Cascades to Substituted Indoles

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This paper describes the synthesis of dithioindoles from the free-radical cyclizations of arylisonitriles having pendant alkynes. Also described is the synthesis of substituted indoles and spiro-fused indoles from the coupling of dithioindoles with active hydrogen-containing compounds.

Introduction

Although Fischer first described their generation some 115 years ago, the synthesis of indoles continues to receive attention.[1,2] The presence of indole subunits in a number of bioactive molecules undoubtedly plays a key role in the continued activity in this area.[3] From our perspective, those approaches to substituted indoles that have employed free-radical cyclizations[2] or indolenines from gramine fragmentations[4] have stood out. This is not only because of the high reactivity of each of these species but it is also a result of the relatively mild and neutral reaction conditions that are required for their synthesis. Thus, in the course of using radical or indolenine intermediates, one can incorporate sensitive functionality without having to be overly concerned with unwanted side reactions.[5,6]

We became interested in arylisonitrile−alkyne free radical cascades out of a desire to incorporate both radical cyclizations and indolenine couplings into the same reaction sequence.[7−11] This notion came from a consideration of the mechanism that Fukuyama has proposed for the corresponding arylisonitrile-alkene cyclizations.[12,13] Assuming that arylisonitrile−alkynes followed a similar pathway, their cyclization would result in an unprecedented free-radical approach to indolenines (i.e., **4**) and, through the incorporation of nucleophiles into the reaction mixture, the synthesis of highly substituted indoles (Scheme 1).[14]

While our main focus was the sequence depicted in Scheme 1 beginning with the 5-*exo*-*dig* cyclization of **2**, a potentially competitive 6-*endo*-*dig* cyclization would provide an entry into substituted quinolines. As quinolines are present in a variety of interesting structures we also found this possibility intriguing.[15]

Described herein is the successful demonstration of the sequence depicted in Scheme 1 through the synthesis of bis-thiol and 2-stannyl indoles from the radical cyclizations of arylisonitriles having pendant alkynes. Also described here are our experiments showing that bisthioindoles are synthetically useful through their coupling with active hydrogen compounds and their conversion into spiro-fused indolethioimidates.

Results and Discussion

As it seemed probable that the alkynyl substitution might be important in the ultimate indole:quinoline product ratio, a variety of substituted alkynylisonitriles were synthesized in two steps from 2-iodoformanilide (Table 1). Sonogashira coupling reactions provided *o*-alkynylformanilides **7a**−**e** from **6**.[16] Dehydration of the formanilides gave cyclization precursors **8a**−**e**.[17,18]

With arylisonitrile−alkynes in hand, we subjected them to Fukuyama's conditions using an excess of Bu_3SnH to ensure the reduction of any indolenine that was formed (i.e., NuH in Scheme 1 = Bu_3SnH). Delightfully

(1) (a) Fischer, E.; Jourdan, F. *Ber.* **1883**, *16*, 2241. (b) Fischer, E.; Hess, O. *Ber.* **1884**, *17*, 551.

(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 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.

(4) For examples of the synthesis of substituted indoles from gramine fragmentations, see: (a) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323. (b) Smith, A. B., III; Haseltine, J. N.; Visnick, M. *Tetrahedron* **1989**, *45*, 2431. (c) Remers, W. A.; Brown, R. K. In *Indoles*; Houlihan, W. J., Ed.; Heterocyclic Compounds; Wiley-Interscience: New York, 1972; Part One, pp 200−203.

(5) Radical reactions are generally run under neutral conditions. See: (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1.

(6) For examples of the generation of indolenines in the presence of sensitive functionality, see ref 4.

(7) For a review of cascade sequences in organic synthesis, see: Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.

(8) For a preliminary account of this work see: Rainier, J. D.; Kennedy, A. R.; Chase, E. *Tetrahedron Lett.* **1999**, *40*, 6325.

(9) Curran and co-workers have developed and applied isonitrile−alkyne radical cyclizations in synthesis. See: (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127. (b) Curran, D. P.; Ko, S.-B.; Josien, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2683. (c) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67.

(10) Nanni and co-workers have also investigated arylisonitrile-alkyne radical reactions. See: Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotto, P.; Tundo, A. *Tetrahedron* **1995**, *51*, 9045.

(11) For other isonitrile radical reactions, see: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 6, 177. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (c) References 9, 10, 12, 13, and 27.

(12) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127.

(13) Aryl isonitrile−alkene cyclizations have been used to generate complex indoles. See ref 12 and: (a) Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043. (b) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519.

