A [3 + 2] and [4 + 3] Cycloaddition Approach to N-Heterocycles via Pd-Catalyzed TMM Reactions with Imines

Barry M. Trost* and Christopher M. Marrs

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080

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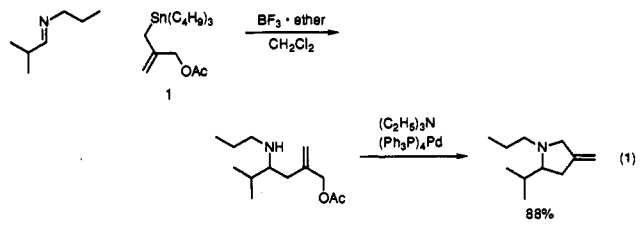
Abstract: The question of cycloadditions of (trimethylenemethane)palladium complexes to heteroatom unsaturation is probed in the context of pyrrolidine syntheses. Whereas simple imines fail to react, imines possessing an electron-withdrawing group at either the carbon or nitrogen enhance the electrophilicity of the imine sufficiently to make it an excellent acceptor. Palladium(0) complexes catalyze cycloadditions of 2-((trimethylsilyl)methyl)allyl esters to *N*-tosyl- and *N*-nitroimines. The stronger electron-withdrawing nature of the nitro group permits nitrimines derived from relatively hindered ketones to participate. Conjugated cisoid imines lead to [4 + 3] cycloadditions—a process which constitutes an azepine synthesis. Substituted TMM precursors cycloadd with high regioselectivity. The results are consistent with a two-step addition process. Some of the simple examples explored to determine the scope and limitations of the process reveal simple syntheses of proline and nicotine analogues. The successful employment of imines as direct acceptors for TMM–PdL_2 opens a new chapter on metal-catalyzed cycloadditions.

The widespread importance of pyrrolidines stimulates the search for new synthetic strategies. Among the most effective strategies for ring construction is cycloaddition—a strategy that has been applied for the synthesis of pyrrolidines mainly through 1,3-dipolar cycloaddition of azomethine ylides.[1,2] On the other hand, cycloadditions to imines have not been a viable strategy, in part, because of the absence of a suitable all-carbon 1,3-dipole and, in part, because of the low reactivity of imines toward additions.

Our discovery of a facile all-carbon 1,3-dipole synthon in the form of a (trimethylenemethane)palladium complex[3] induced us to explore its reactivity toward simple imines with no success. We modified the strategy by converting the trimethylenemethane unit into a more conventional synthon for a 1,3-dipole by synthesizing the organostannane **1** which undergoes very smooth imine addition in the presence of a Lewis acid, and the resulting adduct cyclizes to the desired pyrrolidines when exposed to a Pd(0) catalyst (eq 1).[4] This two-step protocol is effective with



(1)

a very wide diversity of imines and proceeds in very high yields. A related sequence employing organozinc intermediates has been reported by the Klumpp group.[5]

Nevertheless, the attractiveness of a one-step protocol with our ((trimethylsilyl)methyl)allyl acetate (**2**) precursor lured us to continue to search for a suitable system. The report of Kemmit and Jones that imines undergo Ni or Pd catalyzed cycloaddition with 2-((trimethylsilyl)methyl)allyl mesylate and, in a few cases, acetate suggested that the one-step sequence was feasible.[6] Unfortunately, our group had difficulties reproducing this approach.

A potential solution may be inferred from the success of *N*-sulfonylimines in Diels–Alder reactions[7] since there seems to be a very good correlation, in general, between Pd-catalyzed trimethylenemethane cycloadditions and the Diels–Alder reaction. The difficulty lies in the purity of the *N*-tosylimines since in many instances these species are employed as crude intermediates or generated *in situ*.[8] The requirement for nonprotic conditions and the potential sensitivity of a catalytic process to minor impurities made such protocols unattractive. Our discovery of a very convenient high-yielding method for making *N*-tosylimines[9] provided the vehicle to explore their potential as TMM–PdL_2 acceptors. The success of these studies led to the examination of other "activated" imines as suitable acceptors. Thus, imines bearing other electron-withdrawing groups on nitrogen (nitro and acyl) and/or carbon were also examined. Herein, we report the successful cycloaddition to imines and its scope and limitations.

Cycloadditions of *N*-Tosylimines. Our initial attempt explored the reaction of imine **3** (Ar = Ph) with the TMM precursor **2a** using tetrakis(triphenylphosphine)palladium (**4**) generated *in situ* by reducing palladium acetate in the presence of triphenylphosphine with *n*-butyllithium. The nearly quantitative yield of

(1) For reviews, see: Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231. Pearson, W. H. In *Studies in Natural Products Chemistry*; Rahman, A. U., Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 323. Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, *27*, 981. Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89. Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.

(2) For some interesting recent approaches involving the equivalent of [4 + 1] additions, see: Pearson, W. H.; Bergneier, S. C.; Degan, S.; Lin, K.-C.; Poon, Y.-F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5719. Andersson, P. G.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 8696.

(3) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429; **1983**, *105*, 2315. For a review, see: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. Also, see: Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77.

(4) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778.

(5) Van der Leuw, J.; Van der Baan, J. L.; Scholter, H.; Out, G. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.* **1988**, *29*, 3579.

(6) Jones, M. D.; Kemmitt, R. D. *Chem. Commun.* **1986**, 1201.

(7) For reviews, see: Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525.

(8) For various synthetic methods, see: Lichtenburger, J.; Fleury, S.; Barrett, B. *Bull. Soc. Chim. Fr.* **1955**, 669. Kretov, A. E.; Abrazhanova, E. A. *J. Chem. Chem. USSR (Engl. Transl.)* **1957**, *27*, 2051. Albrecht, R.; Kresze, G.; Mlakar, B. *Chem. Ber.* **1964**, *87*, 487. Naddaka, V. I.; Gar'kin, V. P.; Obayan, K. V. *Zh. Org. Khim.* **1981**, *17*, 2020. Derkach, N. Y.; Barashenkov, G. G.; Slosarendo, E. *Zh. Org. Khim.* **1982**, *17*, 2020. Suzuki, H.; Takeda, S.; Hanazaki, Y. *Chem. Lett.* **1985**, 679. Jennings, W. B.; Lovely, C. S. *Tetrahedron Lett.* **1988**, *29*, 3725. Sisko, J.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 3037. Holmes, A. B.; Hamley, P.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Synlett* **1991**, 29. Suzuki, H.; Nakaya, K.; Matano, Y.; Ogawa, T. *Chem. Lett.* **1991**, 105. Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777.

(9) Trost, B. M.; Marrs, C. *J. Org. Chem.* **1991**, *56*, 6468.

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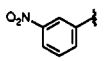
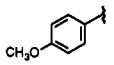
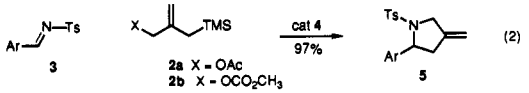
Table I. Cycloadditions with Aryl Tosylimines[a]

entry	3, Ar =	TMM precursor	ligand[b]	T (°C)	isolated yield (%)
1	Ph	**2a**	Ph_3P	64	97
2		**2b**	$(iC_3H_7O)_3P$	40	90
3		**2a**	$(iC_3H_7O)_3P$	64	95
4		**2b**	$(iC_3H_7O)_3P$	40	94
5		**2a**	Ph_3P	64	95
6		**2b**	$(iC_3H_7O)_3P$	40	99
7		**2a**	Ph_3P	64	98

[a] See eq 2. [b] Palladium acetate is employed as the palladium source in all cases.

methylenepyrrolidine **5** (Ar = Ph) led to an examination of other aryl imines. Both electron-poor and electron-rich aryl imines

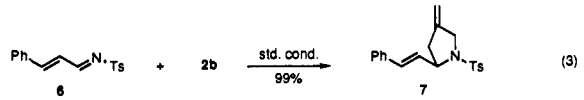


(2)

participate in cycloaddition in excellent yields (see Table I) in refluxing THF. The choice of ligand appears relatively unimportant. Both triphenylphosphine and triisopropyl phosphite serve as satisfactory ligands. The ease of generation of the active catalyst by simply reacting triisopropyl phosphite with palladium acetate in which the phosphite serves as both reductant and ligand[10] led to its adoption for the general procedure. No advantages are apparent using $(dba)_3Pd_2{\cdot}CHCl_3$ as the palladium source. The greater convenience of palladium acetate made it the palladium source of choice.

Using the carbonate **2b** TMM precursor rather than the acetate allows the reaction to be performed at lower temperatures. Since substrates bearing both electron-rich (Table I, entry 6) and electron-poor (Table I, entry 4) aryl rings cycloadd at this lower temperature, the protocol employing the carbonate precursor **2b** may be the preferred one for aryl substrates in general.

The *N*-tosylimine from cinnamaldehyde **6** undergoes cycloaddition to the imine and not to the double bond to give pyrrolidine **7** (eq 3). Interestingly, even the aliphatic conjugated imine **8** participates (eq 4). In such cases, the issue of deprotonation as



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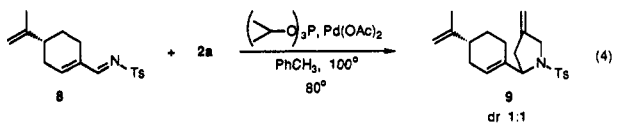


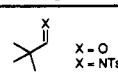
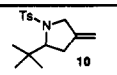
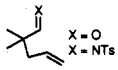
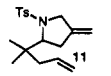
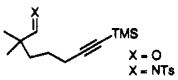
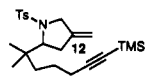
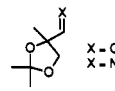
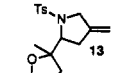
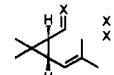
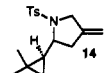
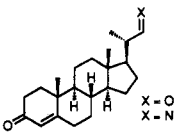
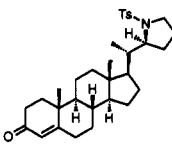
(4)

well as double-bond addition arises. The good yield of pyrrolidine **9**, albeit as a diastereomeric mixture, reveals that neither is a serious problem.

The success of the cycloaddition of eq 4 emboldened us to examine aliphatic tosylimines (Table II and eq 5). The sensitivity of these imines toward decomposition, largely hydrolysis, led to their formation from the starting aldehyde and direct use in the

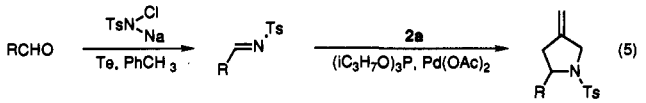
(10) Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668. Trost, B. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1985**, *107*, 1293.

Table II. Cycloadditions with Aliphatic *N*-Tosylimines[a]

entry	precursor	solvent	cycloadduct	yield[b] (%)
1		$PhCH_3$		90
2		$PhCH_3$		50[c]
3		$PhCH_3$		80
4		$PhCH_3$		50[c,d]
5		1,4-dioxane		22[c,d]
6		1,4-dioxane		76

[a] All reactions were performed with TMM precursor **2a** at 100° in the stated solvent. [b] Since the imines were not purified, yields are based upon starting aldehyde. [c] Yields not optimized. [d] 1:1 diastereomeric ratio.

