

Sulfur Ylide-Initiated Thio-Claisen Rearrangements. The Synthesis of Highly Substituted Indolines

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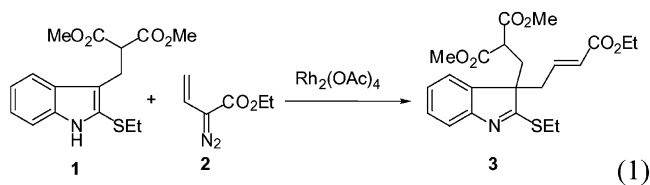
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The coupling of rhodium carbenoids from vinyl diazoacetates with 2-thio-3-alkyl indoles was found to generate C(3) quaternary substituted indolines via a thionium ylide-initiated [3,3]-sigmatropic rearrangement.

Introduction

The presence of C(3) quaternary substitution in a wide variety of interesting indoline-containing natural and nonnatural products has inspired a number of groups, including ours, to develop new and improved routes to their synthesis.^{1–3} Our contributions to this area began with the somewhat surprising result that was obtained when we attempted to couple vinyl diazoacetate **2** with 2-thio-3-alkylindole **1** in the presence of rhodium acetate (eq 1).⁴ Rather than the anticipated C–S insertion product that had been observed with diazomalones and diazo- β -ketoesters, we isolated C(3) quaternary-substituted indoline **3**.



When combined with our ability to generate 2-thio-3-alkylindoles from the coupling of isonitrile-alkyne radical

TABLE 1. Coupling of **1** with Monosubstituted Vinyl Diazoacetates

entry	diazo	R'	R''	conditions ^a	product ^b	dr ^c	yield
1	4	Me	H	A	8	2:1	95%
2	5	CO ₂ Et	H	A	9	2:1	93%
3	6	Ph	H	B	10	1:1	95%
4	7	H	Cl	B	11	3:1	98%

^a A: PhH, reflux. B: CH₂Cl₂, rt. ^b Relative stereochemistry of the major diastereomer is shown. This assignment was based upon the X-ray structural determination of **25** (Table 3 and Supporting information). ^c Determined by ¹H NMR.

cascades and C(10) fragmentation–coupling reactions,⁵ we felt that the **1** → **3** transformation might prove to be useful in the synthesis of highly substituted indoline ring systems. However, to achieve this goal it was clear to us that we needed to have a better sense of the scope and limitations of this reaction. Herein, we report the results of these efforts.

Generation of Indolines Having C(3) Quaternary Substitution. In addition to the reaction illustrated in eq 1, our initial experiments had demonstrated that the coupling of thioindole **1** with vinyl diazoacetates was insensitive to methyl and carboxyethyl substitution on the terminus of the vinyl diazoacetate (Table 1, entries 1 and 2).⁴ In an effort to gain a better understanding of the range of monosubstituted olefins capable of undergoing this transformation, we synthesized phenyl- and chloro-substituted vinyl diazoacetates **6**⁶ and **7**,⁶ respectively, and examined their coupling with thioindole **1**. To

(5) (a) Rainier, J. D.; Kennedy, A. R.; Chase, E. *Tetrahedron Lett.* **1999**, *40*, 6325. (b) Rainier, J. D.; Kennedy, A. R. *J. Org. Chem.* **2000**, *65*, 6213.

(6) Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *J. Org. Chem.* **1997**, *62*, 1630.

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(1) For recent reviews of indole-containing natural products, see: (a) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155.

(2) For a recent review covering approaches to the synthesis of indoles, see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

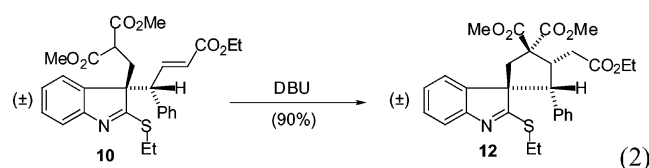
(3) For representative examples of the synthesis of indolines having quaternary substitution at C(3) see: (a) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (b) Overman, L. E.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465. (c) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (d) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. (e) Nakazawa, K.; Hayashi, M.; Tanaka, M.; Aso, M.; Suemune, H. *Tetrahedron: Asymmetry* **2001**, *12*, 897. (f) Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675. (g) Fujii, K.; Kawabata, T.; Ohmori, T. *Heterocycles* **1998**, *47*, 951. (h) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543. (i) Booker-Milburn, K. I.; Fedouloff, M.; Paknoham, S. J.; Strachan, J. B.; Melville, J. L.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 4657.

