), 1.38 (t, J = 8.0 Hz, 1-H), 1.30−1.20 (m, 2-H), 1.03 (t, J = 8.0 Hz, 3-H). Anal. Calcd for $C_{21}H_{27}N_3O_2ClF_3$: C, 56.57; H, 6.10; N, 9.42. Found: C, 56.65; H, 6.13; N, 9.37.

5-Ethyl-3-[3-(trifluoromethyl)phenyl]pyridazine (16f). This compound was prepared according to the general procedure given for Table 1 above from the corresponding tetrahydropyridazines by treatment with 5 equiv of NaOH in DMSO/water at 100 °C for 1 h. After workup, chromatography on a Prep-500 and recrystallization from cyclohexane afforded the compound as a white solid (1.0 g, 33% yield): mp 71−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (bs, 1-H), 8.34 (s, 1-H), 8.22 (d, J = 8.0 Hz, 1-H), 7.70 (d, J = 8.0 Hz, 1-H), 7.68 (bs, 1-H), 7.60 (t, J = 8.0 Hz, 1-H), 2.75 (q, J = 8.0 Hz, 3-H), 1.35 (t, J = 8.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.4, 143.8, 137.4, 131.4 (q, J = 32.4 Hz), 130.3, 129.4, 126.4 (q, J = 3.8 Hz), 124.0 (q, J = 3.8 Hz), 124.0 (q, J = 271.0 Hz), 122.8, 25.8, 13.7. Anal. Calcd for $C_{13}H_{11}N_2F_3$: C, 61.90; H, 4.40; N, 11.11. Found: C, 61.84; H, 4.39; N, 11.09.

Ethyl 4-Chloro-6-ethoxy-5,6-dihydro-5-methyl-3-phenyl-1(4*H*)-pyridazinecarboxylates (14g and 15g). These compounds were prepared according to the general procedure given for Table 1 above and were isolated by separation of the crude reaction mixture on a Prep-500 to give **14g** as a yellow oil (5.35 g, 66% yield) and **15g** as a white solid (2.08 g, 26% yield).

Data for **14g**: RI 1.5558; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.60 (m, 2-H), 7.20−7.10 (m, 3-H), 5.28 (s, 1-H), 4.31 (s, 1-H), 4.22−4.05 (m, 2-H), 3.44 (q, J = 7.0 Hz, 2-H), 2.65 (q, J = 7.4 Hz, 1-H), 1.18 (t, J = 7.0 Hz, 3-H), 0.99 (t, J = 7.0 Hz, 3-H), 0.75 (d, J = 7.4 Hz, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 143.4, 134.9, 129.3, 128.1, 126.1, 80.5, 63.6, 62.8, 45.7, 36.0, 16.2, 14.7, 14.2. Anal. Calcd for $C_{16}H_{21}N_2O_3Cl$: C, 59.17; H, 6.52; N, 8.62. Found: C, 58.87; H, 6.56; N, 8.48.

Data for **15g**: mp 84−86 °C from EtOAc/cyclohexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.35 (m, 2-H), 7.20−7.08 (m, 3-H), 5.33 (d, J = 3.2 Hz, 1-H), 5.14 (d, J = 6.3 Hz, 1-H), 4.21−4.05 (m, 2-H), 3.44 (q, J = 7.2 Hz, 2-H), 2.39 (qdd, J = 6.9, 6.3, 3.2 Hz, 1-H), 1.18 (t, J = 7.2 Hz, 3-H), 0.98 (t, J = 7.2 Hz, 3-H), 0.85 (d, J = 6.9 Hz, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 147.9, 135.9, 128.8, 127.7, 127.4, 83.7, 64.0, 62.8, 51.8, 34.7, 14.9, 14.2, 12.4. Anal. Calcd for $C_{16}H_{21}N_2O_3Cl$: C, 59.17; H, 6.52; N, 8.62. Found: C, 59.41; H, 6.57; N, 8.68.

5-Methyl-3-phenylpyridazine (16g). This compound was prepared according to the general procedure given for Table 1 above and was isolated by separation on the Prep-500. Compound **16g** was obtained as an off-white solid (2.08 g, 68% yield): mp 89−91 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, 2.5 Hz, 1-H), 8.15−8.05 (m, 2-H), 7.68 (d, J = 2.5, 1-H), 7.60−7.50 (m, 3-H), 2.45 (s, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 151.4, 137.6, 136.2, 129.6, 128.7, 126.9, 124.0, 18.3. Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.57; H, 5.93; N, 16.40.

Ethyl 4-Chloro-6-ethoxy-5,6-dihydro-5-methyl-3-[3-(trifluoromethyl)phenyl]-1(4*H*)-pyridazinecarboxylates (14h and 15h). These compounds were prepared according to the general procedure given for Table 1 above and were separated from the crude mixture by chromatography on the Prep-500. Compound **14h** was obtained as a white solid (4.53 g, 40% yield), and **15h** was obtained as a clear oil (1.56 g, 14% yield).

Data for **14h**: mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1-H), 8.05 (d, J = 8.0 Hz, 1-H), 7.62 (d, J = 8.0 Hz, 1-H), 7.51 (t, J = 8.0 Hz, 1-H), 5.51 (s, 1-H), 4.50 (s, 1-H), 4.43−4.30 (m, 2-H), 3.66 (q, J = 7.0 Hz, 2-H), 2.88 (bq, J = 8.0 Hz, 1-H), 1.40 (t, J = 7.0 Hz, 3-H), 1.20 (t, J = 7.0 Hz, 3-H), 0.98 (d, J = 8.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 142.2, 136.0, 130.8 (q, J = 33.2 hz), 129.5, 128.8, 125.9 (q, J = 2.3 Hz), 124.0 (q, 269.5 Hz), 123.2 (q, J = 3.8 Hz), 80.8, 64.0, 63.2, 45.8, 36.2, 16.4, 14.9, 14.3. Anal. Calcd for $C_{17}H_{20}N_2O_3ClF_3$: C, 51.98; H, 5.13; N, 7.13. Found: C, 52.13; H, 5.18; N, 7.06.

Data for **15h**: RI 1.4947; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1-H), 7.80 (d, J = 8.0 Hz, 1-H), 7.61 (d, J = 8.0 Hz, 1-H), 7.50 (t, J = 8.0 Hz, 1-H), 5.55 (d, J = 3.0 Hz, 1-H), 5.35 (d, J = 6.0 Hz, 1-H), 4.41−4.27 (m, 2-H), 3.65 (q, J = 8.0 Hz, 2-H), 2.62 (qdd, J = 7.0, 6.0, 3.0 Hz, 10 lines, 1-H), 1.38 (t, J = 8.0 Hz, 3-H), 1.18 (t, J = 8.0 Hz, 3-H), 1.05 (d, J = 7.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 146.3, 136.8, 130.9, 130.4 (q, J = 32.4 Hz), 128.3, 125.5 (q, J = 3.8 Hz), 124.5 (q, J = 3.0 Hz), 124.0 (q, J = 269.5 Hz), 83.9, 64.3, 63.2, 51.7, 34.7, 15.0, 14.3, 12.4. Anal. Calcd for $C_{17}H_{20}N_2O_3ClF_3$: C, 51.98; H, 5.13; N, 7.13. Found: C, 52.06; H, 5.16; N, 7.03.