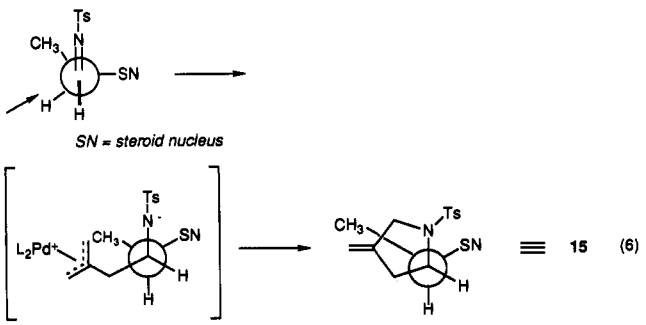
cycloaddition without purification. Thus, the yield is based upon the starting aldehyde. The greater sluggishness of these substrates to nucleophilic addition necessitated somewhat higher temperatures, with both toluene and dioxane being equally effective. Both nonenolizable (Table II, entries 1–4) and enolizable (Table II, entries 5 and 6) *N*-tosylimines succeed. No attempt has been



(5)

made to optimize yields. The lower yields observed in entries 2, 4, and 5 (Table II) may reflect the state of the *N*-tosylimine rather than cycloaddition since the *N*-tosylimines are utilized without any purification.

Whereas pyrrolidines **13** and **14** are diastereomeric mixtures (Table II, entries 4 and 5), the adduct of steroidal imine **15** (Table II, entry 6) appears homogenous by both spectroscopic and chromatographic criteria. This observation parallels our results from cycloaddition to the corresponding aldehyde.[11] By analogy to that case, a Felkin–Anh model allows assignment of the stereochemistry as depicted in eq 6.

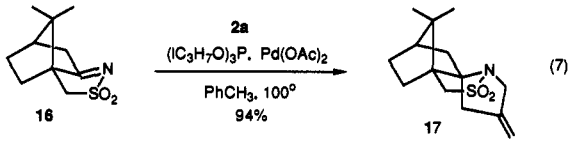


(6)

While *N*-tosylimines derived from aldehydes appear to be very general in their participation in Pd-catalyzed TMM cycloaddi-

(11) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902.

tions, sulfonylimines derived from ketones have been more varied. Thus, the strained camphorsulfonic acid derived imine **16**[12] and imine **18** derived from an enone both gave high yields of cycloadducts **17** and **19** (eqs 7 and 8). Adduct **17** is diastereomerically pure with the stereochemistry assigned on the basis of least hindered attack, as demonstrated in other additions to this imine.[12] On the other hand, no cycloadduct is obtained from the *N*-tosylimines of 2-hexanone or cyclooctanone. Ease of enolization in these latter cases may account for this difference in behavior.



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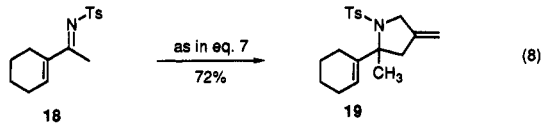
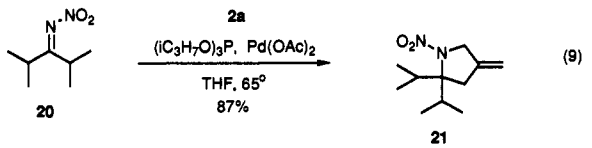


(8)

Cycloadditions of Nitrimines. Nitrimines[13] represent an almost unexplored class of activated imines; yet, the strong activating nature of the nitro group makes these analogues quite attractive as potential acceptors in cycloaddition. Furthermore, while the aldehyde derivatives are quite sensitive and difficult to handle, the ketone analogues are sufficiently stable and volatile that they can be purified by distillation. In this respect, they have an advantage over the *N*-tosylimines. The possibility of expanding the scope of ketone imine acceptors led to our study of their cycloadditions.

These acceptors are readily available by treatment of the ketoxime with nitrous acid.[13] The known nitrimines **20**[13b] and **22**[13a,d] were subjected to cycloadditions under our standard conditions in THF at reflux. Gratifyingly, these hindered imines participate quite satisfactorily in the cycloaddition (eqs 9 and 10). Interestingly, the acetate TMM precursor **2a** proved



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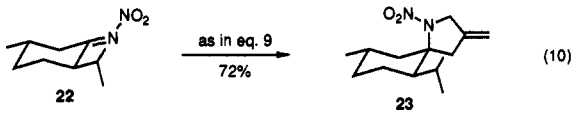


(10)

effective, whereas the carbonate precursor **2b** did not. The enhanced basicity of the reaction system associated with this latter reagent due to liberation of methoxide may account for this behavior. The adduct of menthone imine **23** is formed with a 17:1 diastereoselectivity. By a combination of ^{1}H NMR techniques and spin decoupling, the full tentative assignment for the major adduct is depicted in Figure 1, on the basis of this data. While these hindered acceptors gave good yields of cycloadducts, the unhindered nitrimines from cyclohexanone and 2-nonanone

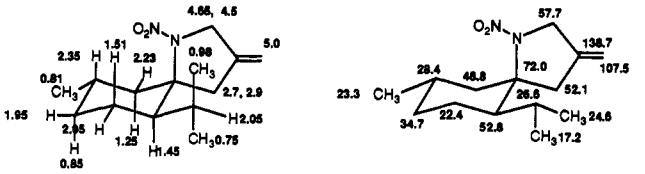
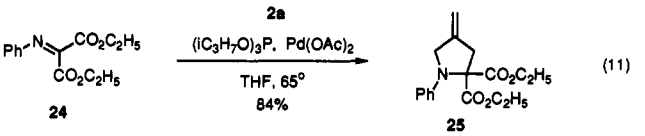


Figure 1. Assignment of ^{1}H and ^{13}C NMR resonances for menthyl nitrimine cycloadduct.

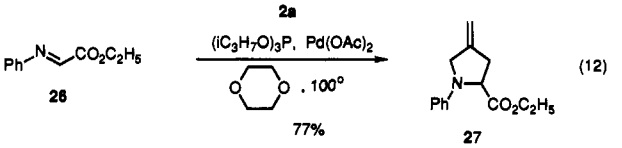
failed. Ease of enolization in these latter cases again may account for this observation.

Other Imines. Whereas enhanced reactivity of the imine in the above acceptors was achieved by placing an electron-withdrawing group on nitrogen, placing this group on the imine carbon normally also increases reactivity.[14] Interest in proline analogues led to our exploration of ketomalonate imine **24** (eq 11). The cycloadduct **25** forms under rather mild conditions.



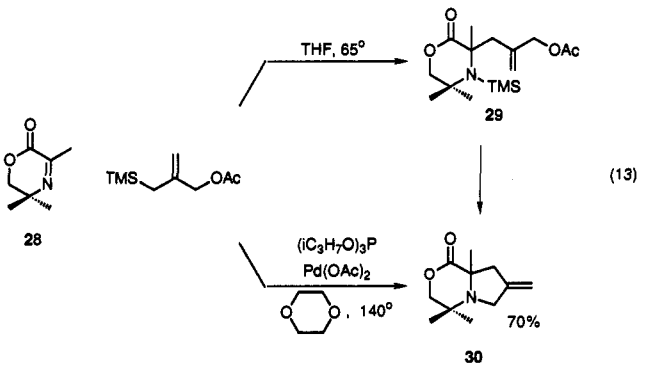
(11)

Removing one of the esters as in glyoxalate imine **26** still allows excellent cycloaddition but requires a somewhat higher temperature to give ethyl 4-methylene-*N*-phenylprolinate (**27**) (eq 12).



(12)

The cyclic pyruvate imine **28** proved quite interesting. Under our normal conditions in THF at reflux, a 1:1 adduct of the TMM precursor **2a** and the imine forms, as established by a molecular ion peak at *m/e* 327.1924 (calcd for $C_{16}H_{29}NO_4Si$ 327.1866). The ^{1}H and ^{13}C NMR spectra clearly reveal the structure as the product of simple addition of allyl silane **29**. The presence of both the TMS and acetate units is indicated by signals at δ 1.5 (^{13}C) and δ 0.2 (^{1}H) and δ 170.7 and 52.4 (^{13}C) and δ 2.10 (^{1}H), respectively. Increasing the temperature results in the formation of a second product. At 140 °C, the second product is the exclusive one (70% yield) and its structure is easily assigned as the cycloadduct **30** (eq 13) on the basis of its spectroscopic properties.



(13)

Azepine Formation by [4 + 3] Cycloaddition. Imines derived from α,β-unsaturated aldehydes and ketones can, in principle, undergo initial 1,2 or 1,4 addition—the former leading to the [3 + 2] (with the imine) and the latter to either [3 + 2] (with the olefin) or [4 + 3] cycloadducts. Our examples (e.g., **6**, **8**, and **18**) so far reveal only [3 + 2] cycloadditions with the imine.

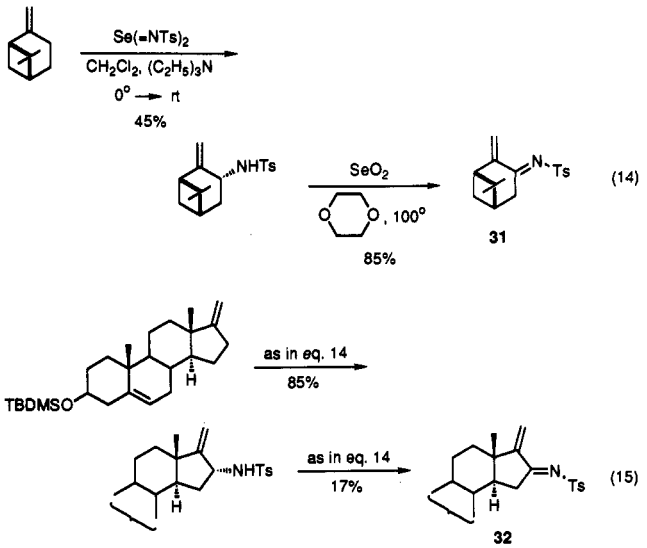
(12) (a) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477. (b) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035. (c) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397.

(13) (a) For a leading recent reference, see: Bondavalli, F.; Schenone, P.; Ranise, A. *Synthesis* **1979**, 830. Also, see: (b) Adamopouos, S.; Bolton, A. J.; Tadayoni, R.; Webb, G. *J. Chem. Soc., Perkin Trans. I* **1987**, 2073. (c) Suggitt, J. W.; Myers, G. S.; Wright, G. F. *J. Org. Chem.* **1947**, *12*, 373. (d) Houben, J.; Pfankuch, E. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 586.

(14) Cf. Koch, T. H.; Olesen, J.; De Niro, J. *J. Org. Chem.* **1975**, *40*, 14. Tietze, L. F.; Bratz, M. *Chem. Ber.* **1989**, *122*, 997.

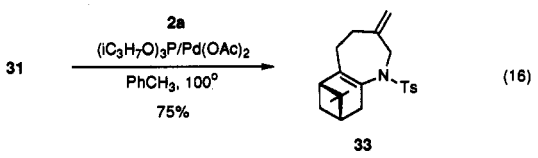
While such additions to aldimines **6** and **8** are not surprising, such an addition to ketimine **18** is more surprising in light of our earlier experiences in cycloadditions to carbonyl partners.[11,15] Assessing the selectivity derived from the effect of olefin substitution, we examined sterically more accessible conjugated imines.

Two sulfonylimines possessing sterically more accessible double bonds were prepared by allylic amination[16] followed by further oxidation with selenium dioxide,[17] as outlined in eqs 14 and 15, following literature precedents for both steps. While the pinene

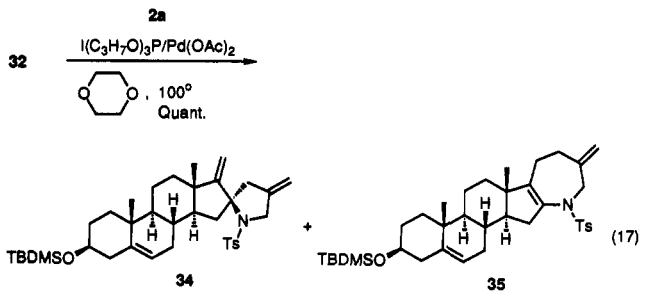


example gave an excellent yield for the selenium dioxide dehydrogenation step, the same procedure gave imine **32** in a disappointing yield. Since our objective was the exploration of their cycloadditions, we did not pursue improvements in their syntheses.