(14) A possible complication with the mechanism depicted in Scheme 1 is the intermolecular addition of the radical to the alkyne rather than the isonitrile. See: Leardini, R.; Nanni, D.; Zanardi, G. *J. Org. Chem.* **2000**, *65*, 2763.

(15) Ito and co-workers have demonstrated that the anionic cyclization of arylisonitriles having pendant alkynes provides quinolines. See: Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977.

(16) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551.

(17) Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, *4*, 400.

(18) **8b**,**c**,**e**,**f** were not stable to purification in our hands. Each of these showed the expected isonitrile IR stretch (i.e., **8b**: 2119 cm^{-1}; **8c**: 2124 cm^{-1}; **8e**: 2124 cm^{-1}; **8f**: 2130 cm^{-1}).

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Scheme 1

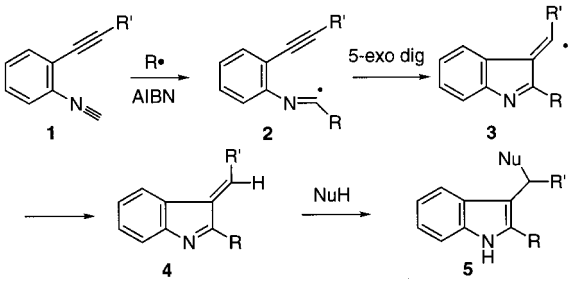
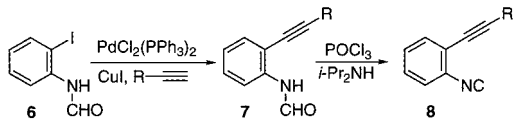


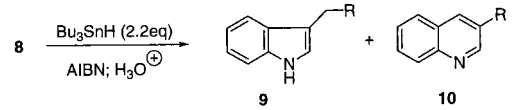
Table 1. Arylisonitrile−Alkyne Syntheses



entry	R	**7**	yield (**7**) (%)	**8**	yield (**8**) (%)
1	TMS	**a**	93	**a**	82
2	Ph	**b**	100	**b**	*a*
3	Bu	**c**	100	**c**	*a*
4	*t*-Bu	**d**	92	**d**	100
5	CH_2OBn	**e**	57	**e**	*a*

[a] Isonitrile was not purified prior to the free-radical cyclization.

Table 2. Bu_3SnH-Mediated Arylisonitrile−Alkyne Free-Radical Cyclizations

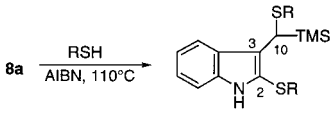


entry	isonitrile	R	**9**:**10**	yield (%)
1	**8a**	TMS	1:0	82
2	**8b**	Ph	2.2:1	41
3	**8c**	8u	1:5.3	63
4	**8d**	*t*-Bu	14:1[b]	60
5	**8e**	CH_2OBn	2:1	11
6	**8f**[a]	H	0:1	18

[a] From TBAF hydrolysis of the **10a** TMS group. [b] **10d** was isolated as the 2-stannylated quinoline.

for us, the treatment of TMS-alkyne **8a** with 2 equiv of Bu_3SnH and 10% AIBN in either benzene or acetonitrile resulted in indole **9a**[19] in 82% yield after acidic workup to protodestannylate the 2-stannylindole product (Table 2, entry 1).[20] None of the corresponding quinoline was detected.[21] In a similar fashion, phenyl substituted alkyne **8b** gave indole **9b**[12] as the major product. However, the overall yield was lower and **9b** was obtained along with the corresponding quinoline **10b**[22] in a 2.2:1 product ratio respectively (entry 2). In contrast, butyl-substituted alkyne **8c** provided quinoline **10c**[17] as the major product of a 5.3:1 mixture (entry 3). In an effort to ascertain whether silicon's ability to stabilize α-radicals[23] or its steric destabilization of the 6-endo pathway through its interactions with Bu_3Sn during the transition state were responsible for the observed selectivity of **8a** we synthesized *tert*-butyl alkyne **8d**. When **8d** was exposed to the radical conditions we isolated a mixture of indole **9d** and quinoline **10d**[24] in a 14:1 ratio respectively (entry 4). Thus, it appears that the 5-*exo*-*dig* cyclization of **8a** is largely due to the steric destabilization of the 6-*endo*-*dig* cyclization manifold.