5-Methyl-3-[3-(trifluoromethyl)phenyl]pyridazine (16h). This compound was prepared according to the general procedure given for Table 1 above. The corresponding tetrahydropyridazines were treated with 5 equiv of 2.5 N NaOH in DMSO at 100 °C for 15 min. After workup, the residue was recrystallized from EtOAc/cyclohexane to give the product as an off-white solid (1.4 g, 76% yield): mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, J = 2.5 Hz, 1-H), 8.32 (s, 1-H), 8.22 (d, J = 8.0 Hz, 1-H), 7.70 (d, J = 8.0 Hz, 1-H), 7.68 (d, J = 2.5 Hz, 1-H), 7.60 (t, J = 8.0 Hz, 1-H), 2.42 (s, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 152.1, 138.2, 137.3, 131.3 (q, J = 32.4 Hz), 130.3, 129.4, 126.4 (q, J = 3.8 Hz), 124.1, 124.0 (q, J = 268.0 Hz), 123.9 (q, J = 3.8 Hz), 18.4. Anal. Calcd for $C_{12}H_9N_2F_3$: C, 60.51; H, 3.81; N, 11.76. Found: C, 60.42; H, 3.82; N, 11.72.

Ethyl 4-Chloro-5,6-dihydro-6-(4-morpholinyl)-5-phenyl-3-[3-(trifluoromethyl)phenyl]-1(4*H*)-pyridazinecarboxylates (14i and 15i). These compounds were prepared according to the general procedure given for Table 1 above and were separated from the crude reaction by chromatography on a Prep-500. Compound **14i** was obtained as a white solid (6.67 g, 46% yield), and **15i** was obtained as a white solid (5.70 g, 39% yield).

Data for **14i**: mp 116−117 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1-H), 8.15 (d, J = 8.0 Hz, 1-H), 7.78 (d, J = 8.0 Hz, 1-H), 7.65 (t, J = 8.0 Hz, 1-H), 7.40−7.30 (m, 3-H), 7.15−7.05 (m, 2-H), 5.02 (s, 1-H), 4.93 (s, 1-H), 4.35 (q, J = 8.0 Hz, 2-H), 3.90−3.75 (m, 4-H), 3.00−2.70 (m, 4-H), 1.38 (t, J = 8.0 Hz, 3-H). Anal. Calcd for $C_{24}H_{25}N_3O_3ClF_3$: C, 58.13; H, 5.08; N, 8.47. Found: C, 58.20; H, 5.10; N, 8.45.

Data for **15i**: mp 134−135 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1-H), 8.05 (d, J = 8.0 Hz, 1-H), 7.75 (d, J = 8.0 Hz, 1-H), 7.63 (t, J = 8.0 Hz, 1-H), 7.50−7.40 (m, 3-H), 7.40−7.30 (m, 2-H), 5.42 (d, J = 6.0 Hz, 1-H), 5.15, (d, J = 5.2 ha, 1-H), 4.40−4.30 (m, 2-H), 3.90 (apparent bt, J = 6.0 Hz, 1-H), 3.80−3.70 (m, 4-H), 2.85−2.75 (m, 4-H), 1.40 (t, J = 8.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 149.9, 137.0, 136.3, 131.5 (q, J = 32.6), 129.5, 129.5, 129.3, 128.7, 126.8 (q, J = 3.7 Hz), 124.5 (q, J = 4.0 Hz), 124.5 (q, J = 272.46 Hz), 75.6, 67.4, 63.4, 50.0, 49.5, 44.5, 14.4. Anal. Calcd for $C_{24}H_{25}N_3O_3ClF_3$: C, 58.13; H, 5.08; N, 8.47. Found: C, 58.22; H, 5.09; N, 8.44.

5-Phenyl-3-[3-(trifluoromethyl)phenyl]pyridazine (16i). This compound was prepared according to the general proce-

dure given for Table 1 above. The corresponding tetrahydropyridazines were treated with 5.0 equiv of KOH in EtOH at reflux for 3 h. After workup, the crude solid was recrystallized from EtOAc/CH_2Cl_2 to give the product as a white solid (5.0 g, 82% yield): mp 188−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, J = 2.5 Hz, 1-H), 8.48 (s, 1-H), 8.40 (d, J = 8.0 Hz, 1-H), 8.00 (d, J = 2.5 Hz, 1-H), 7.80−7.70 (m, 3-H), 7.60 (t, J = 8.0 Hz, 1-H), 7.50−7.40 (m, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 148.5, 139.3, 136.9, 134.2, 132.0 (q, J = 32.0 Hz), 130.2, 130.1, 129.4, 129.4, 127.0, 126.5 (q, J = 3.8 Hz), 123.9 (q, J = 3.8 Hz), 122.0 (q, J = 268.0 Hz), 120.8. Anal. Calcd for $C_{17}H_{11}N_2F_3$: C, 68.00; H, 3.69; N, 9.33. Found: C, 68.03; H, 3.72; N, 9.25.

4,6-Bis[3-(trifluoromethyl)phenyl]pyridazine (16j). This compound was prepared according to the general procedure given for Table 1 above. The azodiene reaction was performed first and after workup, the tetrahydropyridazine mixture was treated with 5.0 equiv of KOH in EtOH for 2 h. After workup, the product was recrystallized from EtOAc/cyclohexane to give a white solid (2.3 g, 43% yield): mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 2.5, 1-H), 8.52 (s, 1-H), 8.45 (d, J = 8.0 Hz, 1-H), 8.15 (d, J = 2.5 Hz, 1-H), 8.08 (s, 1-H), 8.02 (d, J-8.0 Hz, 1-H), 7.90−7.70 (m, 4-H). Anal. Calcd for $C_{18}H_{10}N_2F_6$: C, 58.70; H, 2.74; N, 7.61. Found: C, 58.60; H, 2.78; N, 7.56.

Ethyl 4-Chloro-5,6-dihydro-5-(1-methylethyl)-6-(4-morpholinyl)-3-[3-(trifluoromethyl)phenyl]-1(4*H*)-pyridazinecarboxylates (14k and 15k). These compounds were prepared according to the general procedure given for Table 1 above. Compound **14k** was isolated from the crude azodiene reaction by trituration with EtOAc and filtration and was obtained as a white solid (8.77 g, 65% yield). Chromatography of the mother liquor on a Prep-500 gave **15k** as a yellow oil (1.35 g, 10% yield).

Data for **14k**: mp 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1-H), 7.92 (d, J = 7.9 Hz, 1-H), 7.54 (d, J = 7.9 Hz, 1-H), 7.43 (t, J = 7.9 Hz, 1-H), 4.83 (bs, 1-H), 4.60 (s, 1-H), 4.33−4.20 (m, 2-H), 3.60−3.48 (m, 4-H), 2.63−2.55 (m, 2-H), 2.45 (dd, J = 8.8, 1.9 Hz, 1-H), 2.40−2.33 (m, 2-H), 1.37−1.27 (m, 1-H), 1.28 (t, J = 7.2 Hz, 3-H), 0.96 (d, J = 6.6 Hz, 3-H), 0.91 (d, J = 6.6 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 146.2, 136.7, 131.5 (q, J = 32.4 Hz), 130.4, 129.5, 126.7 (q, J = 3.8 Hz), 124.6 (q, J = 272.5 Hz), 124.0 (q, J = 3.8 Hz), 69.3, 66.8, 63.5, 49.7, 46.2, 45.1, 29.6, 21.0, 20.6, 14.4. Anal. Calcd for $C_{21}H_{27}N_3O_3ClF_3$: C, 54.61; H, 5.89; N, 9.10. Found: C, 54.68; H, 5.90; N, 9.03.