Exposing imine **31** to TMM precursor **2a** using triisopropyl phosphite and palladium acetate produces an adduct whose spectral data indicate the formation of an azepine, **33** (eq 16).

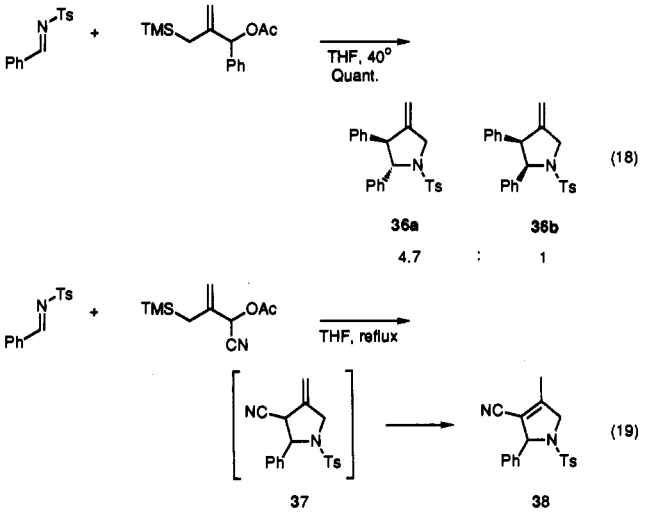


On the other hand, steroid imine **32** gives a quantitative yield of an approximately 1:1 mixture of the 1,2-[3 + 2] and [4 + 3] cycloadducts **34** and **35**, respectively (eq 17). The structural



assignments are readily apparent from the spectroscopic data. The stereochemistry of cycloadduct **34**, whose spectroscopic and chromatographic properties indicate that it is homogeneous, is assigned only on the basis of least hindered attack anti to the angular C-17 methyl group.

Substituted TMM–PdL_2 in Cycloadditions. A brief examination of the cycloadditions with substituted TMM precursors[18,19] explores the utility of this approach for construction of more elaborate pyrrolidines. Using the *N*-tosylimine from benzaldehyde as our test substrate, cycloadditions with both the phenyl- and cyano-substituted TMM units were pursued.[18b] Using the triisopropyl phosphite–palladium acetate catalyst system, both cycloadditions proceeded in high yield and excellent regioselectivity to give the adducts **36a,b** and **38** (eqs 18 and 19). In the



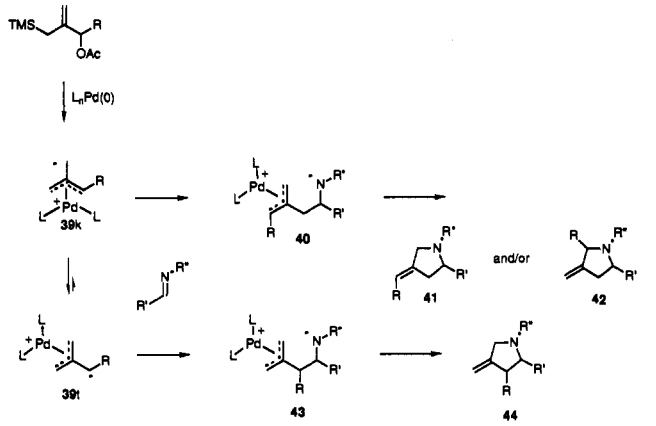
former case, the cycloadduct is formed as 4.7:1 mixture of the diastereomers. The stereochemistry is assigned on the basis of the 9.6- and 5.7-Hz coupling between the benzylic hydrogens for the major and minor products. MM2 calculations indicate a dihedral angle of 163 and 28° for the *E* and *Z* isomers, respectively, allowing the major isomer to be assigned as *E*. In the latter case, the initial cycloadduct **37** is not observed. Isomerization to the thermodynamically more stable endocyclic conjugated isomer **38** occurs rapidly under the reaction conditions.

Discussion

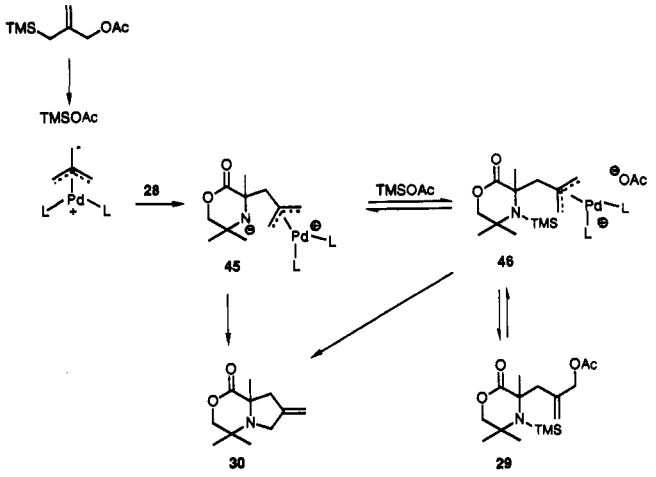
A new general and efficient cycloaddition approach for the construction of pyrrolidines derives from the chemistry of palladium complexes of trimethylenemethane. Whereas, simple imines fail to serve as suitable acceptors for this reactive intermediate, in our hands, increasing their polarization by placing an electron-withdrawing group on either the nitrogen or carbon of the imine suffices to make the imine an excellent acceptor. *N*-Nitro groups appear more effective than *N*-sulfonyl groups. Combined with the greater ease of their purification, these overlooked imine derivatives may be more generally useful as reactive imines. The success in these cycloadditions is somewhat surprising considering the reported cleavage of nitrimines with carbon nucleophiles[13] and the likelihood that these reactions involve a two-step process wherein the first step is addition of a carbon nucleophile (*vide infra*). The major limitation derives from the propensity of the imine derivative to enolize. Thus, heavily substituted imine derivatives like **20** and **22**, whose cycloadditions may have been anticipated to be disfavored by steric hindrance, serve as good acceptors since enolization is inhibited, whereas the unhindered derivatives like the *N*-nitrimine from cyclohexanone and 2-nonanone, where enolization should be facile, fail. A similar trend is observed for the *N*-tosylimines.

(15) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408.
(16) Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269. Sharpless, K. B.; Singer, S. P. *J. Org. Chem.* **1976**, *41*, 2504; **1978**, *43*, 1448 and earlier references therein.
(17) Magnus, P.; Mugrage, B. *J. Am. Chem. Soc.* **1990**, *112*, 462.
(18) (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5972. (b) Trost, B. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1985**, *107*, 1075.
(19) For the case of a sulfur-substituted TMM cycloaddition to an imine, see: Trost, B. M.; Matelich, M. C. *J. Am. Chem. Soc.* **1991**, *113*, 9007.

Scheme I. Mechanistic Rationale for Cycloaddition of Imines

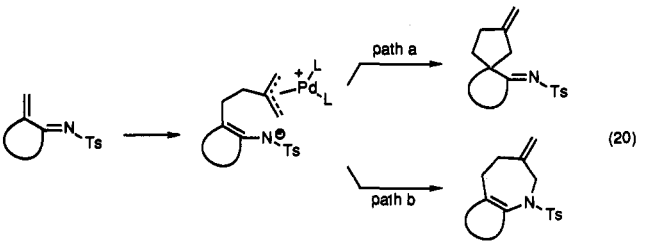


Scheme II. TMM Cycloaddition to a C-Activated Imine



The mechanism of this cycloaddition is best understood in terms of a two-step process[20] as outlined in Scheme I. Direct evidence for this scheme derives from the cycloaddition to cyclic imine **28** wherein a noncyclic product, **29**, is the kinetic product. As we pointed out previously,[21] this type of product does not likely arise by a direct "Lewis acid" catalyzed addition of the allyl silane but via a TMM–PdL$_2$ intermediate as outlined in Scheme II. The nonstabilized nature of the nitrogen anion in the initial adduct **45** makes its silylation with either a TMM precursor or the silyl acetate both kinetically and thermodynamically favorable. Collapse of the ion pair **46** by charge neutralization accounts for the simple addition product **29**. In a slower but irreversible reaction, either **45** or **46** may collapse to pyrrolidine **30**. Thus, the kinetic product **29**, when resubjected to the palladium catalyst, reenters the reaction manifold allowing the intermediates to be drained more slowly but irreversibly into the pyrrolidine product **30**. When the nitrogen atoms, as in **40** or **43** (Scheme I), is stabilized by either a tosyl group or even a phenyl, this alternative path is not observed. Nevertheless, it provides strong support for the zwitterion **40** or **43** as a result of a nucleophilic addition to the imine. Stabilization of this anion does not appear to be the controlling factor regarding the structural requirement for an imine to be a TMM acceptor. Imine electrophilicity which can be enhanced by placing an electron-withdrawing group on either nitrogen *or* carbon appears to be the dominant influence.

This two-step mechanism nicely rationalizes cycloadditions with α,β-unsaturated imines, acceptors that prove to be especially interesting since initial attack can occur either directly at the imine carbon leading to a pyrrolidine or in a conjugated fashion leading to either a cyclopentyl imine or an azepine. Placing a substituent at the β-carbon of the conjugated system leads only to direct imine addition. On the other hand, reduction of steric hindrance at the β-carbon can open up the prospect for conjugate addition. With a rigidly cisoid α,β-unsaturated imine, the zwitterion that results from conjugate addition can collapse either at carbon to give the spirocyclopentane (eq 20, path a) or at nitrogen to give the azepine (eq 20, path b). The excellent



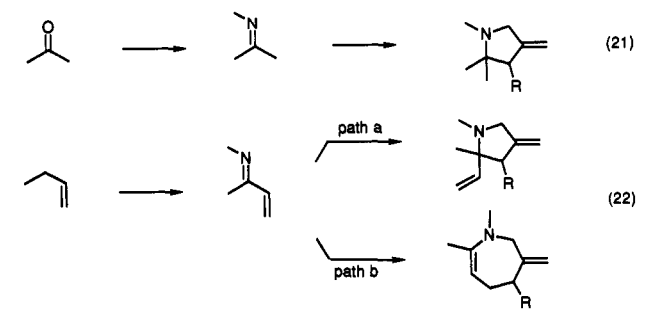
(20)

nucleophilicity of sulfonamide anions with respect to π-allylpalladium species[22] combined with steric factors favors the latter path. The dual behavior of pregnane imine **32** presumably arises from a kinetic discrimination in the initial attack although we cannot exclude a competition between cyclization of the zwitterion from addition of the TMM–PdL$_2$ at the imine carbon and its collapse back to starting materials, which ultimately leads to reaction as in eq 20. The lower steric hindrance associated with the imine carbon of pregnane derivative **32** compared to that of carvopinone imine **31** accounts for their different propensities for 1,2 vs 1,4 additions.

With a substituted TMM precursor, the kinetic TMM species **39k** should lead to adduct **41** or **42**, whereas the thermodynamic TMM complex **39t** should lead to adduct **44**.[18a] Only the latter is observed. These results parallel the regioselectivity observed with aldehyde acceptors and the phenyl-substituted TMM species. The good diastereoselectivity with the phenyl-substituted TMM has not been observed with other TMM acceptors (cf. aldehydes[11]) and may derive from a buttressing of the three substituents R, R′, and R″ in the transition state leading to **43**. The successful trapping of the less reactive cyano-substituted TMM species stands in contrast to the corresponding behavior of aldehydes.[11] These results suggest that the *N*-tosylimines may be more reactive acceptors than carbonyl compounds.