(4) Kennedy, A. R.; Taday, M. H.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2407.

our delight, when **6** and **7** were added to a solution of $\text{Rh}_2(\text{OAc})_4$, **1**, and CH_2Cl_2 at room temperature, we isolated **10** and **11** in 95 and 98% yields, respectively.

In addition to the overall efficiency of these transformations, three features are worthy of note. First, the coupling results in the selective formation of the (*E*)-olefin isomer.⁷ Second, these reactions are run in the absence of protection on the indole nitrogen and proceed without any evidence of NH insertion. Finally, the products result from the selective coupling of the 3-position on the indole with the vinyl terminus of the vinyl diazoacetate.

As a demonstration of the synthetic potential of thioimidates **8–11**, we transformed one of the diastereomers of thioimide **10** into spirocycle **12**⁸ in 90% yield by simply treating it with DBU (eq 2). The presence of the spirocyclic framework of **12** in a number of intriguing natural products speaks to the utility of these coupling reactions.⁹



Generation of Indolines Having C(3) Vicinal Quaternary Substitution. Having demonstrated that a variety of monosubstituted vinyl diazoacetates undergo coupling with **1** in the presence of $\text{Rh}_2(\text{OAc})_4$, we chose to investigate disubstituted vinyl diazoacetates. These experiments would not only give us a better understanding of the reaction scope but also, if successful, enable us to access a plethora of interesting indoline natural products having C(3) vicinal quaternary substitution.¹⁰

With this in mind, we examined the coupling of dimethyl vinyl diazoacetate **13**⁶ with thioindole **1** (Table 2). Slow addition of **13** to a solution of **1**, $\text{Rh}_2(\text{OAc})_4$, and CH_2Cl_2 at room temperature resulted in the formation of indoline **15** in 86% yield. As in the reactions of the monosubstituted vinyl diazoacetates with **1**, **15** was formed exclusively as its (*E*)-olefin isomer. Similarly, the coupling of vinyl diazoacetate **14**⁶ with **1** resulted in the formation of thioimide **16** in 96% yield. Clearly, these experiments demonstrate that sterically encumbered indolines can be obtained using this methodology.

When the size of the substituents on the terminus of the vinyl diazoacetate was increased to diphenyl, the reaction entered a new manifold (eq 3). That is, the coupling of vinyl diazoacetate **17**⁶ with **1** led to the formation of thioimide **18** as a 1:1 mixture of diastereomers in 71% yield. Overall, **18** results from the coupling of **1** with **17** at the carbenoid-bearing carbon.

(7) The corresponding (*Z*)-olefin isomer was not observed by ¹H NMR spectroscopy.

(8) Determined by ¹NMR experiments. See Supporting Information for details.

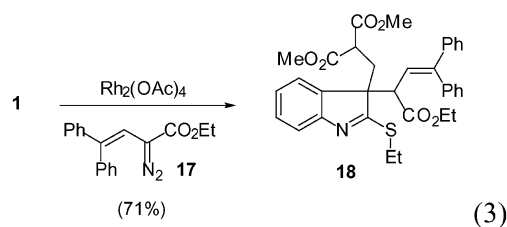
(9) For example, the paraherquamides contain spirofused oxindoles analogous to **12**. The Williams group has been at the forefront of the synthetic studies towards these agents. See: Williams, R. M.; Cao, J.; Tsujishima, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2540 and references therein.

(10) Examples include paraherquamides (see ref 9) and a number of dimeric indoles. The Overman group has been at the forefront of efforts in this latter area. See ref 3b and references therein.

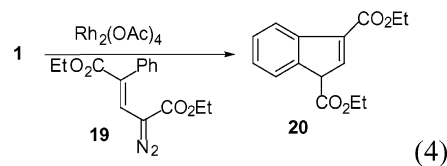
TABLE 2. Coupling of 1 with Disubstituted Vinyl Diazoacetates

Entry	R	R'	indoline	Yield
13: R, R' = Me	Me	Me	15	86%
14: R = Me, R' = Ph	Me	Ph	16	96% ^a

^a Formed as a 1.5:1 mixture of diastereomers as determined by ¹H NMR integration.