Data for **15k**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1-H), 7.80 (d, J = 8.0 Hz, 1-H), 7.55 (d, J = 8.0 Hz, 1-H), 7.40 (t, J = 8.0 Hz, 1-H), 4.95 (d, J = 6.0 Hz, 1-H), 4.80 (d, J = 3.0 Hz, 1-H), 4.18 (q, J = 7.0 Hz, 1-H), 3.50−3.40 (m, 4-H), 2.50−2.40 (m, 4-H), 2.15−2.00 (m, 1-H), 1.75−1.65 (m, 1-H), 1.20 (t, J = 7.0 Hz, 3-H), 0.97 (d, J = 6.5 Hz, 1-H), 0.95 (d, J = 6.5 Hz, 1-H). Anal. Calcd for $C_{21}H_{27}N_3O_3ClF_3$-0.25 C_6H_{12}: C, 55.96; H, 6.26; N, 8.70. Found: C, 56.18; H, 6.25; N, 8.47.

5-(1-Methylethyl)-3-[3-(trifluoromethyl)phenyl]pyridazine (16k). This compound was prepared according to the general procedure given for Table 1 above and was obtained from the corresponding mixture of tetrahydropyridazine diastereomers by treatment with 5.0 equiv of KOH in EtOH at reflux for 4 h. After workup and recrystallization from EtOAc/cyclohexane, the product was obtained as a white solid (2.12 g, 38% yield): mp 67−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, J = 2.5 Hz, 1-H), 8.40 (s, 1-H), 8.35 (d, J = 8.0 Hz, 1-H), 7.82 (d, J = 8.0 Hz, 1-H), 7.77 (d, J = 2.5 Hz, 1-H), 7.70 (t, J = 8.0 Hz, 1-H), 3.10 (m, 1-H), 1.45 (d, J = 7.0 Hz, 6-H). Anal. Calcd for $C_{14}H_{13}N_2F_3$: C, 63.15; H, 4.92; N, 10.52. Found: C, 62.92; H, 4.97; N, 10.44.

Ethyl 4-Chloro-5,6-dihydro-6-(4-morpholinyl)-5-(trifluoromethyl)-3-[3-(trifluoromethyl)phenyl]-1(4*H*)-pyridazinecarboxylates (14l and 15l). These compounds were prepared according to the general procedure given for Table 1 above and were separated from the crude azodiene reaction by Prep-500 chromatography to give **14l** as a white solid (3.62 g, 25% yield) and **15l** as a yellow oil (2.37 g, 17% yield).

Data for **14l**: mp 134−135 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1-H), 7.94 (d, J = 7.8 Hz, 1-H), 7.61 (d, J = 7.8 Hz, 1-H), 7.50 (t, J = 7.8 Hz, 1-H), 5.17 (s, 1-H), 4.85 (s, 1-H), 4.38−4.28 (m, 2-H), 3.65−3.50 (m, 5-H), 2.65−2.50 (m, 4-H), 1.32 (t, J = 7.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 145.4, 137.1, 133.1 (q, J = 32.3 Hz), 131.7, 131.0, 128.5 (q, J = 3.7 Hz), 126.4 (q, J = 281.6 Hz), 125.9 (q, J = 272.6 Hz), 125.3 (q, J = 4.0 Hz), 68.1, 66.4 (q, 2.4 Hz), 65.4, 50.7, 47.3 (q, J = 25.6 Hz), 40.4 (q, J = 2.8 Hz), 15.7. Anal. Calcd for $C_{19}H_{20}N_3O_3ClF_6$: C, 46.78; H, 4.13; N, 8.61. Found: C, 46.87; H, 4.17; N, 8.53.

Data for **15l**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1-H), 8.00 (d, J = 8.0 Hz, 1-H), 7.78 (d, J = 8.0 Hz, 1-H), 7.65 (t, J = 8.0 Hz, 1-H), 5.50 (d, J = 7.0 Hz, 1-H), 5.23 (d, J = 4.0 Hz, 1-H), 4.48−4.40 (m, 2-H), 3.80−3.70 (m, 4-H), 3.30−3.20 (m, 1-H), 2.85−2.70 (m, 4-H), 1.45 (t, J = 7.0 Hz, 3-H).

5-(Trifluoromethyl)-3-[3-(trifluoromethyl)phenyl]pyridazine (16l). This compound was prepared according to the general procedure given for Table 1 above and was obtained from the corresponding mixture of tetrahydropyridazine diastereomers by treatment with 5.0 equiv of KOH in EtOH at reflux for 3 h. After workup the product was recrystallized from cyclohexane to give a white solid (1.35 g, 85% yield): mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1-H), 8.50 (s, 1-H), 8.40 (d, J = 8.0 Hz, 1-H), 8.15 (s, 1-H), 7.90 (d, J = 8.0 Hz, 1-H), 7.80 (t, J = 8.0 Hz, 1-H). Anal. Calcd for $C_{12}H_6N_2F_6$: C, 49.33; H, 2.07; N, 9.59. Found: C, 49.23; H, 2.10; N, 9.50.

Ethyl 4-Chloro-5,6-dihydro-6-(4-morpholinyl)-3-phenyl-6-(trifluoromethyl)-1(4*H*)-pyridazinecarboxylates (14m and 15m). These compounds were prepared according to the general procedure given for Table 1 above and were separated from the crude azodiene reaction by Prep-500 chromatography to **14m** as a white solid (5.68 g, 54% yield) and **15m** as a yellow oil (1.56 g, 15% yield).

Data for **14m**: mp 173−175 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.85 (m, 2-H), 7.55−7.45 (m, 3-H), 5.30 (s, 1-H), 5.02 (s, 1-H), 4.50−4.40 (m, 2-H), 3.80−3.60 (m, 5-H), 2.80−2.60 (m, 4-H), 1.45 (t, J = 7.0 Hz, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 144.5, 133.7, 129.5, 128.0, 126.0, 124.0 (q, J = 279.8), 66.0, 64.1, 63.0, 48.6, 45.5 (q, J = 25.4 Hz), 38.6 (q, J = 2.8 Hz), 13.9. Anal. Calcd for $C_{18}H_{21}N_3O_3ClF_3$: C, 51.50; H, 5.04; N, 10.01. Found: C, 51.39; H, 4.99; N, 9.89.

Data for **15m**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.60 (m, 2-H), 7.40−7.30 (m, 3-H), 5.40 (d, J = 6.0 Hz, 1-H), 5.05 (d, J = 3.0 Hz, 1-H), 4.30−4.20 (m, 2-H), 3.60−3.50 (m, 4-H), 3.10−2.95 (m, 1-H), 2.70−2.50 (m, 4-H), 1.30 (t, J = 7.0 Hz, 3-H).

3-Phenyl-5-(trifluoromethyl)pyridazine (16m). This compound was prepared according to the general procedure given for Table 1 above and was obtained from the corresponding mixture of tetrahydropyridazine diastereomers by treatment with 5.0 equiv of KOH in EtOH at reflux for 1.5 h. After workup, the product was recrystallized from EtOAc/cyclohexane to give a white solid (1.84 g, 51% yield): mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, J = 2.5 Hz, 1-H), 8.25−8.15 (m, 2-H), 8.10 (d, J = 2.5 Hz, 1-H), 7.65−7.55 (m, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 144.5 (q, J = 3.1 Hz), 134.5, 130.7, 129.3 (q, J = 34.7), 128.9, 126.9, 122.0 (q, J = 271.9 Hz), 119.1 (q, J = 3.8 Hz). Anal. Calcd for $C_{11}H_7N_2F_3$: C, 58.93; H, 3.15; N, 12.50. Found: C, 59.00; H, 3.18; N, 12.47.