In all cases, the active catalyst was formed *in situ* by reduction of palladium acetate with triisopropyl phosphite, which also served as the ligand. These reactions further verify the general utility of this phosphite ligand for TMM cycloadditions. It is especially interesting that this ligand served effectively in the reactions of the cyano-substituted TMM, since our previous results suggested a stronger donor ligand like triphenylphosphine was required for its participation with olefinic acceptors.[18b]

Synthetically, this cycloaddition provides a useful, general approach to pyrrolidines from either carbonyl partners (eq 21) or olefins (eq 22, path a). In our hands, the only requirement



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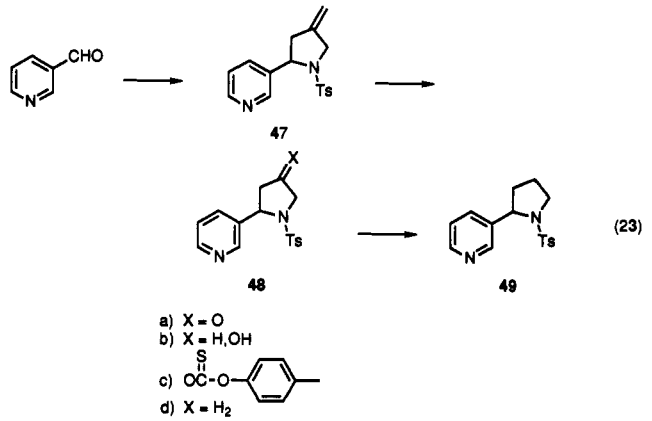
(22)

regarding the imine is that it must be activated by the presence

(20) Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687.
(21) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6432; **1983**, *105*, 2326.
(22) Byström, S. E.; Aslanian, R.; Bäckvall, J.-E. *Tetrahedron Lett.* **1985**, *26*, 1749.

of an electronegative group. We have no explanation for the difference between our results and those of Kemmitt and Jones who report successful Pd-catalyzed cycloadditions with either **2a** or its corresponding mesylate and *N*-phenylbenzaldimine.

Using *C*-carboxy-substituted TMM entities, this route provides ready access to novel 3-substituted proline analogues. The importance of 3-hydroxypyrroline lends special interest to such derivatives. Simple access to nicotine analogues also arises (eq 23). The adduct **47**, available in only two steps from 3-pyridinecarboxaldehydes, provides a simple entry to nicotine analogues as well as nicotine itself.[23] Ozonolysis provides ketone **48a**—a useful entity for further elaboration. Alternatively, ozonolysis with a reductive workup (69%) followed by radical-based deoxygenation[24] (62%) generated *N*-tosylnornicotine (**48d**). Dissolving metal reduction[25] effects N-detosylation to complete a synthesis of nornicotine (**49**).[26,27] To the extent that cyclic imines are available, bicyclic N-heterocycle like pyrrolizidines and indolizidines, etc., would also be available. Thus, the successful employment of imines as acceptors for TMM–PdL_2 opens a new chapter in palladium-catalyzed cycloadditions.



(23)

Experimental Section

General Techniques. Solvents and reagents were distilled before use: benzene, dichloromethane, 1,2-dichloroethane, acetonitrile, diisopropylamine, hexane, pyridine, triethylamine, chlorotrimethylsilane, and methyl chloroformate from calcium hydride; dimethylformamide from barium hydroxide; ether and tetrahydrofuran (THF) from sodium benzophenone ketyl; and toluene and dioxane from sodium. Flash chromatography employed E. Merck silica gel (Kieselgel 60, 200–400 mesh). Analytical thin-layer chromatography was performed with 0.2-mm coated commercial silica gel plates (E. Merck, DC-Plastikfolien, Kieselgel 60 F_{254}). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Boiling points are also uncorrected. Kugelrohr distillation was performed on a Büchi GKR-50 glass tube oven.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-300 (300 MHz), Varian Gemini-200 (200 MHz), Nicholet NT-300 (300 MHz), or Varian XL-400 (400 MHz) spectrophotometer. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane, or in ppm relative to the singlet as 7.24 ppm for chloroform-*d*. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; and br, broad. Coupling constants are reported in hertz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini 300 (75 MHz), a Varian Gemini 200 (50 MHz), and a Varian XL-400 (100 MHz) spectrophotometer and are reported in ppm with the center line of the triplet for chloroform-*d* set at δ 77.00. Routine ^{13}C NMR spectra were fully decoupled by broad-band decoupling.

Infrared (IR) spectra were recorded in 0.1-mm path length sodium chloride solution cells on a Nicolet 205 FTIR or Perkin-Elmer 1420 spectrophotometer. High-resolution mass spectra (MS) were recorded on an AE1-MS902, Kratos MS25, or Kratos MS9 spectrometer at an ionizing current of 98 mA and an ionizing voltage of 70 eV, unless otherwise noted, and are reported as *m/e* (relative intensity). (MS9 data analyses were performed at the Mass Spectrometry Facility at the University of California, San Francisco).

Low-resolution mass spectra were recorded on a Hewlett-Packard gas chromatography/mass spectrometer, using a Hewlett-Packard 5890A gas chromatograph with a 25-m × 0.25-mm i.d. SE-30 column and a Hewlett-Packard 5970 Series mass selective detector with an ionizing voltage of 70 eV. Microanalyses were performed by Robertson Laboratory Inc., Madison, NJ.

Analytical gas chromatography (GC) was performed on a Varian Model 3700 gas chromatograph using an ALLTECH 25-m × 0.25-mm i.d. SE-30 column with flame ionization detection. The temperature program used was T_i = 70 °C, 2 min; T_f = 250 °C; and rate = 40 °C/min, hold additional 15 min.

Synthesis of Substrates. Imines were synthesized as previously recorded[9] except as follows.

Ethyl (*N*-Phenylimino)malonate (24). Ethyl oxomalonate (1.04 g, 10 mmol) and aniline (0.94 g, 10 mmol) were dissolved in 20 mL of toluene, and the reaction mixture was stirred at 100 °C for 2 h in a Dean–Stark apparatus. The solvent was removed *in vacuo*, and the imine was purified by flash chromatography with 9:1 hexane–ether. Kugelrohr distillation (170 °C at 0.1 mm) yielded 1.0 g (45%). IR ($CDCl_3$): 1240, 1320, 1255, 1180 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, J = 10 Hz, 2H), 7.21 (t, J = 10 Hz, 1H), 7.0 (d, J = 10 Hz, 2H), 4.45 (q, J = 7 Hz, 2H), 4.15 (q, J = 7 Hz, 2H), 1.40 (t, J = 7 Hz, 3H), 1.05 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7, 147.9, 129.0, 126.9, 119.6, 62.9, 61.9, 13.8, 13.4. Anal. Calcd for $C_{13}H_{15}NO_4 \cdot 1.25\ H_2O$: C, 57.45; H, 6.49; N, 5.15. Found: C, 57.31; H, 6.21; N, 5.18. HRMS: calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1007.

Ethyl (*N*-Phenylimino)acetate (26). Ethyl glyoxylate[28] (1.04 g, 10 mmol) was dissolved in 30 mL of dichloroethane and heated to 60 °C. Aniline (0.94 g, 10 mmol) was added followed by 3A molecular sieves (3 g). The reaction mixture was stirred for 2 h. The solvent was removed *in vacuo*, and the imine was purified by distillation (120 °C at 0.1 mm), yielding 1.64 g (93%). IR ($CDCl_3$): 1740, 1720, 1370, 1345, 1300, 1280, 1215, 1195, 1030 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.45 (t, J = 10 Hz, 2H), 7.37 (d, J = 10 Hz, 1H), 7.30 (d, J = 10 Hz, 2H), 4.45 (q, J = 7 Hz, 2H), 1.43 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 151.5, 129.5, 128.6, 121.5, 61.9, 13.9 (missing signals due to weak signal of quaternary aromatic carbons). MS: calcd for $C_{10}H_{11}NO_2$ 177.0799 (M^+), found 177.0795.

Carvopinone *N*-Tosylimine (31). 2α-Toluenesulfonamido-β-pinene[16] (1.03 g, 3.36 mmol) was dissolved in 7 mL of "wet" dioxane to which was added selenium dioxide (0.44 g, 2.5 mmol). The reaction mixture was heated at 100 °C for 30 min. The solution was then filtered through Celite, the solvent was removed *in vacuo*, and the imine was purified by flash chromatography with 8:1 hexane–ether, yielding 0.87 g (85%) of a solid, mp 138–9 °C (ether-hexane). IR ($CDCl_3$): 2940, 1575, 1370, 1160, 1090 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.9 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 6.1 (s, 1H), 5.05 (s, 1H), 3.35 (s, 2H), 2.75 (t, J = 6 Hz, 1H), 2.61 (m, 1H), 2.45 (s, 1H), 2.2 (m, 1H), 1.31 (s, 3H), 1.25 (d, J = 11 Hz, 1H), 0.8 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 25.4, 31.5, 37.0, 38.0, 40.2, 48.7, 118.5, 127.2, 129.5, 138.7, 143.6, 148.9, 180.8. Anal. Calcd for $C_{17}H_{21}NO_2S \cdot 0.3H_2O$: C, 66.08; H, 7.05; N, 4.53. Found: C, 66.08; H, 6.82; N, 4.36. HRMS: calcd for $C_{17}H_{21}NO_2S$ (M^+) 303.1292, found 303.1291.

3β-(*tert*-Butyldimethylsiloxy)-16α-toluenesulfonamido-17-methylenepregn-5-ene. Selenium (0.26 g, 3.3 mmol) and Chloramine-T (1.25 g, 5.5 mmol) were mixed and stirred in 11 mL of methylene chloride for 24 h. 3β-(*tert*-Butyldimethylsiloxy)-17-methylenepregn-5-ene[29] (1.1 g, 2.7 mmol) was added at 0 °C, and then triethylamine (182 mL, 10 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Sodium hydroxide (10 mL, 1 M) and 50 mL of ether were added, and the solution was stirred an additional

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(27) For other recent syntheses, see: Leete, E.; Chedekel, M. R.; Boden, G. B. *J. Org. Chem.* **1972**, *37*, 4465. Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2547. Alberci, G. F.; Andrieux, J.; Adam, G.; Plet, M. M. *Tetrahedron Lett.* **1983**, *24*, 1937. Bash, F. Z.; Di Bernardis, J. F. *Tetrahedron Lett.* **1984**, *25*, 5271. Brunner, H.; Kurzinger, A.; Mahboobi, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim, Ger.)* **1988**, *321*, 73.

(28) Kelley, T. R.; Schmidt, T.; Haggerty, J. G. *Synthesis* **1972**, 544.

(29) Cf. Schmuff, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404.