Table 3. Thiol-Mediated Free-Radical Cyclizations of 8a



entry	R	indole	yield (%)
1	Et	**11**	86
2	Bu	**12**	66
3	Ph	**13**	49
4	CH_2CH_2OH	**14**	94
5	CH_2CH_2OTBS	**15**	60
6	$CH_2CH_2CO_2Me$	**16**	72

Having shown that the free-radical cyclization of **8a** leads to indoles, we set out to trap the indolenine intermediate with nonhydride (hydrogen atom) nucleophiles. Unfortunately, we have been unsuccessful in our attempts to couple **4a** (Scheme 1, R = Bu_3Sn, R′ = TMS) with oxygen or nitrogen nucleophiles in the presence of Bu_3SnH.[25] Apparently, indolenine **4a** (R = Bu_3Sn, R′ = TMS) has a relatively high affinity for tin hydride as even the use of substoichiometric quantities of Bu_3SnH and excess alcohol or amine resulted in the isolation of mixtures of reduced indole **9a** along with unreacted starting material **8a**.[26]

We were undaunted by our inability to couple **4a** (R = Bu_3Sn, R′ = TMS) with non-hydrogen nucleophiles as we believed that we might be able to circumvent the reduction problem by simply inducing the free-radical cyclization of **8a** with a reagent other than Bu_3SnH. In this regard, thiols were attractive as they might both initiate the radical cascade and act as nucleophiles in the reaction with the indolenine.[27] Gratifyingly, bis-thioindole **11** was isolated in 86% yield when isonitrile **8a** was allowed to react with ethanethiol and AIBN (Table 3, entry 1). As depicted, the use of the same conditions with other alkyl and aryl thiols also gave bis-thiol indoles. These reactions clearly demonstrate that the free-radical cyclization of arylisonitriles having pendant alkynes can be used to generate indoles. These experiments also demonstrate that the indolenine intermediates formed during these sequences are susceptible to attack by nucleophiles.[28]

We became intrigued by the synthetic possibilities associated with bis-thioindoles **11**−**16**. From our perspective it appeared that they might serve as versatile

(19) Ishibashi, H.; Nishida, K.; Ikeda, M. *Synth. Commun.* **1993**, *23*, 2381.

(20) The protodestannylated products were more robust and thus easier to purify than the 2-stannylindoles.

(21) Tamao, K.; Kodama, S.; Nakajima, I.; Kumada, M. *Tetrahedron* **1982**, *38*, 3347.

(22) Úbeda, J. I.; Villacampa, M.; Avendaño, C. *Synthesis* **1998**, 1176.

(23) For examples of silicon's influence on free-radical cyclizations, see: (a) Gillmann, T.; Hülsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257. (b) Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 925. (c) Wilt, J. W.; Aznavoorian, P. M. *J. Org. Chem.* **1978**, *43*, 1285.

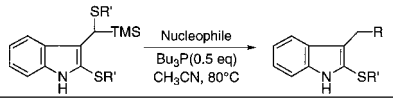
(24) **10d** was isolated as the 2-tributylstannylquinoline adduct. Acidic workup failed to give protodestannylated product.

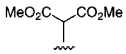
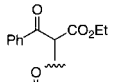
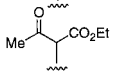
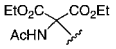
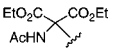
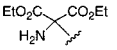
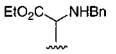
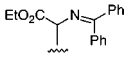
(25) We have attempted to couple the intermediate indolenine with diethylamine, aniline, benzylamine, and methanol.

(26) The reduction sequence could be the result of a heterolytic or homolytic process. For the homolytic reduction of isoelectronic enones, see: Enholm, E. J.; Whitley, P. E. *Tetrahedron Lett.* **1996**, *37*, 559. For an example of the use of Bu_3SnH in hydride reductions of imminium ions, see: Palmisano, G.; Lesma, G.; Nali, M.; Rindone, B.; Tollari, S. *Synthesis* **1985**, 1072.

(27) (a) Saegusa first demonstrated the reactivity of isonitriles with thiol radicals. See: Saegusa, T.; Kobayashi, S.; Ito, Y. *J. Org. Chem.* **1970**, *35*, 2118. More recently, Bachi and Nanni have independently coupled thiol radicals with isonitriles. See: (b) Bachi, M. D.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, 7752. (c) Camaggi, C. M.; Leardini, R.; Nanni, D.; Zanardi, G. *Tetrahedron* **1998**, *54*, 5587.