3-Ethyl-4-methyl-6-phenylpyridazine (16n and 8). This compound was prepared according to the general procedure given for Table 1 above by treating the crude azodiene reaction with 1.1 equiv of KO*t*-Bu in *t*-BuOH at rt for 23 h. After workup and chromatography on the Prep-500, the product was obtained as a brown solid (22% yield). See **8** above for the analytical data.

3-Ethyl-4-methyl-6-[3-(trifluoromethyl)phenyl]pyridazine (16o). This compound was prepared according to the general procedure given for Table 1 above by performing the azodiene reaction followed by workup. The crude residue was then treated with 5 equiv of KOH in EtOH for 3 h. After workup, the product was obtained as a white solid (1.0 g, 12% yield): mp 49−51 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1-H), 8.20 (d, J = 8.0 Hz, 1-H), 7.62 (d, J = 8.0 Hz, 1-H), 7.05 (s, 1-H), 7.05 (t, J = 8.0 Hz, 1-H), 2.98 (q, J = 8.0 Hz, 2-H), 2.38 (s, 3-H), 1.38 (t, J = 8.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 155.8, 137.3, 136.7, 131.2 (q, J = 32.4 Hz), 129.9, 129.3, 126.0 (q, J = 7.6 Hz), 124.5,

124.0 (q, J = 271.0 Hz), 122.7 (q, J = 3.8 Hz), 26.4, 18.2, 12.2. Anal. Calcd for $C_{14}H_{13}N_2F_3$: C, 63.15; H, 4.92; N, 10.52. Found: C, 62.92; H, 4.98; N, 10.46.

3-Methyl-6-phenylpyridazine (16p). This compound was prepared according to the general procedure given for Table 1 above and was obtained as a brown solid directly from the azodiene reaction after chromatography on a Prep-500 (1.2 g, 13% yield): mp 98−100 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (apparent d, J = 7.0 Hz, 2-H), 7.72 (d, J = 9.0 Hz, 1-H), 7.55−7.45 (m, 3-H), 7.48 (d, J = 9.0 Hz, 1-H), 2.75 (s, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 157.1, 136.4, 129.7, 128.9, 127.2, 126.8, 123.8, 22.0. Anal. Calcd for $C_{11}H_{10}N_2$·0.25 H_2O: C, 75.62; H, 6.06; N, 16.03. Found: C, 75.48; H, 5.86; N, 15.91.

3-Methyl-6-[3-(trifluoromethyl)phenyl]pyridazine (16q). This compound was prepared according to the general procedure given for Table 1 above and was obtained as a white solid directly from the azodiene reaction after chromatography on a Prep-500 (1.44 g, 21% yield): mp 102−104 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1-H), 8.30 (d, J = 8.0 Hz, 1-H), 7.48 (d, J = 9.0 Hz, 1-H), 7.78 (d, J = 8.0 Hz, 1-H), 7.68 (t, J = 8.0 Hz, 1-H), 7.49 (d, J = 9.0 Hz, 1-H), 2.82 (s, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 155.6, 137.0, 131.2 (q, J = 32.4 Hz), 129.8, 129.3, 127.2, 126.1 (q, J = 3.7 Hz), 123.8 (q, J = 271.0 Hz), 123.6, 123.5 (q, J = 3.9 Hz), 21.8. Anal. Calcd for $C_{12}H_9N_2F_3$: C, 60.51; H, 3.81; N, 11.76. Found: C, 60.45; H, 3.81; N, 11.74.

3-Methyl-6-[3-(trifluoromethyl)phenyl]-4-pyridazinecarboxylic Acid (16r). This compound was prepared according to the general procedure given for Table 1 above by treatment of the crude azodiene reaction after workup with 5 equiv of NaOEt in EtOH at reflux for 4 h. The solvent was removed, and the mixture was poured into water. The pH was adjusted to 7 with dilute HCl, and the water was extracted three times with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and evaporated *in-vacuo* to give the acid as a brown solid after recrystallization from EtOAc (1.82 g, 22% yield): mp 189−190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65−8.50 (m, 3-H), 7.97 (d, J = 8.0 Hz, 1-H), 7.87 (t, J = 8.0 Hz, 1-H), 2.98 (s, 3-H), the acid proton was not observed; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 156.7, 156.1, 136.1, 130.5, 130.0, 129.9, 129.6 (q, J = 31.7 Hz), 126.3 (q, J = 2.9 Hz), 123.7 (q, 271.0 Hz), 123.5, 122.9 (q, J = 3.6 Hz), 20.9. Anal. Calcd for $C_{13}H_9N_2O_2F_3$·0.25HCl: C, 53.60; H, 3.20; N, 9.62. Found: C, 53.69; H, 3.45; N, 9.64.

Diethyl 6-(1-Morpholinyl)-3-[3-(trifluoromethyl)phenyl]-1,5(6*H*)-pyridazinedicarboxylate (17). This compound was prepared according to the general procedure given for Table 1 above and was isolated from the azodiene reaction by chromatography on a Prep-500 as a yellow solid (8.76 g, 55% yield): mp 128−129 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1-H), 8.10 (d, J = 8.0 Hz, 1-H), 7.70 (s, 1-H), 7.62 (t, J = 8.0 Hz, 1-H), 6.30 (s, 1-H), 4.60−4.40 (m, 2-H), 3.70−3.60 (m, 4-H), 2.70−2.50 (m, 4-H), 1.52 (t, J = 8.0 Hz, 3-H), 0.98 (t, J = 8.0 Hz, 3-H). Anal. Calcd for $C_{21}H_{24}N_3O_5F_3$: C, 55.38; H, 5.31; N, 9.23. Found: C, 55.26; H, 5.35; N, 9.21.

Ethyl 5-Acetyl-6-(4-morpholinyl)-3-[3-(trifluoromethyl)phenyl]-1(6*H*)-pyridazinecarboxylate (18). This compound was prepared according to the general procedure given for Table 1 above and was isolated from the azodiene reaction by chromatography on the Prep-500 as a yellow solid (8.61 g, 69% yield): mp 133−135 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.05 (m, 2-H), 7.75 (d, J = 8.0 Hz, 1-H), 7.76 (t, J = 8.0 Hz, 1-H), 7.55 (s, 1-H), 6.38 (s, 1-H), 4.55−4.45 (m, 2-H), 3.65−3.60 (m, 4-H), 2.60 (s, 3-H), 2.60-2.50 (m, 4-H), 1.51 (t, J = 7.0 Hz, 3-H). Anal. Calcd for $C_{20}H_{22}N_3O_4F_3$: C, 56.47; H, 5.21; N, 9.88. Found: C, 56.53; H, 5.23; N, 9.80.