Table III. Experimental Details for Cycloadditions

Pyrrolidine	Procedure	imine wt, g (mmol)	product wt, g	yield, %	mp, °C	chrom solvnt ratio, hexane-ether
 Z = Ts						
R = Ph	A	0.065 (0.250)	0.076	97	119–120	4:1
R = 2-chlorophenyl	B	0.073 (0.248)	0.0773	90	129–130	5:1
R = 3-nitrophenyl	A	0.076 (0.250)	0.085	95	127–128	2:1
R = 3-pyridyl	B	0.065 (0.250)	0.074	94	70–7	only ether
R = 2-anisyl	B	0.072 (0.250)	0.0815	95	101–2	5:1
R = piperonyl	B	0.076 (0.251)	0.090	Q	132–3	5:1
R = 2-furyl	A	0.062 (0.249)	0.074	98	oil	5:1
7	B	0.071 (0.249)	0.084	99	oil	6:1
9	C	0.152 (0.500)	0.143[a]	80	oil	15:1
10	C	0.120 (0.502)	0.132	90	117–8	9:1
11	C	0.066 (0.238)	0.0395[a]	50	74–5	8:1
12	C	0.091 (0.251)	0.0931	80	108–110	8:1
13	C	0.15 (0.504)	0.090[a]	51	oil	2:1
14	C	0.152 (0.498)	0.040[a]	22	oil	7:1
15	C(dioxane)	0.12 (0.249)	0.102	76	oil	2:1
17	C	0.107 (0.502)	0.126	95	oil	1:1
19	C	0.139 (0.497)	0.144	88	oil	5:1
21	C	0.079 (0.499)	0.0923	87	oil	24:1
23	C	0.102 (0.514)	0.069[b]	72	oil	24:1
25	C(dioxane)	0.118 (0.474)	0.120	84	oil	10:1
27	C(THF)	0.089 (0.526)	0.0894	77	oil	20:1
30	D	0.071 (0.503)	0.068	70	oil	15:1
36	B	0.065 (0.250)	0.150[c]	Q	108–111	4:1
38	B	0.062 (0.238)	0.085	Q	oil	1:1

[a] A 1:1 diastereomeric mixture. [b] A 17:1 diastereomeric mixture. [c] A 4.7:1 diastereomeric mixture.

15 min. The solution was filtered through Celite, washed with saturated sodium chloride, 10% aqueous hydrochloric acid, saturated sodium bicarbonate, and water, extracted with ether, and dried with magnesium sulfate. The solvent was removed *in vacuo*, and the sulfonamide was purified by flash chromatography with 3:1 hexane–ether, yielding 0.7 g (85%). IR ($CDCl_3$): 2930, 1160, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 10 Hz, 2H), 7.43 (d, J = 10 Hz, 2H), 5.30 (s, 1H), 3.80 (s, 1H), 3.69 (s, 1H), 4.4 (d, J = 8 Hz, 1H), 4.21 (s, 1H), 3.51–3.43 (m, 1H), 2.45 (s, 3H), 2.30–2.15 (m, 2H), 1.95–1.85 (m, 1H), 1.80 (d, J = 15 Hz, 2H), 1.75–1.55 (m, 4H), 1.55–1.38 (m, 4H), 1.25–1.0 (m, 3H), 0.98 (s, 3H), 0.87 (s, 9H), 0.73 (s, 3H), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 163.0, 143.5, 141.9, 129.9, 127.3, 120.7, 104.7, 72.5, 54.7, 52.1, 50.4, 43.5, 42.7, 37.2, 36.6, 35.6, 34.2, 31.9, 31.3, 31.2, 25.7, 21.2, 20.4, 19.2, 18.2, 18.0, –4.9. MS: calcd for $C_{33}H_{51}NO_3SSi$ ($M^+ - C_4H_9$) 512.2656, found 512.2623.

3β-(*tert*-Butyldimethylsiloxy)-16-(tosylimino)-17-methylenepregn-5-ene (32). Sulfonamide **32** (0.61 g, 1.07 mmol) and selenium dioxide (0.161 g, 1.45 mmol) were dissolved in 2 mL of dioxane. After being heated at 100 °C for 1 h, the solution was filtered through Celite, the solvent was removed *in vacuo*, and the imine was purified by flash chromatography with 6:1 hexane–ether, yielding 0.106 g (17%). IR ($CDCl_3$): 2930, 2860, 1755, 1600, 1460, 1380, 1315, 1300, 1255, 1155, 1090, 920, 885 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 10 Hz, 2H), 7.35 (d, J = 10 Hz, 2H), 5.95 (s, 1H), 5.55 (d, J = 10 Hz, 1H), 5.35 (s, 1H), 5.11 (s, 1H), 4.3 (m, 1H), 3.51–3.43 (m, 2H), 3.27 (dd, J = 18, 8 Hz, 1H), 2.55–2.39 (m, 4H), 2.31–2.15 (m, 2H), 2.10 (d, J = 13 Hz, 1H), 2.03 (d, J = 13 Hz, 1H), 1.82 (d, J = 13 Hz, 1H), 1.77–1.47 (m, 6H), 1.43–1.25 (m, 2H), 1.12–1.05 (m, 5H), 0.87 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.8, 158.1, 143.9, 141.9, 138.1, 129.6 (2C), 127.5 (2C), 120.6, 113.3, 72.4, 51.2, 50.3, 42.7, 42.6, 37.1, 36.7, 35.2, 34.7, 31.9, 31.4, 30.9, 25.8 (3C), 21.3, 20.4, 19.2, 18.4, 18.0, –4.8 (2C). MS: calcd for $C_{33}H_{39}NO_3SSi$ (M^+) 567.3156, found 567.3144.

General Procedures for Cycloadditions. Procedure A: (aromatic sulfonimines). Sulfonimine (0.25 mmol) and (2-(acetoxymethyl)-3-allyl)-trimethylsilane (0.11 g, 0.6 mmol, 2.4 equiv) were dissolved in 0.5 mL of THF to which 10% of a catalyst, typically a 0.5-mL aliquot of a 2.5-mL THF solution containing palladium acetate (0.028 g, 0.125 mmol), triphenylphosphine (0.170 g, 0.65 mmol), and *n*-butyllithium (0.166 mL, 1.5 M in hexane), was added. The reaction mixture was heated at reflux for 1.5 h. The reaction mixture was filtered through a plug of silica gel and purified by flash chromatography.

Procedure B (improved procedure for aromatic sulfonimines). Sulfonimine (0.5 mmol) and 2-((trimethylsilyl)methyl)allyl methyl carbonate (0.1 g, 0.5 mmol, 1.3–2.0 equiv) were dissolved in 0.5 mL of a THF solution containing palladium acetate (0.0224 g, 0.1 mmol), and triisopropyl phosphite (0.148 mL, 0.125 g, 0.6 mmol) was added. The reaction mixture was heated at 40 °C for 25 h, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography.

Procedure C (aliphatic sulfonimines and other reluctant imines). Sulfonimine (0.25–0.5 mmol) and (2-(acetoxymethyl)-3-allyl)trimethylsilane (0.1 g, 0.54 mmol, 1.3–2.0 equiv) were dissolved in 0.5 mL of toluene (or dioxane) and heated to reflux, to which 10% of a catalyst, typically a 0.5-mL aliquot of a 3.0-mL THF solution containing palladium acetate (0.0673 g, 0.3 mmol) and triisopropyl phosphite (0.444 mL, 0.374 g, 1.8 mmol), was added. The reaction mixture was heated at reflux for 4 h, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography.

Procedure D (for very reluctant imines). Imine (0.071 g, 0.5 mmol) and (2-(acetoxymethyl)-3-allyl)trimethylsilane, (0.6 g, 2.9 mmol, 1.1 equiv) were dissolved in 0.25 mL of dioxane to which 10% of a catalyst, typically 0.25 mL of a dioxane solution containing palladium acetate (0.051 g, 0.23 mmol) and triisopropyl phosphite (0.333 mL, 0.281 g, 1.35 mmol) preheated to 80 °C and then cooled, was added. The reaction mixture was heated in a sealed screw cap microvial at 140 °C for 2.5 h, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography.

All *N*-tosyl-4-methylenepyrrolidines characteristically stain with iodine and ceric ammonium molybdate. Experimental details for each run are summarized in Table III.

Spectral Data for Cycloadducts of Table III. *N*-Tosyl-2-phenyl-4-methylenepyrrolidine. IR ($CDCl_3$): 3005, 1335, 1215, 1160, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 10 Hz, 2H), 7.30–7.19 (m, 7H), 4.98 (s, 1H), 4.95–4.92 (m, 2H), 4.10 (d, J = 14 Hz, 2H), 2.77 (m, 1H), 2.57 (d, J = 18 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 142.0, 135.5, 129.5 (2C), 128.3 (2C), 127.4 (2C), 126.3 (2C), 108.2, 63.1, 52.5, 41.3, 21.5 (missing signals due to weakness of quaternary carbons). Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.46; MW, 313.1138. Found: C, 68.62; H, 6.41; N, 4.36; MW, 313.1130.

***N*-Tosyl-2-(2-chlorophenyl)-4-methylenepyrrolidine.** IR ($CDCl_3$): 1600, 1590, 1350, 1160, 1090, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, J = 10 Hz, 2H), 7.55 (d, J = 10 Hz, 1H), 7.45 (d, J = 10 Hz, 2H), 7.30–7.10 (m, 3H), 5.37 (dd, J = 10, 2 Hz, 1H), 5.0 (s, 1H), 4.85 (s, 1H), 4.21 (d, J = 17 Hz, 1H), 4.05 (d, J = 17 Hz, 1H), 2.85–2.73 (m, 1H), 2.45 (s, 3H), 2.37 (d, J = 18 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 142.4, 140.3, 134.5, 131.6, 129.5 (2C), 128.6 (2C), 127.8 (2C), 127.7, 127.0, 108.9, 60.2, 53.1, 40.5, 21.3. Anal. Calcd for

$C_{18}H_{18}ClNO_2S$: C, 62.15; H, 5.26; N, 4.03; MW, 347.0748. Found: C, 62.30; H, 5.37; N.377; MW, 347.0777.

***N*-Tosyl-2-(3-nitrophenyl)-4-methlenepyrrolidine.** IR ($CDCl_3$): 1535, 1350, 1165, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, J = 10 Hz, 1H), 8.05 (s, 1H), 7.70 (d, J = 9 Hz, 1H), 7.62 (d, J = 10 Hz, 2H), 7.50 (t, J = 7 Hz, 1H), 7.28 (m, 2H), 5.07 (s, 1H), 505–4.95 (m, 2H), 4.20 (d, J = 13Hz, 1H), 4.11 (d, J = 13 Hz, 1H), 2.90–2.76 (m, 1H), 2.50 (br s, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 142.0, 132.9, 129.9 (2C), 129.7, 127.6 (2C), 122.6, 121.4, 109.3, 62.2, 52.6, 41.3, 21.3 (missing signals due to weak signal of quaternary carbons). MS: calcd for $C_{18}H_{18}N_2O_2S$ 358.0988, found 358.0920.

***N*-Tosyl-2-(3-pyridyl)-4-methylenepyrrolidine.** IR ($CDCl_3$): 1600, 1590, 1430, 1345, 1165, 1060, 810 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.5 (br s, 2H), 7.65–7.56 (m, 3H), 7.25 (d, J = 10 Hz, 2H), 7.2–7.15 (m, 1H), 5.05 (s, 1H), 4.95 (s, 1H), 4.90 (dd, J = 13, 2 Hz, 1H), 4.1 (br s, 2H), 2.85–2.75 (m, 1H), 2.45 (d, J = 18 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 142.3, 137.6, 134.6, 134.1, 129.7, 127.4 (2C), 123.4, 108.9, 60.9, 52.5, 41.2, 21.5 (missing signals due to weak signals of quaternary carbons). Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.71; MW, 314.1090. Found: C, 64.68; H, 5.80; N, 8.91; MW, 314.1084.

***N*-Tosyl-2-anisyl-4-methylenepyrrolidine.** IR ($CDCl_3$): 1620, 1605, 1590, 1519, 1500, 1470, 1442, 1440, 1349, 1252, 1182, 1162, 1100, 1062, 1042, 1022, 901, 833, 819, 715, 662 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 10 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.16 (d, J = 10 Hz, 2H), 6.78 (d, J = 10 Hz, 2H), 4.95 (s, 1H), 4.91 (s, 1H), 4.87 (dd, J = 10.1 Hz, 1H), 4.10 (d, J = 14 Hz, 1H), 4.05 (d, J = 14 Hz, 1H), 3.78 (s, 3H), 2.78–2.69 (m, 1H), 2.45 (d, J = 18 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 243.5, 143.2, 135.7, 134.0, 129.4, (2C), 127.6 (2C), 127.4 (2C), 113.7 (2C), 108.0, 62.6, 55.2, 52.3, 41.3, 21.5. Anal. Calcd for $C_{19}H_{21}NO_3S{\cdot}1.0H_2O$: C, 63.14; H, 6.41; N, 3.87. Found: C, 63.47; H, 6.13; N, 3.66. HRMS: calcd for $C_{19}H_{21}NO_3S$ 343.1243, found 343.1217.