Table 4. Bis-Thioindoles as Alkylating Agents with Active Hydrogen Compounds



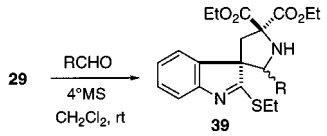
entry	Nucleophile	R	R'	Product	Yield
1	$CH_2(CO_2CH_3)_2$		Et	**24**	82%
2	$PhC(O)CH_2CO_2Et$ **17**		Et	**25**	33%
3	$CH_3C(O)CH_2CO_2Et$ **18**		Et	**26**	57%
4	$CH(NHAc)(CO_2Et)_2$ **19**		Et	**27**	98%
5	$CH(NHAc)(CO_2Et)_2$ **19**		CH_2CH_2OTBS	**28**	59%
6	$CH(NH_2)(CO_2Et)_2$ **20**		Et	**29**	96%
7	$EtO_2CCH_2N{=}CHPh$ **21**		Et	**30**	61%[a]
8	$EtO_2CCH_2N{=}C(Ph)_2$ **22**		Et	**31**	80%
9	Cyclohexanone		Et	**32**	40%
10	$AcNHCH_2CO_2Et$ **23**		Et	**32**	12%

[a] After reduction of the imine with $NaCNBH_3$.

intermediates in the synthesis of other, more highly substituted species. For example, a C-10 anion (generated via deprotonation,[29] thioether reduction,[30,31] or fluoride induced desilylation[32]) could be used in coupling reactions with electrophiles. Conversely, elimination of the C-10 thioether in a gramine-like fashion would provide a C-10 electrophile that would then be amenable to coupling reactions with nucleophiles. Although Poppelsdorf and Holt had previously found simple 3-ethylthiomethylindole to be unreactive to gramine alkylation reactions with active hydrogen compounds,[33] we were confident that **11**−**16** would be more reactive by virtue of the fact that the C-2 thioether would aid in the elimination sequence.

We elected to pursue the use of the bis-thioindoles as electrophiles as the success of these investigations would circumvent our inability to trap indolenines with non-hydrogen nucleophiles from the tin mediated radical sequence. Therefore, our initial investigations targeted the alkylation of pronucleophiles with bis-ethanethiol adduct **11** utilizing Somei's conditions (Table 4).[34] We were extremely pleased to be able to isolate malonate adduct **24** in 82% yield after subjecting **11** to dimethylmalonate, Bu_3P (50 mol %), and acetonitrile at reflux (entry 1). Interestingly, we had not only formed the desired carbon−carbon bond through the displacement of the ethanethiol group but we had also replaced the TMS group with a hydrogen. Sufficiently intrigued by this result, we subjected other acidic hydrogen containing nucleophiles to the coupling conditions; ketoesters **17** and **18**, diethylacetamidomalonate **19**, diethylaminomalonate **20**, and glycine Schiff bases **21**[35] and **22**[36] gave **25**, **26**, **27**, **29**, **30**, and **31** respectively. On the other hand, acetamidoglycine **23** and cyclohexanone failed to provide adduct giving low to moderate yields of bis-thiol **32**.[37] This reaction is also amenable to thioether substitution as **15** gave coupled product **28** when it was exposed to the Bu_3P conditions and acetamidomalonate **19**.

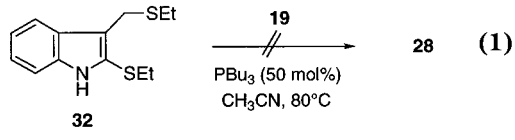
Table 5. Spiro Fused Thioimidates

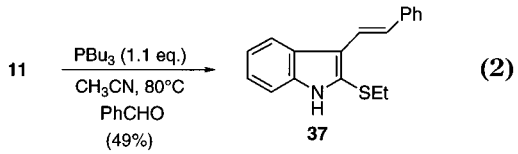


entry	R	**39**	yield (%)
1	Et	**a**	86[a]
2	Me	**b**	80[b]

[a] 5:1 mixture of diastereomers. [b] 2:1 mixture of diastereomers.

The TMS group appears to be critical for the success of the reaction. No coupling products were observed when bis-thiol adduct **32** lacking the TMS group was re-subjected to the alkylation conditions; this reaction resulted in the recovery of **32** (eq 1).





Our current mechanistic hypothesis, based on the proposal by Somei for the analogous gramine fragmentation reaction and taking into account the necessity of the TMS group, is illustrated in Scheme 2 for **11**.[34] We believe that ylide **34** is generated after formation of the phosphonium salt **33** and loss of TMS cation. Protonation of the ylide and deprotonation of the active hydrogen compound leads to **35**. Carbon−carbon bond formation occurs either via direct displacement of tributylphosphine or via an intermediate indolenine; both of these species act to regenerate Bu_3P and provide the observed products.