6-[3-(Trifluoromethyl)phenyl]-4-pyridazinecarboxylic acid (19). This compound was prepared according to the general procedure given for Table 1 above. The azodiene reaction was performed to generate the crude dihydropyridazine **17** which was treated after workup with 5.0 equiv of KOH in EtOH at reflux for 3 h. The solvent was removed and the mixture was poured into water, extracted once with CH_2Cl_2 and acidified to pH = 1 with 12 N HCl. The acid **19** precipitated and was collected as a brown solid (247 g, 79% yield): mp 200−202 °C after trituration with EtOAc; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (d, J = 2.5 Hz, 1-H), 8.70 (d, J = 2.5 Hz, 1-H), 8.60 (s, 1-H), 8.58 (d, J = 8.0 Hz, 1-H), 7.98 (d, J = 8.0 Hz, 1-H), 7.87 (t, J = 8.0 Hz, 1-H), the acid proton was not observed; ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 164.7, 157.7, 148.5, 136.1, 130.8, 129.9, 129.5 (q, J = 34.0 Hz), 129.4, 128.5 (q, J = 3.8 Hz), 123.7 (q, 270.8 Hz), 123.3 (q, J = 3.8 Hz). Anal. Calcd for $C_{12}H_7N_2O_2F_3$: C, 53.74; H, 2.63; N, 10.45. Found: C, 53.49; H, 2.69; N, 10.31.

Ethyl 6-[3-(Trifluoromethyl)phenyl]-4-pyridazinecarboxylate (20). This compound was prepared according to the general procedure given for Table 1 above. Compound **17** was isolated by Prep-500 chromatography and was then heated in refluxing DMF for 30 min. After workup, the compound was obtained as a brown solid (3.28 g, 47 % yield): mp 131−132 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 2.5 Hz, 1-H), 8.50 (s, 1-H), 8.42 (d, J = 2.5 Hz, 1-H), 8.39 (d, J = 8.0 Hz, 1-H), 7.82 (d, J = 8.0 Hz, 1-H), 7.72 (t, J = 8.0 Hz, 1-H), 4.55 (q, J = 8.0 Hz, 2-H), 1.52 (t, J = 8.0 Hz, 3-H). Anal. Calcd for $C_{14}H_{11}N_2O_2F_3$: C, 56.76; H, 3.74; N, 9.46. Found: C, 56.82; H, 3.77; N, 9.41.

1-[6-[3-(Trifluoromethyl)phenyl]-4-pyridazinyl]ethanone (21). This compound was prepared according to the general procedure given for Table 1 above. Compound **18** was then heated to 175 °C in DMSO followed by partitioning between EtOAc/water. The crude product was recrystallized from EtOAc/cyclohexane and was obtained as a brown solid (2.09 g, 53% yield): mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, J = 2.5 Hz, 1-H), 8.50 (s, 1-H), 8.42 (d, J = 8.0 Hz, 1-H), 8.32 (d, J = 2.5 Hz, 1-H), 7.88 (d, J = 8.0 Hz, 1-H), 7.79 (t, J = 8.0 Hz, 1-H), 2.84 (s, 1-H). Anal. Calcd for $C_{13}H_9N_2OF_3$·0.25H_2O: C, 57.68; H, 3.54; N, 10.35. Found: C, 57.56; H, 3.38; N, 10.32.

Ethyl 4-Chloro-5,6-dihydro-5-methoxy-6-(4-morpholinyl)-3-[3-(trifluoromethyl)phenyl]-1(4*H*)-pyridazinecarboxylates (22−24). The morpholine enamine of methoxyacetaldehyde (11.20 g, 0.0783 mol, 1.17:1 mixture of trans:cis isomers) and Hünig's base (25 mL, 0.1424 mol) were stirred in CH_2Cl_2 (300 mL) at rt under N_2 while **13** (24.40 g, 0.0712 mol) was added dropwise as a solution in CH_2Cl_2 (100 mL) over 30 min. The mixture was heated at reflux for 1 h, and then the organic layer was washed 3 × 100 mL with water. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give a crude oil which was separated into three components by chromatography on the Prep-500. Compound **22** was isolated as a white solid (7.86 g, 25% yield). Compound **23** was isolated as a white solid (6.48 g, 20% yield). Compound **24** was isolated as a yellow oil (5.30 g, 16% yield).

Data for **22**: mp 99−100 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1-H), 7.98 (d, J = 7.8 Hz, 1-H), 7.57 (d, J = 7.8 Hz, 1-H), 7.47 (t, J = 7.8 Hz, 1-H), 4.99 (dd, J = 2.6, 1.4 Hz, 1-H), 4.61 (dd, J = 1.4, 1.4 Hz, 1-H), 4.42−4.32 (m, 2-H), 4.20 (dd, J = 2.6, 1.44 Hz, 1-H), 3.70−3.60 (m, 4-H), 3.49 (s, 3-H), 2.72−2.58 (m, 4-H), 0.85 (t, J = 7.1 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 144.8, 137.9, 132.9 (q, J = 32.4 Hz), 131.5, 130.9, 128.1 (q, J = 3.7 Hz), 126.0 (q, J = 272.5 Hz), 125.2 (q, J = 4.0 Hz), 77.8, 70.9, 68.1, 65.1, 59.5, 51.3, 43.7, 15.8. Anal. Calcd for $C_{19}H_{23}N_3O_4ClF_3$: C, 50.73; H, 5.15; N, 9.34. Found: C, 50.86; H, 5.16; N, 9.27.

Data for **23**: mp 143−144 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1-H), 7.98 (d, J = 8.1 Hz, 1-H), 7.59 (d, J = 8.1 Hz, 1-H), 7.48 (t, J = 8.1 Hz, 1-H), 5.18 (bd, J = approximately 3 Hz, 1-H), 5.06 (dd, J = 5.4, 1.0 Hz, 1-H), 4.31 (q, J = 7.1 Hz, 2-H), 3.81 (dd, J = 5.4, 3.3 Hz, 1-H), 3.60−3.50 (m, 4-H), 3.52 (s, 3-H), 2.80−2.70 (m, 2-H), 2.55−2.45 (m, 2-H), 1.42 (t, J = 7.1 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 145.7, 137.3, 133.0 (q, J = 32.5 Hz), 131.8, 131.0, 128.3 (q, J = 3.8 Hz), 125.9 (q, J = 272.5 Hz), 125.4 (q, 3.9 Hz), 78.9, 69.9, 68.4, 65.2, 59.2, 52.1, 46.6, 15.8. Anal. Calcd for $C_{19}H_{23}N_3O_4ClF_3$: C, 50.73; H, 5.15; N, 9.34. Found: C, 50.81; H, 5.16; N, 9.33.

Data for **24**: RI 1.5180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1-H), 7.88 (d, J = 8.0 Hz, 1-H), 7.65 (d, J = 8.0 Hz, 1-H), 7.55 (t, J = 8.0 Hz, 1-H), 5.23 (d, J = 4.6 Hz, 1-H), 5.15 (d, J = 4.6 Hz, 1-H), 4.45−4.30 (m, 2-H), 3.92 (t, J = 4.6 Hz, 1-H), 3.75−3.65 (m, 4-H), 3.60 (s, 3-H), 2.70−2.55 (m, 4-H), 1.42 (t,

J = 8.0 Hz, 3-H), 1.30 (t, J = 8.0 Hz, 3-H). Anal. Calcd for $C_{19}H_{23}N_3O_4ClF_3$: C, 50.73; H, 5.15; N, 9.34. Found: C, 50.81; H, 5.17; N, 9.26.