***N*-Tosyl-2-piperonyl-4-methylenepyrrolidine.** IR ($CDCl_3$): 1505, 1490, 1450, 1446, 1345, 1250, 1166, 1100, 1045, 941, 905 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8 Hz, 2H), 7.23 (d, J = 8 Hz, 2H), 6.75–6.65 (m, 3H), 5.91 (d, J = 8 Hz, 2M), 4.95 (s, 1H), 4.93 (s, 1H), 4.82 (dd, J = 9, 1 Hz, 1H), 4.10 (d, J = 19 Hz, 1H), 4.06 (d, J = 19 Hz, 1H), 2.80–2.67 (m, 1H), 2.45 (br s, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 146.8, 143.3, 143.2, 136.0, 135.1, 129.4 (2C), 127.4 (2C), 119.9, 108.2, 107.9, 106.8, 101.0, 62.9, 52.4, 41.5, 21.5. Anal. Calcd for $C_{19}H_{19}NO_4S{\cdot}0.25H_2O$: C, 63.65; H, 6.43; N, 3.87. Found: C, 63.11; H, 5.65; N, 3.55.

***N*-Tosyl-2-furanyl-4-methylenepyrrolidine.** IR ($CDCl_3$): 1345, 1160, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 10 Hz, 2H), 7.20 (d, J = 10 Hz, 2H), 7.18 (s, 1H), 6.25–6.18 (m, 2H), 5.05 (dd, J = 10, 1 Hz), 4.97–4.95 (m, 2H), 4.12 (d, J = 13 Hz, 1H), 3.95 (dd, J = 13, 1 Hz, 1H), 2.75–2.67 (m, 1H), 2.60 (d, J = 13 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 143.4, 143.2, 142.0, 135.2, 129.5 (2C), 127.3 (2C), 110.1, 107.9, 107.5, 56.6, 51.5, 38.2, 21.5. HRMS: calcd for $C_{16}H_{17}O_3NS$ (M^+) 303.0930, found 303.0936.

***N*-Tosyl-2-cinnamyl-4-methylenepyrrolidine (7).** IR ($CDCl_3$): 1600, 1497, 1451, 1438, 1349, 1308 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 13.4 Hz, 2H), 7.26 (m, 7H), 6.53 (d, J = 19 Hz, 1H), 5.95 (dd, J = 19, 7 Hz, 1H), 4.95 (s, 2H), 4.44 (m, 1H), 4.0 (d, J = 13 Hz, 2H), 2.62 (m, 1H), 2.42–2.33 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 143.0, 136.3, 135.3, 131.2 (2C), 129.5 (2C), 128.4 (2C), 127.7 (2C), 126.5 (2C), 108.1, 62.0, 51.8, 39.4, 21.5. MS: calcd for $C_{20}H_{21}NO_2S$ (M^+) 339.1294, found 339.1296.

***N*-Tosyl-2-(4α-isopropenyl-1-cyclohexenyl)-4-methylenepyrrolidine (9).** IR ($CDCl_3$): 1670, 1645, 1660, 1495, 1455, 1438, 1377, 1345, 1305 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.65 (m, 2H), 7.30 (d, J = 9 Hz, 2H), 5.65–5.55 (m, 1H), 4.9 (br s, 2H), 4.69 (s, 1H), 4.64 (s, 1H), 4.19 (td, J = 8, 6 Hz, 1H), 4.05–3.95 (m, 2 H), 2.55–2.30 (m, 1H), 2.40 (s, 3H), 2.15–1.80 (m, 2H), 1.8 (s, 3H), 1.75–1.43 (m, 4H), 1.43–0.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0, 149.9, 144.4, 144.1, 143.5, 143.4, 136.8, 136.7, 129.7, 129.6 (2C), 129.5 (2C), 127.8 (2C), 127.7, (2C), 127.5, 124.3, 123.5, 108.7, 108.6, 107.3, 65.3, 65.0, 52.8, 52.5, 40.9, 40.5, 37.6, 37.5, 30.3, 30.2, 27.1, 26.8, 24.0, 23.9, 21.3, 20.5, 20.4 (missing signals due to weak signals of quaternary carbons). HRMS: calcd for $C_{21}H_{27}NO_2S$ (M^+) 357.1764, found 357.1772.

***N*-Tosyl-2-*tert*-butyl-4-methylenepyrrolidine (10).** IR ($CDCl_3$): 2980, 1345, 1165, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.7 (d, J = 10 Hz, 2H), 7.3 (d, J = 10 Hz, 2H), 4.80–4.70 (m, 2H), 4.10 (d, J = 17 Hz, 1H), 3.91 (dd, J = 17, 1 Hz, 1H), 3.72 (d, J = 12 Hz, 1H), 2.4 (s, 3H), 2.3 (d, J = 17 Hz, 1H), 2.0–1.83 (m, 1H), 0.93 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.8, 143.6, 135.6, 129.8 (2C), 127.7 (2C), 105.8, 69.4, 53.3, 35.8, 33.1, 26.7 (3C), 21.3. Anal. Calcd for $C_{16}H_{23}NO_2S{\cdot}0.25H_2O$: C, 64.50; H, 7.95; N, 4.70. Found: C, 64.36; H, 7.60; N, 4.37. HRMS: calcd for $C_{12}H_{14}NO_2S$ ($M^+ - C_4H_9$) 236.0746, found 236.0754.

***N*-Tosyl-2-(2-methyl-4-pentenyl)-4-methylenepyrrolidine (11).** IR ($CDCl_3$): 1345, 1160, 1091, 815 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.7 (d, J = 8 Hz, 2H), 7.4 (d, J = 8 Hz, 2H), 5.9–5.8 (m, 1H), 5.1–5.0 (m, 2H), 4.83–4.75 (m, 2H), 4.11 (d, J = 17 Hz, 1H), 3.97 (d, J = 17 Hz, 1H), 3.8 (d, J = 10 Hz, 1H), 2.45 (s, 3H), 2.38 (d, J = 17 Hz, 1H), 2.15–2.01 (m, 2H), 1.95–1.85 (m, 1H), 0.95 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 146.5, 143.5, 135.3, 134.9, 129.7, (2C), 127.6 (2C), 117.5, 105.8, 68.7, 53.7, 43.9, 38.9, 33.1, 23.7, 23.6, 21.5. HRMS: calcd for $C_{18}H_{25}NO_2S$ ($M^+ - C_6H_{11}$) 237.0746, found 236.0745.

***N*-Tosyl-2-(2-methyl-7-(trimethylsilyl)-6-heptynyl)-4-methylenepyrrolidine (12).** IR ($CDCl_3$): 1345, 1250, 1160, 1090, 1029, 845 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.7 (d, J = 8 Hz, 2H), 7.3 (d, J = 8 Hz, 2H), 4.75 (s, 2H), 4.1 (d, J = 17 Hz, 1H), 3.9 (d, J = 17 Hz, 1H), 3.78 (d, J = 10 Hz, 1H), 2.41 (br s, 4H), 2.31 (d, J = 17 Hz, 1H), 2.25–2.15 (m, 2H), 1.92–1.85 (m, 1H), 1.5–1.3 (m, 3H), 1.95 (s, 3H), 1.84 (s, 3H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 143.5, 135.3, 129.7 (2C), 127.5 (2C), 107.6, 105.7, 68.6, 53.7, 38.5, 38.4, 24.1, 23.5, 23.0, 21.5, 20.6 (2C), 0.2 (3C). MS: calcd for $C_{22}H_{32}NO_2SSi$ ($M^+ - CH_3$) 402.1925, found 402.1933.

***N*-Tosyl-2-(1,1,3-trimethyl-2,5-dioxolan-3-yl)-4-methylenepyrrolidine (13).** IR ($CDCl_3$): 1600, 1450, 1383, 1345, 1263, 1215, 1160, 1095, 1055, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.67 (m, 2H), 7.31–7.22 (m, 2H), 4.85–4.70 (m, 3H), 4.4 (d, J = 13 Hz, 0.5H), 4.35 (d, J = 13 Hz, 0.5H), 4.15–3.85 (m, 2H), 3.75–3.65 (m, 2H), 2.60–2.50 (m, 1H), 2.40 (s, 3H), 2.2–1.90 (m, 2H), 1.4–1.3 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.9, 145.5, 144.0, 143.9, 130.0 (2C), 129.9 (2C), 127.6 (2C), 109.8, 109.5, 106.3, 105.9, 83.4, 83.3, 72.9, 71.4, 65.2, 64.5, 53.5, 53.4, 32.0, 32.6, 27.3, 26.9, 26.2, 25.7, 24.2 (2C), 24.0, 23.9, 21.2, 20.8 (missing signals due to weak signals of quaternary carbons). MS: calcd for $C_{17}H_{22}NO_4S$ ($M^+ - CH_3$) 336.1271, found 336.1292.

***N*-Tosyl-2-(2,2-dimethyl-3-(2-methylpropenyl)cyclopropyl)-4-methylenepyrrolidine (14)** was a 1:1 mixture of diastereomers. IR ($CDCl_3$): 1450, 1340, 1155, 1091, 920, 745, 645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71–7.65 (m, 2H), 7.31–7.21 (m, 2H), 4.95–4.82 (m, 3H), 4.75–4.60 (m, 1H), 4.10–3.83 (m, 2H), 2.44 (s, 3H), 2.25 (s, 1H), 2.15–2.10 (m, 1H), 1.71 (s, 1.5H), 1.67 (s, 1.5H), 1.65 (s, 1.5H), 1.61 (s, 1.5H), 1.27 (s, 1.6H), 1.13 (s, 1.5H), 1.05 (d, J = 13 Hz, 0.5H), 1.0 (d, J = 13 Hz, 0.5H), 1.03 (d, J = 13 Hz, 0.5H), 0.98 (d, J = 13 Hz, 0.5H), 0.95 (s, 3H), 0.65 (dd, J = 13, 10 Hz, 0.5H), 0.55 (dd, J = 13, 10 Hz, 0.5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 144.0, 143.2, 143.0, 140.0, 133.7, 132.7, 129.6, 129.5, 129.4, 127.5, 127.4, 127.3, 123.5, 123.3, 114.5, 107.9, 107.5, 82.0, 64.0, 53.1, 52.0, 51.3, 39.5, 39.0, 38.3, 37.5, 30.2, 28.5, 25.8, 25.7, 22.7, 22.4, 22.1, 21.9, 21.5, 20.0, 18.4, 18.2. MS: calcd for $C_{21}H_{29}NO_2S$ (M^+) 359.1921, found 359.1917.