In contrast to the results with **14** and **17**, vinyl diazoacetate **19**¹¹ underwent intramolecular C–H insertion to generate indene **20** when exposed to $\text{Rh}_2(\text{OAc})_4$ and **1** (eq 4). We observed no product resulting from the coupling of **1** and **19**. In the absence of thioindole, we found that the conversion of **19** into **20** occurred in 88% yield.¹²



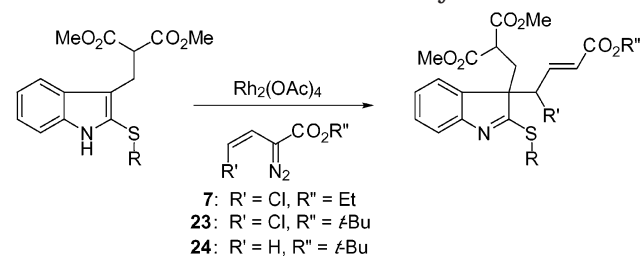
Ester and Thioether Substituent Effects on Coupling Reactions. The diastereoselectivity in the condensation between monosubstituted vinyl diazoacetates and thioindoles was only marginally affected by substitution on the thioether (Table 3). When chloro-substituted vinyl diazoacetate **7** was coupled with 2-isopropylthioindole **21**¹³ in the presence of $\text{Rh}_2(\text{OAc})_4$, thioimide **25** was formed in 83% yield as a 3.4:1 mixture of diastereomers (entry 1). A 3:1 ratio of diastereomers had been observed when ethyl thioindole **1** was used (Table 1).

Similarly, the steric environment about the diazoester had little influence on the diastereoselectivity of the coupling reaction. For example, the coupling of *tert*-butyl ester **23** with **21** resulted in the formation of **26** in approximately the same diastereomeric ratio as the corresponding ethyl ester (Table 3, entries 1 and 2).

(11) Davies, H. M. L.; Clark, D. M.; Alligood, D. B.; Eiband, G. R. *Tetrahedron* **1987**, *43*, 4265.

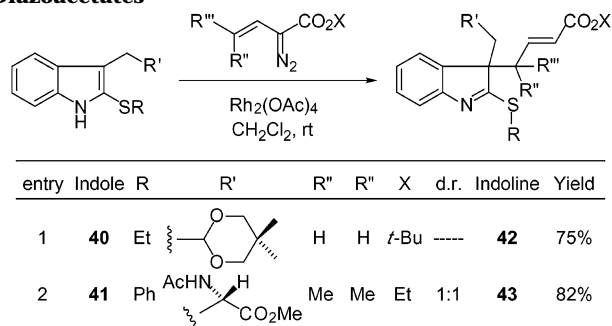
(12) There are numerous examples of related reactions. See: Doyle, M. P.; McKerverve, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley & Sons: New York, 1998; 325–336.

(13) From the free radical cyclization of (2-isocyanophenylethynyl) trimethylsilane with 2-propanethiol followed by fragmentation coupling with dimethylmalonate. See Supporting Information and ref 5b.

TABLE 3. Effect of Thioether and Diazoester Substitution on the Diastereoselectivity

entry	indole	R	R'	R''	indoline	dr ^a	yield
1	21	<i>i</i> -Pr	Cl	Et	25	3.4:1	83%
2	21	<i>i</i> -Pr	Cl	<i>t</i> -Bu	26	3.6:1	79%
3	22	Ph	H	<i>t</i> -Bu	27		80%

^a Determined by integration of the vinyl protons in the crude ¹H NMR spectra.