Ethyl 2-[2,2,2-Trichloro-1-phenylethylidene]hydrazinecarboxylate (25). Compound **10** (42.30 g, 0.205 mol) and NCS (63.83 g, 0.478 mol) were heated at reflux in CCl_4 (800 mL) under N_2 for 2 h, cooled, and filtered. The solvent was removed, and the crude **12** was taken up in SO_2Cl_2 (400 mL) and heated at reflux for 8 h using a dry ice−acetone condenser under N_2. The crude compound was recrystallized from cyclohexane to give a white solid (53.75 g, 84.6% yield): mp 156−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.56 (m, 4-H), 7.44−7.41 (m, 2-H), 4.27 (q, J = 9.3 Hz, 2-H), 1.31 (t, J = 9.3 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 148.2, 131.6, 130.7, 130.4, 128.4, 96.7, 63.4, 15.1. Anal. Calcd for $C_{11}H_{11}N_2O_2Cl_3$: C, 42.68; H, 3.58; N, 9.05. Found: C, 42.61; H, 3.57; N, 9.01.

General Procedure for the Reactions of Trichlorohydrazone 25 with Electron Rich Olefins (Tables 3 and 4). Compound **25** and EtN(i-Pr)$_2$ (2.0 equiv) were stirred in the specified solvent under N_2. The enamine was then added dropwise in 0.5 equiv portions/0.5 h. The loss of the azodiene was monitored by TLC. The mixture was then partioned between EtOAc/H_2O, the organic layer was dried ($MgSO_4$) and filtered through SiO_2, and the solvent was removed *in-vacuo*. The residue was chromatographed on the Prep-500 and/or recrystallized.

Ethyl [3-Chloro-4-ethyl-5-(4-morpholinyl)-2-phenyl-1*H*-pyrrol-1-yl]carbamate (26a) and 4-chloro-5-ethyl-3-phenylpyridazine (27a). Compound **25** (2.030 g, 6.556 mmol), EtN(i-Pr)$_2$ (2.0 equiv), and *trans*-1-morpholino-1-butene (1.480 g, 10.496 mmol) were heated at reflux in CH_2Cl_2 (50.0 mL) under N_2 for 6 h. Workup as described above for Table 3 afforded a crude oil which was purified by Prep-500 chromatography using 15% EtOAc/cyclohexane followed by RP-HPLC with 75% acetonitrile/H_20 to give **27a** as a yellow oil (0.230 g, 16.1% yield) and **26a** as a white solid (0.360 g, 14.6% yield).

Data for **26a**: mp 191.0−193.0 °C; ^{1}H NMR (400 MHz, acetone-d_6). δ 9.05 (s, 1-H), 7.48 (d, J = 7.4 Hz, 2-H), 7.41 (t, J = 7.4 Hz, 2-H), 7.31 (t, J = 7.4 Hz, 1-H), 4.28−4.05 (m, 2-H), 3.70−3.62 (m, 4-H), 3.15−3.08 (m, 4-H), 2.76 (q, J = 7.5 Hz, 2-H), 1.24 (t, J = 6.9 Hz, 3-H), 1.20 (t, J = 7.5 Hz, 3-H); ^{13}C NMR (100 MHz, acetone-d_6). δ 157.5, 137.3, 130.7, 130.3, 128.8, 128.1, 126.8, 115.9, 108.4, 68.4, 62.3, 52.5, 17.9, 15.8, 15.0; GC-MS (EI) 377 (M^+, 1-Cl). Anal. Calcd for $C_{19}H_{24}N_3O_3Cl$: C, 60.39; H, 6.40; N, 11.12. Found: C, 60.32; H, 6.32; N, 10.95.

Data for **27a**: RI 1.5966; ^{1}H NMR (400 MHz, $CDCl_3$). δ 9.38 (s, 1-H), 7.90−7.87 (m, 2-H), 7.65−7.55 (m, 3-H), 2.95 (q, J = 7.5 Hz, 2-H), 1.43 (t, J = 7.5 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$). δ 161.1, 151.9, 143.0, 137.8, 136.7, 130.9, 130.7, 129.4, 25.0, 13.3; GC-MS: 218 (M^+, 1-Cl). Anal. Calcd for $C_{12}H_{11}N_2Cl$: C, 65.91; H, 5.07; N, 12.81. Found: C, 65.81; H, 5.14; N, 12.76.

Ethyl [3-Chloro-4-methoxy-5-(4-morpholinyl)-2-phenyl-1*H*-pyrrol-1-yl]carbamate (26b). Compound **25** (2.051 g, 6.625 mmol), EtN(i-Pr)$_2$ (2.0 equiv), and 1-morpholino-2-methoxyethene (3.0 mL, 3.090 g, 21.578 mmol) were stirred in CH_2Cl_2 (50.0 mL) under N_2 at rt. After 2.5 h, the azodiene was gone by TLC. After workup, according to the general procedure for Table 3, the crude compound was purified by Prep-500 chromatography using 25% EtOAc/ hexanes to give **26b** as a white solid (0.266 g, 11% yield).

Data for **26b**: mp 174.6−175.7 °C; ^{1}H NMR (400 MHz, acetone-d_6). δ 9.16 (s, 1-H), 7.51 (d, J = 7.4 Hz, 2-H), 7.45 (t, J = 7.4 Hz, 2-H), 7.36 (t, J = 7.4 Hz, 1-H), 4.25−4.04 (m, 2-H), 3.89 (s, 3-H), 3.78−3.62 (m, 4-H), 3.11 (bs, 4-H), 1.27 (t, J = 7.0 Hz, 3-H); ^{13}C NMR (100 MHz, acetone-d_6). δ 157.3, 135.6, 130.6, 130.0, 129.9, 128.7 128.0, 125.1, 116.3, 67.9, 62.4, 62.1, 52.3, 14.7; GC-MS (EI) 379 (M^+, 1-Cl). Anal. Calcd for $C_{18}H_{22}N_3O_4Cl$-0.25 H_2O: C, 56.25; H, 5.90; N, 10.93. Found: C, 56.24; H, 5.97; N, 11.18.

Ethyl [3-Chloro-4-(1-methylethyl)-5-(4-morpholinyl)-2-phenyl-1*H*-pyrrol-1-yl]carbamate (26c) and 4-Chloro-5-(1-methylethyl)-3-phenylpyridazine (27c). Compound **25** (2.030 g, 6.557 mmol), EtN(i-Pr)$_2$ (2.0 equiv), and *trans*-1-morpholino-3-methyl-1-butene (4.0 mL, 3.380 g, 21.806 mmol) were heated at reflux in CH_2Cl_2 (50.0 mL) under N_2 for 24 h. After workup as described above for Table 3, the crude oil was purified by Prep-500 chromatography using 20% EtOAc/ hexanes to give **27c** as a white solid (0.549 g, 36.0% yield) and **26c** as a tan solid (0.594 g, 23% yield).

Data for **26c**: mp 176.0−178.0 °C; ^{1}H NMR (400 MHz, acetone-d_6). δ 9.12 (s, 1-H), 7.50−7.34 (m, 5-H), 4.25−4.10 (m, 2-H), 3.71 (bs, 4-H), 3.21 (septet, J = 7.2 hz, 1-H), 3.11 (bs, 4-H), 1.40 (d, J = 7.2 hz, 6-H), 1.26 (t, J = 7.2 hz, 3-H); APT ^{13}C NMR (75 MHz, acetone-d_6) δ positive peaks, 156.0, 135.0, 129.8, 126.0, 119.0, 106.0, 68.0, 61.0, 52.0; δ negative peaks, 130.0, 128.0, 127.0, 25.0, 21.5, 14.0; GC-MS 391 (M^+, 1-Cl). Anal. Calcd for $C_{20}H_{26}N_3O_3Cl$: C, 61.30; H, 6.69; N, 10.72. Found: C, 61.15; H, 6.62; N, 10.58.