***N*-Tosyl-2-(3-oxopregn-4-en-20-yl)-4-methylenepyrrolidine (15).** IR ($CDCl_3$): 1660, 1340, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 10 Hz, 2H), 7.23 (d, J = 10 Hz, 2H), 5.71 (br s, 1H), 4.90 (s, 1H, 4.80 (s, 1H), 4.70 (s, 1H), 3.6 (d, J = 17 Hz, 1H), 3.45 (d, J = 17 Hz, 1H), 2.43 (s, 3H), 2.41–2.20 (m, 3H), 2.10–1.95 (m, 2H), 1.90–1.80 (m, 1H), 1.83 (s, 3H), 1.78 (s, 3H), 1.75–1.62 (m, 5H), 1.6–1.3 (m, 2H), 1.30–1.01 (m, 5H), 1.18 (s, 3H), 1.0–0.6 (m, 3H), 0.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.9, 171.6, 144.6, 143.5, 140.6, 135.0, 129.6 (2C), 127.8 (2C), 114.9, 57.5, 56.3, 55.2, 52.8, 44.0, 38.5, 38.1, 35.7, 35.6, 33.8, 32.7, 31.8, 31.7, 24.3, 23.9, 21.4, 20.7, 20.0, 18.4, 17.2, 12.9 (missing signal due to weak signal of a quarternary carbon). MS: calcd for $C_{33}H_{45}NO_3S$ (M^+) 535.3123, found 535.3042.

13,13-Dimethyl-3-methylene-5-aza-6,6-dioxo-6-thiatetracyclo[7.4.1.1^{1,5}]-dodecane (17). IR ($CDCl_3$): 1310, 1170, 1145, 1130, 1075, 900 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.15 (d, J = 1 Hz, 1H), 5.05 (d, J = 1 Hz, 1H), 4.32 (d, J = 17 Hz, 1H), 3.65 (d, J = 17 Hz, 1H), 3.32 (m, 2H), 2.75 (d, J = 17 Hz, 1H), 2.25 (m, 2H), 1.90 (m, 3H), 1.60 (m, 1H), 1.30 (m, 5H), 1.0 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 107.7, 79.4, 52.6, 50.0, 49.7, 48.1, 45.6, 43.9, 43.5, 28.5, 26.4, 21.5, 19.9. Anal. Calcd for $C_{14}H_{21}NO_2S{\cdot}1.0H_2O$: C, 58.91; H, 8.12; N, 4.91. Found: C, 59.27; H, 7.96; N, 4.69. HRMS: calcd for $C_{14}H_{21}NO_2S$ (M^+) 267.1342, found 267.1285.

***N*-Tosyl-2-cyclohex-1-enyl-2-methyl-4-methylenepyrrolidine (19).** IR ($CDCl_3$): 1340, 1160, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.8 (d, J = 10 Hz, 2H), 7.3 (d, J = 10 Hz, 2H), 5.7 (br s, 1H), 4.9 (s, 2H), 4.05 (s, 2H), 2.7 (d, J = 17 Hz, 1H), 2.40 (s, 3H), 2.30 (d, J = 17 Hz, 1H), 2.10–2.05 (m, 2H), 1.95–1.90 (m, 2H), 1.60–1.40 (m, 4H), 1.4 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 142.9, 139.7, 138.31, 129.4,

(2C), 127.5 (2C), 122.4, 107.0, 71.0, 53.4, 47.5, 25.1, 24.5, 23.9, 22.6, 21.9, 21.3. HRMS: calcd for $C_{19}H_{25}NO_2S$ ($M^+ - CH_3$) 316.1607, found 316.1383.

N-Nitro-2,2-diisopropyl-4-methylenepyrrolidine (21). IR ($CDCl_3$): 1495, 1340, 1300, 1260 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.0 (s, 2H), 4.5 (s, 2H), 2.7 (m, 4H), 0.96 (d, J = 7 Hz, 6H), 0.95 (d, J = 7 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 140.0, 108.2, 79.0, 58.7, 38.9, 34.0 (2C), 18.8 (2C), 18.6 (2C). MS: calcd for $C_8H_{13}N_2O_2$ ($M^+ - C_3H_7$) 169.0978, found 169.0975.

β-Spiro[2β-isopropyl-5α-methylcyclohexane-1,2'-N-nitro-4-methylenepyrrolidine] (23 major). IR ($CDCl_3$): 1500, 1355, 1345, 1333, 1305, 1265 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.0 (s, 2H), 4.65 (d, J = 20 Hz, 1H), 4.5 (d, J = 20 Hz, 1H), 2.90 (d, J = 18 Hz, 1H), 2.57 (d, J = 18 Hz, 1H), 2.41–2.30 (m, 1H), 2.25–2.19 (m, 1H), 2.10–1.99 (m, 2H), 1.95–1.87 (m, 1H), 1.53–1.40 (m, 2H), 1.25 (dd, J = 15, 12 Hz, 1H), 0.98 (d, J = 7 Hz, 3H), 0.85 (dd, J + 12, 1 Hz, 1H), 0.81 (d, J = 7 Hz, 3H), 0.75 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 107.5, 72.0, 57.7, 52.8, 52.1, 48.3, 34.7, 28.4, 26.5, 24.5, 23.3, 22.3, 17.2. MS: calcd for $C_{14}H_{24}N$ ($M^+ - NO_2$) 206.1910, found 206.1907.

α-Spiro[2β-isopropyl-5α-methylcyclohexane-1,2'-N-nitro-4-methylenepyrrolidine] (23 minor). IR ($CDCl_3$): 1500, 1347, 1305, 1265 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.10 (s, 1H), 5.07 (s, 1H), 4.67 (d, J = 20 Hz, 1H), 4.31 (d, J = 20 Hz, 1H), 2.90 (d, J = 18 Hz, 1H), 2.87 (d, J = 18 Hz, 1H), 2.55 (d, J = 18 Hz, 1H), 2.03–1.95 (m, 1H), 1.90–1.83 (m, 1H), 1.60–1.40 (m, 5H), 1.15–1.05 (m, 1H), 0.98 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H), 0.85 (d, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 109.7, 75.5, 55.5, 47.5, 46.0 (2C), 39.8, 29.7, 27.6 (4C), 23.9. MS: calcd for $C_{14}H_{24}N$ ($M^+ - NO_2$) 206.1910, found 206.1907.

N-Phenyl-2-dicarbethoxy-4-methylenepyrrolidine (25). IR ($CDCl_3$): 1735, 1600, 1505, 1467, 1350, 1285, 1245, 1195, 1155, 1060, 860 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.23–7.15 (m, 2H), 6.81–6.64 (m, 3H), 5.1–5.05 (m, 2H), 4.20 (q, J = 7 Hz, 4H), 4.16 (br s, 2H), 1.17 (t, J = 7 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.2 (2C), 145.5, 141.8, 128.6 (2C), 118.0, 114.0 (2C), 107.3, 73.5, 61.8 (2C), 54.4, 44.5, 13.7 (2C). MS: calcd for $C_{17}H_{21}O_4N$ (M^+) 303.1470, found 303.1472.

N-Phenyl-2-carbethoxy-4-methylenepyrrolidine (27). IR ($CDCl_3$): 1750, 1600, 1505, 1465, 1365, 1280, 1180, 1035, 890 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (t, J = 6 Hz, 2H), 6.75 (t, J = 6 Hz, 1H), 6.6 (d, J = 8 Hz, 2H), 5.15 (s, 1H), 5.29 (s, 1H), 4.5 (dd, J = 9, 1 Hz, 1H), 4.3–4.05 (m, 4H), 3.2–3.05 (m, 1H), 2.75 (d, J = 19 Hz, 1H), 1.2 (t, J = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 144.2, 129.4 (2C), 117.4, 112.4 (2C), 107.2, 60.8, 60.3, 52.6, 36.8, 13.9. MS: calcd for $C_{14}H_{17}O_2N$ (M^+) 231.1260, found 231.1260.

2-Methylene-5,5-dimethyl-7-oxa-8-oxo-9-methylindolizidine (30). IR ($CDCl_3$): 1665, 1470, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.07 (br s, 1H), 5.03 (br s, 1H), 4.47 (br s, 2H), 3.57 (d, J = 12 Hz, 1H), 3.43 (d, J = 12 Hz, 1H), 2.90 (d, J = 17 Hz, 1H), 2.55 (d, J = 17 Hz, 1H), 1.99 (s, 3H), 1.13 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 145.5, 105.4, 100.4, 70.4, 68.0, 52.8, 41.8, 26.0, 25.1, 21.8. MS: calcd for $C_{11}H_{17}NO_2$ (M^+) 195.1260, found 195.1257.

N-Tosyl-2,3-diphenyl-4-methylenepyrrolidine (36). IR ($CDCl_3$): 1160, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.6 (d, J = 10 Hz, 2H), 7.5 (d, J = 10 Hz, 0.6H), 7.3–7.15 (m, 8.5H), 7.15–6.95 (m, 6H), 6.66 (d, J = 10 Hz, 2H), 6.56 (d, J = 10 Hz, 2H), 5.2–5.1 (m, 2.4), 4.78–4.67 (m, 1.6H), 4.5–4.3 (m, 3H), 4.0 (d, J = 15 Hz, 1H), 3.75 (d, J = 15 Hz, 0.29H), 2.4 (s, 4.3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 145.7, 143.3, 138.4, 134.8, 130.4, 129.5, 128.6, 128.3, 127.8, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 125.9, 125.5, 110.0, 109.5, 68.3, 55.93, 53.5, 52.8, 21.5. Anal. Calcd for $C_{24}H_{23}NO_2S \cdot {}^2/_3H_2O$: C, 71.78; H, 6.10; N, 3.48. Found: C, 71.78; H, 6.08; N, 3.25. HRMS: calcd for $C_{24}H_{23}NO_2S$ (M^+) 389.1450, found 389.1451.

N-Tosyl-2-phenyl-3-cyano-4-methylpyrrolidine. IR ($CDCl_3$): 2230, 1665, 1605, 1599, 1460, 1440, 1360, 1310, 1170, 1105 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.5 (d, J = 10 Hz, 2H), 7.35–7.27 (m, 3H), 7.27–7.18 (m, 4H), 5.6 (br s, 1H), 4.41 (d, J = 16 Hz, 1H), 4.32 (d, J = 18, 3 Hz, 1H), 2.4 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 144.2, 137.9, 129.9 (2C), 129.0 (2C), 127.4 (2C), 127.3 (2C), 113.1, 110.9, 70.1, 58.4, 21.3, 14.1 (missing signal due to weak signals of quaternary carbon). MS: calcd for $C_{19}H_{18}N_2O_2S$ (M^+) 338.1090, found 338.1067.

2-Oxo-3-methyl-3-(2-(acetoxymethyl)allyl)-N-(trimethylsilyl)-5,5-dimethylmorpholine (29). From general procedure C, 0.071 g (0.503 mmol) of imine **28** in THF at reflux gave 0.080 g (50% yield) of the titled compound as an oil after flash chromatography with 15:1 hexane–ether. IR ($CDCl_3$): 1735, 1655, 1375, 1250, 1145, 1087, 1050, 1030, 875 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.17 (s, 1H), 5.03 (s, 1H), 4.65 (d, J = 15 Hz, 1H), 4.59 (d, J = 15 Hz, 1H), 3.49 (d, J = 15 Hz, 1H), 3.44 (d, J = 15 Hz, 1H), 2.65 (d, J = 15 Hz, 1H), 2.51 (d, J = 15 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.13 (s, 3H), 1.05 (s, 3H), 0.20 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 165.2, 138.7, 116.8, 95.2, 68.0, 57.4, 52.4, 42.0, 26.5, 24.8, 22.0, 20.6, 1.5 (3C). MS: calcd for $C_{16}H_{23}9NO_4Si$ (M^+) 327.1866, found 327.1924.

