

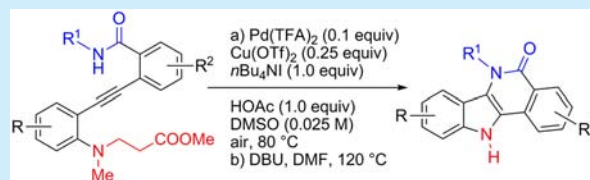
2-(Methoxycarbonyl)ethyl as a Removable N-Protecting Group: Synthesis of Indoloisoquinolinones by Pd(II)-Catalyzed Intramolecular Diamination of Alkynes

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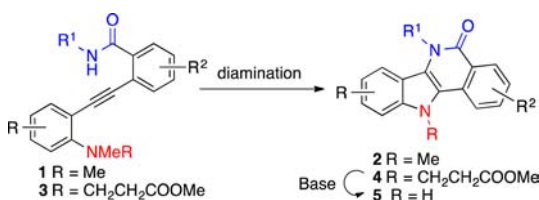
Supporting Information

ABSTRACT: Pd(II)-catalyzed double cyclization of 1,2-diarylethynes bearing an *N*-methyl-*N*-[2-(methoxycarbonyl)ethyl]amino and an aminocarbonyl group at the *ortho* positions of the two aromatic rings afforded the tetracyclic *N*-[2-(methoxycarbonyl)ethyl]indoloisoquinolinones in good to excellent yields. The *N*-[2-(methoxycarbonyl)ethyl] group is readily removed under basic conditions (DBU, DMF, 120 °C) to afford the corresponding tetracycles with a free indolyl nitrogen in excellent yields. The 2-(methoxycarbonyl)ethyl as a removable *N*-protecting group is illustrated in other Pd(II)- and Pd(0)-catalyzed and selenium-mediated transformations.



Palladium-catalyzed diamination¹ of alkenes has attracted much attention in recent years.² Interestingly, the corresponding diamination of alkynes has been far less studied.³ We recently reported that 2-(*N,N*-dimethylamino)-phenylethynyl benzamides **1** readily cyclized to tetracyclic indoloisoquinolinones **2**⁴ in the presence of Pd(OAc)₂ under aerobic conditions (Scheme 1).^{5,6} This domino diamination

Scheme 1. Pd-Catalyzed Diamination of Alkynes: Synthesis of Indoloisoquinolinones



process proceeded in a highly ordered fashion with excellent regio- and chemoselectivity. While the yields of this reaction are generally excellent with a wide range of substrates, the drawback of this process is that it inherently afforded *N*-methylated tetracycles. This is a severe limitation since most of indoles need the free *N*-H function to be biologically active.

From a synthetic perspective, removal of the *N*-methyl group from the indolyl nitrogen is a daunting problem that in fact is not an isolated issue. Indeed, easily available and functionalized anilines are attractive starting materials for the synthesis of many nitrogen heterocycles such as indoles and quinolinones via either formation of a C–C or a C–N bond. Many transformations require an appropriate *N*-protecting group leading to *N*-substituted heterocycles, and the nature of the *N*-substituent is often crucial to the success of the reaction. While electron-withdrawing *N*-acyl, *N*-carbamoyl, or *N*-sulfonyl protecting

groups are frequently introduced to the cyclization precursors, the *N*-alkyl group is sometimes mandatory to ensure the occurrence of the desired transformation.^{7–11}

In light of the recurrence of an *N*-alkyl substituent in heterocycle synthesis, the difficulties associated with its removal, and the importance of *N*-H function for the bioactivity of heterocycles, the development of an easily removable *N*-alkyl group is of high importance. This *N*-alkyl group should be easily introduced to the starting materials, compatible with the desired transformations but readily removed after cyclization. We report herein that the simple *N*-[2-(methoxycarbonyl)ethyl] group satisfied these criteria. Pd(II)-catalyzed double cyclization of *N*-methyl-*N*-[2-(methoxycarbonyl)ethyl]alkynylanilines (**3**) under aerobic conditions provided *N*-[2'-(methoxycarbonyl)ethyl]-substituted tetracycles **4** via formation of two C–N bonds. Subsequent removal of the *N*-[2-(methoxycarbonyl)ethyl] group under basic conditions provided **5** with a free indolyl nitrogen in good to excellent overall yields (Scheme 1).

In our initial studies aimed at synthesizing indolyl nitrogen-unprotected tetracycles **5**, compounds **6a–f** with different *N*-substituents were prepared (Figure 1). An attempt to cyclize anilines **6a** (*R*¹ = *R*² = H), **6b** (*R*¹ = Me, *R*² = H), **6c** (*R*¹ = Me, *R*² = Ph), and anilide **6d** (*R*¹ = Ac, *R*² = H) was not successful. The

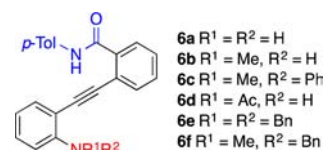
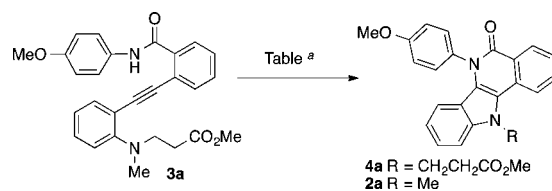


Figure 1. Initial screening of substrates.