(28) It is not clear to us at the present time whether thiol addition to **4a** (R = thioether, R′ = TMS) is occurring heterolytically or homolytically. Both would lead to bis-thiol indoles.

(29) For examples of the deprotonation of thiomethylsilanes see: (a) Ager, D. J.; Cookson, R. C. *Tetrahedron Lett.* **1980**, *21*, 1677. (b) Ager, D. J. *Tetrahedron Lett.* **1980**, *21*, 4759.

(30) For a review on the reductive metalation of phenyl thioethers see: Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.

(31) For an example of the reductive metalation of thiomethylsilanes see: Corey, E. J.; Chen, Z. *Tetrahedron Lett.* **1994**, *35*, 8731.

(32) For an example of the fluoride-induced heterolytic fragmentation of benzylic TMS compounds to the corresponding anions see: Ricci, A.; Fiorenza, M.; Grifagni, M. A.; Bartolini, G. *Tetrahedron Lett.* **1982**, *23*, 5079.

(33) Poppelsdorf, F.; Holt, S. J. *J. Chem. Soc.* **1954**, 4094.

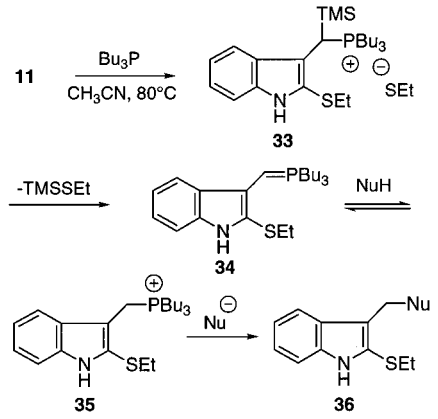
(34) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941.

(35) Stork, G.; Leong, A. Y. W.; Touzin, A. M. *J. Org. Chem.* **1976**, *41*, 3491.

(36) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

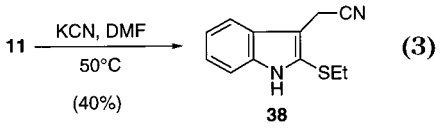
(37) We believe that bis-thioindole **32** comes from an irreversible coupling reaction between ethanethiol and phosphonium salt **35** (Scheme 2).

Scheme 2



Regardless of the sequence of events leading to its formation, we set out to prove the existence of phosphorus ylide **34**. The isolation of Wittig products from the reaction of **11** with an aldehyde would provide indirect evidence for the existence of **34**. Additionally, the success of this experiment would demonstrate the utility of **11** in carbon−carbon bond forming reactions with electrophiles. When bis-thioindole **11** was subjected to the alkylation conditions in the presence of benzaldehyde we were able to isolate styrene **37** in an unoptimized 49% yield (eq 2). Thus, it appears that ylides are important in the use of **11** as an alkylating agent.

Bis-thioindole **11** also acts as an alkylating agent in the absence of Bu_3P. Nitrile **38** was formed in 40% yield when **11** was subjected to KCN and DMF (eq 3).[38]



(3)

Having demonstrated the utility of the 3-ethylmethanethiol group in couplings with electrophiles, we targeted intramolecular Mannich-type (Pictet−Spengler) cyclizations of aminomalonate adduct **29**. Not only would these experiments demonstrate the utility of the 2-thiol group but if successful they would result in the formation of C-3 spiro compounds as are present in a number of bioactive indole natural products including, but not limited to, the spiroindolinone spirotryprostatin.[39,40] Exposure of **29** to 4 Å MS and propionaldehyde or acetaldehyde at room-temperature resulted in the formation of diastereomeric spirothioimidates **39** in high yields (Table 5). These conditions are milder than the "normal" Pictet−Spengler conditions to β-carbolines where elevated temperatures are generally required.[41]

Conclusion

To conclude, we have carried out the synthesis of a number of bis-thioindoles from arylisonitrile−alkyne free radical cascades. These sequences effectively demonstrate that free-radical cyclizations to indolenines can be coupled with indolenine trapping reactions. We have also shown that bis-thioindoles are synthetically useful in the synthesis of other, more functionalized, indoles. This has been demonstrated through their coupling reactions with active hydrogen compounds and through the formation of spiroindoles from intramolecular Mannich cyclizations. We are currently exploring the uses of these processes in the synthesis of highly substituted indole containing natural products.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra for **7c**−**e**, **8a**,**d**, **9d**, **10d**, **11**−**16**, **24**−**32**, **37**, **38**, and **39a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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