TABLE 4. Coupling of Thioindoles with Vinyl Diazoacetates

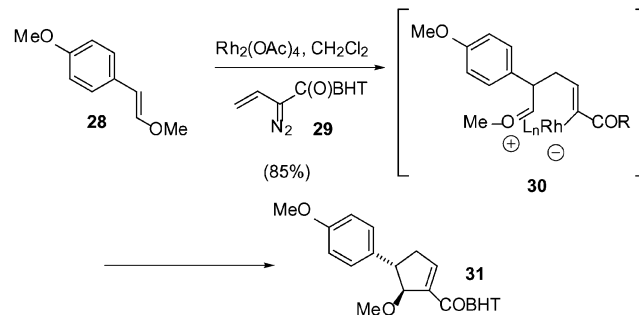
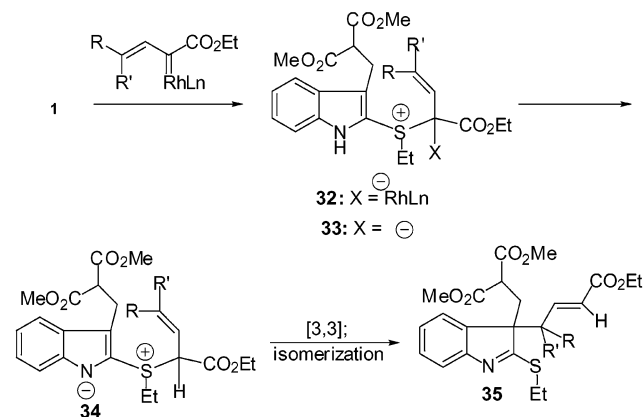
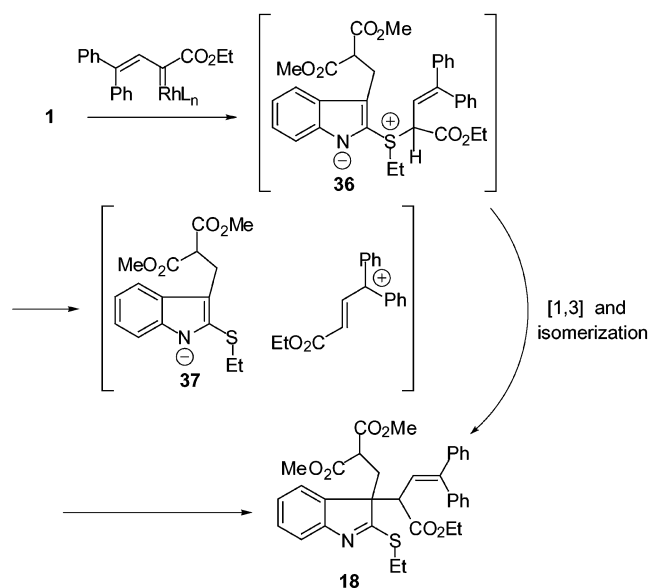
entry	Indole	R	R'	R''	R'''	X	d.r.	Indoline	Yield
1	40	Et		H	H	<i>t</i> -Bu	-----	42	75%
2	41	Ph		Me	Me	Et	1:1	43	82%

Finally, phenyl thioether **22** underwent successful coupling with vinyl diazoacetate **24**, thus demonstrating that the reaction is amenable to nonalkyl substitution on the thioether.

The relative stereochemistry of chlorothioimidate **25** (major diastereomer) was determined through single X-ray diffraction (See Supporting Information).

Proposed Mechanism for Coupling of 2-Thioindoles with Vinyl Diazoacetates. Davies and co-workers observed phenomena similar to that presented here when they attempted to couple pyrroles, enol ethers, dihydrofurans, and cyclopentadienes with unsubstituted vinyl diazoacetates in the presence of rhodium (Scheme 1).¹⁴ They reasoned that the products from these reactions arose from the conjugate addition of the electron-rich olefin with the vinyl terminus of the rhodium carbenoid. Consistent with this notion, terminally substituted vinyl diazoacetates did not give conjugate addition products.

As has been described, we have found the coupling of 2-thioindoles with vinyl diazoacetates to also give conjugate addition products. However, in light of the presence of thioethers and our ability to utilize substituted vinyl diazoacetates in these couplings, we believe that 2-thioindoles proceed through an entirely different mechanism (Scheme 2). As in the coupling of **1** with malonate and β -ketoester rhodium carbenoids,⁴ it is reasonable to

SCHEME 1. Davies' Coupling of Enol Ethers with Vinyl Diazoacetate 29¹⁴**SCHEME 2. Proposed Mechanism for the Coupling of Thioindoles with Vinyl Diazoacetates****SCHEME 3. Proposed Mechanism for the Generation of 18**

assume that the reaction is initiated by the formation of a sulfur ylide intermediate (i.e., **32** and/or **33**, Scheme 2).¹⁵ After proton transfer,^{16,17} the resulting allyl thionium

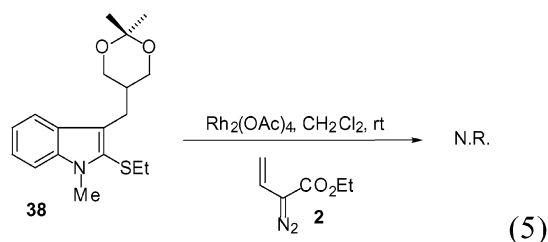
(14) (a) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696. (b) Davies, H. M. L.; Hu, B. *Tetrahedron Lett.* **1992**, *33*, 453. (c) Davies, H. M. L.; Hu, B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535.