Data for **27c**: mp 80.0−82.0 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.21 (s, 1-H), 7.79−7.74 (m, 2-H), 7.60−7.55 (m, 3-H), 3.54 (septet, J = 7.0 Hz, 1-H), 1.43 (d, J = 7.0 Hz, 6-H); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.0, 149.4, 145.6, 137.0, 135.9, 130.2, 129.9, 128.7, 30.0, 21.3; GC-MS (EI) 232 (M^+, 1-Cl). Anal. Calcd for $C_{13}H_{13}N_2Cl$: C, 67,10; H, 5.63; N, 12.04. Found: C, 67.17; H, 5.66; N, 12.08.

Ethyl [3-Chloro-5-(4-morpholinyl)-2,4-diphenyl-1*H*-pyrrol-1-yl]carbamate (26d) and 4-Chloro-3,5-diphenylpyridazine (27d). Compound **25** (2.04 g, 6.589 mmol), EtN(i-Pr)$_2$ (2.0 equiv), and *trans*-1-morpholino-2-phenylethylene (3.17 g, 16.772 mmol) were heated at reflux in CH_2Cl_2 (50.0 mL) for 18 h. After workup, following the general procedure above for Table 3, the crude solid was purified by Prep-500 chromatography using 15% EtOAc/cyclohexane to give **26d** as a tan solid (2.10 g, 75%) and compound **27d** as a tan solid (0.122 g, 7% yield).

Data for **26d**: mp 165−168 °C; ^{1}H NMR (400 MHz, acetone-d_6). δ 9.24 (s, 1-H), 7.56−7.33 (m, 10-H), 4.24−4.09 (m, 2-H), 3.56 (bs, 4-H), 2.92−2.85 (m, 4-H), 1.24 (t, J = 7.0 Hz, 3-H); ^{13}C NMR (100 MHz, acetone-d_6). δ 156.4, 137.3, 132.4, 130.6, 129.4, 128.1, 127.9, 127.6, 127.1, 67.5, 62.4, 51.8, 14.4. Anal. Calcd for $C_{23}H_{24}N_3O_3Cl$: C, 64.86; H, 5.68; N, 9.87. Found: C, 64.98; H, 5.72; N, 9.76.

Data for **27d**: mp 81−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1-H), 7.78−7.40 (m, 10-H); ^{13}C NMR (100 MHz, $CDCl_3$). δ 161.6, 150.9, 140.6, 136.2, 135.8, 133.9, 130.6, 130.5, 130.4, 129.9, 129.6, 129.0; GC-MS 266 (M^+, 1-Cl). Anal. Calcd for $C_{16}H_{11}N_2Cl$: C, 72.05; H, 4.16; N, 10.50. Found: C, 72.15; H, 4.10; N, 10.55.

4-Chloro-6,7-dihydro-3-phenyl-5*H*-cyclopenta[*c*]pyridazine (28). Compound **25** (3.056 g, 9.871 mmol), EtN(i-Pr)$_2$ (2 equiv), and 1-morpholino-1-cyclopentene (2.0 mL, 1.914 g, 12.491 mmol) were heated at reflux in CH_2Cl_2 (50.0 mL) under N_2 for 1.5 h. The solution was then cooled to room temperature and 6 M HCl (0.5 mL) was added and then left to stir for 18 h. After the workup described in the general procedure for Table 4, the crude solid was purified by Prep-500 chromatography using 20% EtOAc/hexane, and **28** was recovered as a tan solid (1.086 g, 48% yield).

Data for **28**: mp 116.0−119.8 °C; ^{1}H NMR (400 MHz, acetone-d_6). δ 7.75−7.72 (m, 2-H), 7.54−7.52 (m, 3-H), 3.29 (t, J = 7.6 Hz, 2-H), 3.13 (t, J = 7.6 Hz, 2-H), 2.27 (pentuplet, J = 7.6 Hz, 2-H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.5, 157.8, 142.7, 136.8, 133.6, 130.4, 130.0, 128.9, 33.4, 31.0, 22.8; GC-MS 230 (M^+, 1-Cl). Anal. Calcd for $C_{13}H_{11}N_2Cl$: C, 67.72; H, 4.81; N, 12.15. Found: C, 67.62; H, 4.85; N, 12.21.

Ethyl 4-Chloro-6,7-dihydro-3-phenyl-1(5*H*)-cinnolinecarboxylate (29) and 4-Chloro-5,6,7,8-tetrahydro-3-phenylcinnoline (30). Compound **25** (2.075 g, 6.702 mmol), EtN(i-Pr)$_2$ (2 equiv), and 1-morpholino-1-cyclohexene (2.0 mL, 1.990 g, 11.898 mmol) were heated at reflux in CH_2Cl_2 (50.0 mL) under N_2 for 5 h. After workup according to the general procedure for Table 4, the crude product was separated by Prep-500 chromatography using 10% EtOAc/hexane to give **29** as a bright yellow solid (0.435 g, 44% yield) and compound **30** as a tan solid (0.147 g, 9% yield).

Data for **29**: mp 95.0−97.0 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.56−7.53 (m, 2-H), 7.46−7.44 (m, 3-H), 6.40 (t, J = 5.0 Hz, 1-H), 4.26 (q, J = 7.4 Hz, 2-H), 2.67 (t, J = 6.6 Hz, 2-H), 2.36−2.31 (m, 2-H), 1.80−1.73 (m, 2-H), 1.29 (t, J = 7.4 Hz, 3-H); ^{13}C NMR (100 MHz, acetone-d_6). δ 154.0, 148.5, 141.4, 135.9, 131.7, 129.9, 129.8, 128.7, 117.5, 113.1, 63.2, 28.5, 25.4,

20.7, 14.7; GC-MS 316 (M^+, 1-Cl). Anal. Calcd for $C_{17}H_{17}N_2O_2Cl$: C, 64.46; H, 5.41; N, 8.84. Found: C, 64.42; H, 5.34; N, 8.92.

Data for **30**: mp 93.4−94.7 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.73−7.71 (m, 2-H), 7.55−7.51 (m, 3-H), 3.30−3.20 (m, 2-H), 2.85−2.70 (m, 2-H), 1.98−1.80 (m, 4-H); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.6, 158.0, 137.2, 137.1, 136.6, 130.4, 129.9, 128.9, 30.9, 26.9, 22.5, 22.4; GC-MS 244 (M^+, 1-Cl). Anal. Calcd for $C_{14}H_{13}N_2Cl$: C, 68.75; H, 5.36; N, 11.45. Found: C, 68.81; H, 5.41; N, 11.36.

***N*-Aminopyrrole 31, 4-Chloro-6,7,8,9-tetrahydro-3-phenyl-5*H*-cyclohepta[*c*]pyridazine (32), and Enamine 33.** Compound **25** (2.025 g, 6.541 mmol), EtN(*i*-Pr)$_2$ (2.0 equiv), and 1-morpholino-1-cycloheptene (1.5 mL, 1.920 g, 10.602 mmol) were heated at reflux in CH_2Cl_2 under N_2 for 4 h. After workup according to the general procedure for Table 4, the crude solid was separated by Prep-500 chromatography using 20% EtOAc/hexane to give three fractions which were further purified by RP-HPLC using 25% H_2O/CH_3CN. Compound **31** was recrystallized from hexane to give a white solid (0.777g, 36% yield). Compound **32** was recrystallized from hexane to give a tan solid (0.201 g, 12% yield). Compound **33** was recrystallized from hexane to give a white solid which was a mixture of two isomers (1.269 g, 31% yield).