Cycloaddition to Carvopinone Imine 31. From procedure C, 0.153 g (0.504 mmol) of **31** gave 0.132 g (75%) of azepine **33** as an oil after chromatography, using 12:1 hexane–ether. IR ($CDCl_3$): 1340, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 4.95 (s, 1H), 4.80 (s, 1H), 4.21 (d, J = 17 Hz, 1H), 4.05 (d, J = 17 Hz, 1H), 2.65 (d, J = 17 Hz, 1H), 2.51 (d, J = 17 Hz, 1H), 2.40 (s, 3H), 2.31 (m, 1H), 2.15 (m, 1H), 2.05 (m, 2H), 1.95 (t, J = 5 Hz, 1H), 1.80–1.60 (m, 2H), 1.25 (s, 3H), 1.20 (d, J = 8 Hz, 1H), 0.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7, 144.8, 143.0, 138.5, 130.0, 129.4 2C), 127.6 (2C), 112.9, 55.8, 48.5, 40.3, 38.7, 35.6, 33.5, 31.5, 31.3, 25.8, 21.3, 20.9. MS: calcd for $C_{21}H_{27}NO_2S$ (M^+) 357.1812, found 357.1773.

Cycloaddition to Pregnane Imine 32. From general procedure C, 0.071 g (0.125 mmol) of imine **32** gave 0.0376 g (48%) of methylenepyrrolidine **34** and 0.0432 g (56%) of azepine **35** after flash chromatography, using 11:1 hexane–ether. **34**: IR ($CDCl_3$) 1155, 1091 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.7 (d, J = 10 Hz, 2H), 7.25 (d, J = 10 Hz, 2H), 5.31 (m, 1H), 4.95 (s, 1H), 4.93 (s, 1H), 4.75 (s, 1H), 4.65 (s, 1H), 4.17 (d, J = 16 Hz, 1H), 4.07 (d, J = 16 Hz, 1H), 3.51–3.43 (m, 1H), 2.55 (s, 1H), 2.45–2.37 (m, 3H), 2.35–2.37 (m, 3H), 2.35–2.21 (m, 1H), 2.21–2.15 (m, 1H), 2.05–1.95 (m, 1H), 1.85–1.75 (m, 2H), 1.75–1.45 (m, 7H), 1.35–1.15 (m, 2H), 1.17 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 1.0–0.95 (m, 1H), 0.90 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.0, 143.0, 142.0, 141.9, 138.3, 129.3 (2C), 127.6 (2C), 120.7, 107.7, 105.3, 74.7, 72.5, 54.0, 52.7, 52.0, 50.6, 43.7, 42.7, 37.5, 37.4, 37.1, 36.7, 31.9, 30.2, 25.8 (3C), 21.3, 20.6, 20.3, 19.2, 18.1, –4.9 (2C) (missing signals due to weak signals of quaternary carbons). MS: calcd for $C_{36}H_{52}NO_3SSi$ ($M^+ - CH_3$) 606.3440, found 606.3542.

35: IR ($CDCl_3$) 1345, 1155, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 10 Hz, 2H), 7.23 (d, J = 10 Hz, 2H), 5.35 (d, J = 5 Hz, 1H), 4.87 (s, 1H), 4.70 (s, 1H), 4.20 (d, J = 19 Hz, 1H), 3.55–3.45 (m, 1H), 2.59–2.57 (m, 1H), 2.40 (s, 3H), 2.34–2.15 (m, 4H), 2.10–1.80 (m, 2H), 1.80–1.35 (m, 10H), 1.30–1.15 (m, 2H), 1.10–0.97 (m, 5H), 0.87 (s, 9H), 0.77 (s, 3H), 0.06 (s, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 145.4, 144.9, 142.2, 141.8, 136.8, 136.5, 129.2 (2C), 127.6 (2C), 121.1, 112.9, 72.5, 56.8, 55.0, 50.5, 46.1, 42.7, 37.0, 36.7, 35.4, 34.1, 32.2, 31.9, 31.3, 30.0, 25.7 (3C), 23.3, 21.4, 20.3, 19.1, 18.1, 15.1, –4.9 (2C). MS: calcd for $C_{37}H_{55}NO_3SSi$ (M^+) 621.3774, found 621.3616.

N-Tosyl-2-(3-pyridyl)-4-oxopyrrolidine (48a). Ozone was bubbled through a solution of N-tosyl-2-(3-pyridyl)-4-methylenepyrrolidine (0.3 g, 1 mmol) in 10 mL of methylene chloride at –78 °C. The reaction was followed by TLC and complete in 10 min. Dimethyl sulfide was added and the solution extracted with chloroform and then dried with magnesium sulfate. The solvent was removed *in vacuo* and the residue purified by flash chromatography with a 4:1 mixture of ether–ethyl acetate, yielding 0.13 g (40%) of ketone. IR ($CDCl_3$): 1760, 1355, 1160, 1090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 1 Hz, 1H), 8.5 (s, 1H), 7.63 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 2H), 7.25 (m, 3H), 5.23 (dd, J = 10, 1 Hz, 1H), 3.95 (d, J = 20 Hz, 1H), 3.85 (d, J = 20 Hz, 1H), 2.86 (dd, J = 20, 10 Hz, 1H), 2.57 (dd, J = 20, 2 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 149.6, 148.0, 134.0, 130.0 (2C), 127.4 (2C), 123.7, 120.5, 58.3, 53.8, 45.7, 21.6. MS: calcd for $C_{16}H_{16}N_2O_3S$ (M^+) 316.0927, found 316.0860.

N-Tosyl-2-(3-pyridyl)-4-hydroxypyrrolidine (48b). Ozone was bubbled through a solution of methylenepyrrolidine **47** (1 g, 3.18 mmol) dissolved in 6 mL of a 1:1 methylene chloride–methanol solution at –78 °C. The reaction was followed by TLC and complete in 10 min. Sodium borohydride (0.36 g, 9.5 mmol) was added at –78 °C. The reaction was stirred at this temperature for 10 min and then allowed to warm to room temperature, with vigorous gas evolution. The solution was washed with 10% sodium hydroxide, extracted with chloroform, and dried with magnesium sulfate. The solvent was removed *in vacuo* and the residue purified by flash chromatography with ethyl acetate, yielding 0.69 g of alcohol (69%) as a solid, mp 136–8 °C (ether). IR ($CDCl_3$): 1598, 1348, 1160, 1090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 0.67 H), 8.45 (s, 0.33 H), 8.42 (d, J = 7 Hz, 0.33H), 8.39 (d, J = 7 Hz, 0.67H), 7.83 (d, J = 10 Hz, 0.67H), 7.68 (d, J = 10 Hz, 0.33H), 7.63 (d, J = 10 Hz, 2 H), 7.30–7.20 (m, 2H), 4.80–4.70 (m, 1H), 4.40 (s, 0.33H), 4.30 (s, 0.67H), 3.75 (dd, J = 14, 7 Hz, 0.33H), 3.62–3.51 (m, 1.67H), 3.91 (br

s, 0.67H), 2.68 (br s, 0.33H), 2.41 (s, 3H), 2.40–2.10 (m, 1H), 1.97–1.90 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 148.1, 147.9, 143.9, 148.9, 134.9, 134.3, 129.8, 129.6, 127.8, 127.6, 123.6, 123.4, 70.1, 69.5, 60.2, 57.1, 43.6, 21.6. Anal. Calcd for $C_{16}H_{18}N_2O_3S \cdot 0.5H_2O$: C, 58.70; H, 5.84; N, 8.56. Found: C, 58.81; H, 5.54; N, 8.18. HRMS: calcd for $C_{16}H_{18}N_2O_3S$ (M^+) 318.1068, found 318.1045.

***N*-Tosyl-2-(3-pyridyl)-4-(((*p*-tolyloxy)thiocarbonyl)oxy)pyrrolidine (48c).** Pyridine (0.5 mL, 6.4 mmol), DMAP (0.05 g, 0.47 mmol), and (*p*-tolyloxy)thiocarbonyl chloride (0.3 g, 1.6 mmol) were added to alcohol **48b** (0.297 g, 0.93 mmol) dissolved in 6 mL of methylene chloride. The reaction was heated overnight at 40 °C. The solution was washed with water and saturated sodium chloride, then extracted with chloroform, and dried with magnesium sulfate. The solvent was removed *in vacuo* and the residue purified by flash chromatography with ether, yielding 0.335 g (77%) of carbonate as a solid, mp 53–4 °C ($CHCl_3$). IR ($CDCl_3$): 1595, 1490, 1350, 1270, 1215, 1200, 1160, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60–8.40 (m, 2H), 7.85–7.60 (m, 3H), 7.35–7.10 (m, 5H), 6.90–6.78 (m, 2H), 5.61–5.50 (m, 1H), 4.85–4.74 (m, 1H), 4.0–3.90 (m, 1H), 3.78 (d, J = 9 Hz, 0.67H), 3.71 (d, J = 9 Hz, 0.33H), 2.70–2.0 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 194.3, 151.3, 149.2, 148.8, 148.2, 144.4, 144.1 136.6, 136.5, 134.5, 134.1, 133.5, 130.1, 130.0, 129.8, 128.7, 127.7, 123.4, 121.2, 81.2, 60.7, 59.7, 54.77, 54.0, 42.0, 39.9, 21.3, 20.6. MS: calcd for $C_{24}H_{24}N_2O_4S_2$ (M^+) 468.1177, found 468.1177.

***N*-Tosyl-2-(3-pyridyl)pyrrolidine (48d).** AIBN (19 mg, 0.1 mmol) and tributyltin hydride (0.5 mL, 1.5 mmol) were added to a solution of thionocarbonate **48c** (0.335 g, 0.71 mmol) dissolved in 14 mL of degassed toluene. The solution was heated to 90 °C overnight. The solvent was removed *in vacuo* and the residue purified by flash chromatography with ether, yielding 0.175 g (81%) of the pyrrolidine as a solid, mp 106–7 °C (ether). IR ($CDCl_3$): 1600, 1425, 1345, 1157, 1090 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.45 (d, J = 10 Hz, 1H), 7.71–7.6 (m, 3H), 7.30 (d, J = 10 Hz, 2H), 7.24–7.19 (m, 1H), 4.73 (dd, J = 8, 5 Hz, 1H), 3.65–3.55 (m, 1H), 3.48–3.35 (m, 1H), 2.41 (s, 3H), 2.10–1.97 (m, 1H), 1.90–1.75 (m, 2H), 1.73–1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 147.9, 143.7, 138.6, 134.5, 134.0, 129.7, 127.5, 123.3, 61.1, 49.4, 35.7, 24.0, 21.5. Anal. Calcd for $C_{16}H_{18}N_2O_2S \cdot {}^1/_7H_2O$: C, 63.01; H, 6.04; N, 9.18. Found: C, 63.02; H, 5.82; N, 8.92. HRMS: calcd for $C_9H_{11}N_2$ ($M^+ - C_7H_7SO_2$) 147.0841, found 147.0911.

Nornicotine. A solution (3 mL) of sodium (0.035 g, 1.5 mmol) and naphthalene (0.36 g, 2.8 mmol) was added dropwise to sulfonamide **48d** (0.2 g, 0.66 mmol) dissolved in 6 mL of THF at –78 °C. The reaction was followed by TLC and quenched with aqueous disodium monoacid phosphate upon disappearance of sulfonamide. The solution was washed with saturated aqueous sodium chloride and extracted with methylene chloride. The solvent was removed *in vacuo* and the residue purified by flash chromatography with a 9:1 mixture of methylene chloride–methanol with 1% ammonium hydroxide, yielding 5.1 mg (52%) of amine. Spectral properties agree with published data.[26] IR ($CDCl_3$): 1730, 1475, 1430, 1375, 1250, 1100, 1050 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.45 (d, J = 3 Hz, 1H), 7.70 (d, J = 7 Hz, 1H), 7.21 (dd, J = 7, 3 Hz, 1H), 4.17–4.07 (m, 1H), 3.20–3.13 (m, 1H), 3.07–2.97 (m, 1H), 2.35–2.13 (m, 2H), 1.95–1.81 (m, 2H), 1.69–1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 148.2, 140.2, 134.1, 123.4, 60.0, 46.9, 34.3, 25.5.

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