(15) For reviews on ylide-initiated cascades (rearrangements and cycloadditions), see: (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Hodgson, D. M.; Pierard, F. Y. T. M.; Stuppel, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

ion **34** undergoes a [3,3]-sigmatropic rearrangement to give indoline **35** after isomerization to the thioimidate.^{18–20}

As was mentioned above (eq 3), the coupling of **1** with diphenyl vinyl diazoacetate **17** results in the formation of **18** from the coupling at the diazo-bearing carbon of the vinyl diazoacetate with C(3) of the indole. Presumably, this reaction also proceeds through an allyl thionium ion (e.g., **36**). However, rather than undergoing a [3,3]-sigmatropic rearrangement as had been observed in the other systems, the presence of the diphenyl substituents on the alkene forces an overall [1,3]-sigmatropic rearrangement to give **18**. Presumably, this occurs via the intermediacy of ionic intermediate **37**.^{21–23}

Consistent with the mechanism proposed in Scheme 2, we have found that *N*-methyl indole **38**²⁴ does not undergo this process. That is, when **38** was subjected to vinyl diazoacetate **2** and Rh₂(OAc)₄, no coupling occurred and thioindole **38** was reisolated in quantitative yield (eq 5).



An alternative mechanism that would be consistent with all of the results presented thus far would couple

(16) For reports from other laboratories of proton transfer to ylide intermediates, see: (a) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1992**, *114*, 593. (b) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1989**, *111*, 6451. (c) Mori, T.; Sawada, Y.; Oku, A. *J. Org. Chem.* **2000**, *65*, 3620.

(17) While we cannot rule it out at the present time, we disfavor the rearrangement of **33** because it would lead to a highly energetic vinyl anion.

(18) We are aware of three other examples of an ylide-initiated [3,3]-sigmatropic rearrangement. See (a) Nakano, H.; Iyata, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1393. (b) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748. (c) Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371. (d) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426.

(19) For examples of thio-Claisen rearrangements in indole systems, see: (a) Bycroft, B. W.; Landon, W. *J. Chem. Soc., Chem. Commun.* **1970**, 168. (b) Bycroft, B. W.; Landon, W. *J. Chem. Soc., Chem. Commun.* **1970**, 967.

(20) For an example of the use of Claisen rearrangements in the synthesis of oxindoles having quaternary substitution at C(3), see ref 3i.

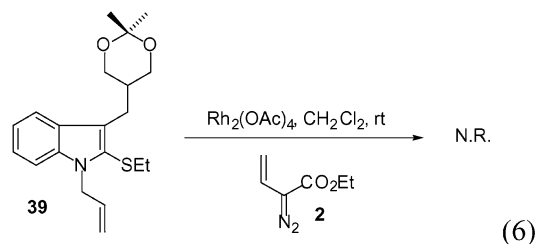
(21) For examples of [1,3]sigmatropic rearrangements in allyl vinyl ethers, see: (a) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488. (b) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6891. (c) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559. (d) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316.

(22) Alternatively, cyclopropanation of the thioindole could be followed by the in situ ring opening of the cyclopropane. Although this mechanism would not be consistent with our results from reactions of other rhodium carbenoids with 2-thioindoles (see ref 4), we cannot rule it out at the present time.

(23) While we cannot rule out the possibility that **35** also comes from an ion pair similar to **37**, the recombination to form vicinal quaternary substitution is not consistent with such a mechanism.

(24) Compound **38** comes from the reduction of malonate **2** with LiAlH₄ followed by acetonide formation and methylation.

an N–H insertion reaction with a [3,3]-rearrangement. To test the viability of this hypothesis, we synthesized allyl indole **39** and subjected it to our rearrangement conditions. The quantitative recovery of starting material from this experiment effectively rules out the N–H insertion initiated pathway (eq 6).



Coupling of C(3)-Substituted Indoles with Vinyl Diazoacetates. Finally, to demonstrate that these reactions can be carried out with indoles having substitution other than malonate at C(3), cyclic acetal **40** and 2-thio-tryptophan methyl ester **41**²⁵ were subjected to Rh₂(OAc)₄ and vinyl diazoacetates **2** and **13**, respectively. These couplings resulted in the isolation of indolines **42** and **43** in 75 and 82% yields, respectively.

Conclusion

From the experiments that have been outlined here, it is clear that 2-thioindoles show remarkable potential as precursors to highly substituted indoline systems. This work has described the generation of C(3) quaternary and C(3) vicinal quaternary substitution via the coupling of vinyl carbenoids with 3-alkyl-2-thioindoles. Our current investigations are focused on optimizing the reactions that we have discovered and, in the process, uncovering more insight into the mechanism. Additionally, we are currently utilizing asymmetric carbenoids in these reactions and taking advantage of these transformations to generate bioactive indoline-containing natural products.

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Supporting Information Available: Complete experimental details and spectroscopic data for compounds **10–12**, **15–27**, and **38–43**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(25) Compound **41** comes from the reaction of CISPh with L-tryptophan methyl ester. See: Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1989**, *30*, 4307.