Data for **31**: mp 177.2−178.1 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.40 (s, 1-H), 7.46−7.34 (m, 5-H), 6.03 (dt, J = 11.6, 1.8 Hz, 1-H), 5.72 (dt, J = 11.6, 5.6 Hz, 1-H), 2.93−2.74 (m, 2-H), 2.46−2.41 (m, 2-H), 2.0−1.91 (m, 2-H), 1.18 (t, J = 7.0 Hz, 3-H); APT ^{13}C NMR (75 MHz, acetone-d_6) δ positive peaks, 154.5, 132.8, 129.5, 114.3, 114.2, 108.0, 61.0, 31.0, 28.0, 22.0; δ negative peaks, 129.6, 128.2, 127.7, 127.0, 119.2, 14.0; GC-MS 330 (M^+, 1-Cl). Anal. Calcd for $C_{18}H_{19}N_2O_2Cl$: C, 65.39; H, 5.79; N, 8.47. Found: C, 65.30; H, 5.81; N, 8.51.

Data for **32**: mp 107.0−112.3 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.56−7.54 (m, 2-H), 7.38−7.36 (m, 3-H), 3.17−3.15 (m, 2-H), 3.02−2.99 (m, 2-H), 1.83−1.77 (m, 2-H), 1.66−1.56 (m, 4-H); ^{13}C NMR (100 MHz, acetone-d_6) δ 165.5, 159.0, 141.5, 137.6, 135.6, 130.4, 129.9, 128.9, 37.0, 32.4, 30.0, 27.0, 26.8; GC-MS 258 (M^+, 1-Cl). Anal. Calcd for $C_{15}H_{15}N_2Cl$: C, 69.67; H, 5.85; N, 10.83. Found: C, 69.41; H, 5.83; N, 10.74.

Data for **33**: mp 156.1−159.6 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.39−8.95 (four s, 1-H), 7.46−7.30 (m, 5-H), 4.13−4.10 (m, 2-H), 3.62−3.60 (m, 4-H), 3.38−3.35 (t, J = 5.6 Hz, 1-H), 2.80−1.60 (m, 12-H), 1.17 (q, J = 6.6 Hz, 3-H); ^{13}C NMR (100 MHz, acetone-d_6). δ 156.5, 134.9, 134.7, 130.8, 130.5, 130.5, 128.9, 128.2, 127.6, 127.6, 118.8, 110.6, 110.6, 67.8, 67.7, 62.4, 59.2, 59.2, 52.5, 52.4, 30.7, 28.2, 27.9, 25.1, 25.1, 24.9, 14.8; GC-MS 344 (M^+ − CO_2Et, 1-Cl). Anal. Calcd for $C_{22}H_{28}N_3O_3Cl$: C, 63.96; H, 7.00; N, 9.73. Found: C, 64.06; H, 7.05; N, 9.69.

***N*-Aminopyrrole (34) and Ethyl [2-Chloro-2-[2-(4-morpholinyl)-2-cycloocten-1-ylidene]-1-phenylethylidene]-hydrazinecarboxylate (35).** Compound **25** (2.016 g, 6.512 mmol), EtN(*i*-Pr)$_2$ (2.0 equiv), and 1-morpholino-1-cyclooctene (2.0 mL, 3.260 g, 16.692 mmol) were heated at reflux in CCl_4 (50.0 mL) for 24 h. After workup according to the general procedure for Table 4, the crude solid was purified by Prep-500 chromatography using 20% EtOAc/hexane. Compound **35** was recrystallized from hexanes to give a white solid which was a mixture of isomers (0.857g, 31% yield). Compound **34** was recrystallized from hexanes to give a white solid (0.071 g, 3% yield).

Data for **34**: mp 114.9−118.2 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.39 (s, 1-H), 7.32−7.18 (m, 5-H), 6.21 (d, J = 11.2 Hz, 1-H), 5.57 (dt, J = 11.2, 7.8 Hz, 1-H), 4.01−3.92 (m, 2-H), 2.80−2.60 (m, 2-H), 2.35−2.25 (m, 2-H), 1.74−1.66 (m, 2-H), 1.55−1.48 (m, 2-H), 1.03 (t, J = 7.2 Hz, 3-H); APT ^{13}C NMR (75 MHz, acetone-d_6) δ positive peaks, 155.5, 131.3, 116.9, 113.8, 113.5, 108.3, 61.5, 26.8, 26.0, 24.0, 22.0; δ negative peaks, 129.5, 129.0, 128.2, 127.8, 121.8, 14.0; GC-MS 344 (M^+, 1-Cl). Anal. Calcd for $C_{19}H_{21}N_2O_2Cl$: C, 66.18; H, 6.14; N, 8.12. Found: 66.21; H, 6.11; N, 8.16.

Data for **35**: mp 170.4−173.7 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.39−9.05 (four s, 1-H), 7.47−7.30 (m, 5-H), 4.12−4.07 (m, 2-H), 3.66−3.62 (m, 4-H), 3.70−3.64 (m, 4-H), 3.57−3.47 (m, 2-H), 2.49−2.38 (m, 2-H), 1.18−1.13 (m, 3-H); ^{13}C NMR (100 MHz, acetone-d_6). δ 156.6, 132.1, 130.8, 130.5, 130.4, 129.0, 129.0, 128.9, 128.1, 117.3, 117.2, 117.1, 113.9, 67.7, 67.7, 62.3, 62.3, 61.2, 61.1, 61.0, 61.1, 61.0, 52.7, 52.6, 33.8, 33.5, 27.2, 26.8, 21.4, 21.3, 21.2, 14.8; GC-MS 344 (M^+, 1-Cl). Anal. Calcd for $C_{23}H_{30}N_3O_3Cl$: C, 63.96; H, 7.00; N, 9.73. Found: C, 64.06; H, 7.05; N, 9.69.

4-Chloro-5,6,7,8-tetrahydro-3-phenylcinnoline (30) from Compound 29. Compound **29** (1.460 g, 4.608 mmol) and 6 M HCl (0.5 mL) were taken up in DMF (40.0 mL) and stirred under N_2 at rt. Within 1 h the reaction was completed as indicated by TLC. The solution was poured into H_2O (200.0 mL) and extracted with EtOAc. The solvent was removed *in-vacuo* recovering a tan solid (0.913 g, 81% yield) which was identical to sample obtained previously. See above for analytical data.

Cyclization of Enamine 33 To Give *N*-Aminopyrrole 31. Compound **33** (0.122 g, 0.292 mmol) was taken up in DMF (2.0 mL) and heated at reflux under N_2 for 4 h. The solution was cooled to room temperature, poured into H_2O, extracted with EtOAc, dried with $MgSO_4$, and filtered, and the solvent was removed *in-vacuo* to give a tan solid. The crude solid was then purified by HPLC using 8% 2-propanol/hexanes to give **31** as a white solid (0.060 g, 62% yield). This sample was identical to the one described above.

Cyclization of Enamine 35 to *N*-Aminopyrrole (34). Compound **35** (0.212 g, 0.491 mmol) was taken up in DMF (20.0 mL) and heated at reflux for 7 h. The solvent was removed *in-vacuo*. The crude solid was partitioned with H_2O/EtOAc. The organic layer was dried with $MgSO_4$ and filtered. The solvent was removed *in-vacuo* to give **34** as a tan solid (0.165g, 97% yield) which was identical to the previously obtained sample described above.

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