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Table 1. Optimization of the Reaction Conditions for the Oxidative Diamination of 3a



entry	Pd	additive (equiv)	temp (°C)	time (h)	conv (%)	4a/2a
1 ^b	Pd(OAc) ₂		80	13	25	1/1
2 ^b	Pd(OAc) ₂		50	13	50	1/12.5
3	Pd(OAc) ₂		80	13	100	1/12.5
4	Pd(TFA) ₂		50	17	70	6/1
5	Pd(TFA) ₂		80	17	85	10/1
6	Pd(TFA) ₂	TsOH (0.10)	50,	21	77 (60) ^c	>30/1
7	Pd(TFA) ₂	1,10-Phen (0.1)	80	14	38	1.5/1
8 ^d	Pd(TFA) ₂	Cu(OTf) ₂ (0.2)	50	26	53	17/1
9	Pd(TFA) ₂	Cu(OTf) ₂ (0.25)	80	14	100 (71) ^c	>30/1

^aReaction conditions: 3a (0.05 mmol), Pd catalyst (0.1 equiv), HOAc (1.0 equiv), *n*-Bu₄Ni (1.0 equiv), and additive in DMSO (2.0 mL), air atmosphere. ^b2.0 equiv of HOAc was used. ^cYield of 4a. ^d4.0 equiv of HOAc was used.

N,N-dibenzyl derivative **6e** (R¹ = R² = Bn) did cyclize under our standard conditions [Pd(OAc)₂ (0.05 equiv), *n*-Bu₄Ni (0.1 equiv), HOAc (2.0 equiv), air (1 atm), DMSO (0.025 M), 80 °C], but the yield of the tetracycle was too low to be synthetically significant. On the other hand, aniline **6f** (R¹ = Me, R² = Bn) underwent the double cyclization to provide the *N*-methylated tetracycle indicating that in situ *N*-debenzylation was faster than the *N*-demethylation under these oxidative conditions.

It is clear from the aforementioned experimental results that the substrate for the double cyclization needed to be *N,N*-dialkylated. We have previously demonstrated that the domino diamination process was initiated by nucleophilic addition of aniline nitrogen to the Pd(II)-coordinated triple bond;¹² this elementary step might be facilitated by the *N,N*-dialkyl group for the following reasons: (a) the two alkyl groups rendered the nitrogen more nucleophilic by inductive effect, and (b) the bulky *N,N*-dialkyl group together with the *o*-alkynyl group could push the amino group out of the plane of the aromatic ring for steric reasons. Consequently, this deconjugation would lead to the increased nucleophilicity of nitrogen. Therefore, in order to extend the methodology to the synthesis of indolo[3,2-*c*]isoquinolinones having a free indole NH group, we needed to use a substrate with an *N*-methyl-*N*-alkylamino group in which the *N*-methyl group would be removed under the diamination conditions while the *N*-alkyl group, stable under the reaction conditions, would be readily deprotected afterward. To reach this goal, we turned our attention to *N*-methyl-*N*-[2-(methoxycarbonyl)ethyl]-*o*-alkynylanilines **3**. To the best of our knowledge, the CH₂CH₂COOMe group has not been proposed as an *N*-protecting group for indoles.¹³

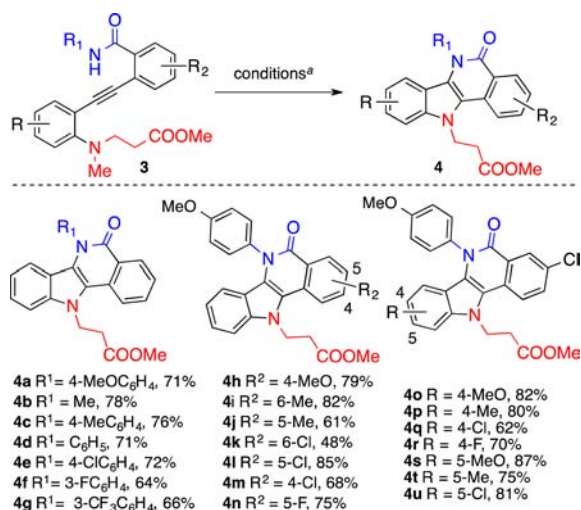
We began our studies using compound **3a** as a test substrate. As it is often associated with transition metal-catalyzed processes; the slight change of the substrate structure entails a complete reoptimization of the reaction conditions. Therefore, the reaction parameters were optimized by systematically varying the palladium sources, the oxidants, the additives, the solvents, and the temperature. The results are summarized in Table 1. Applying the previously optimized conditions [Pd(OAc)₂ (0.05 equiv), *n*-Bu₄Ni (0.1 equiv), HOAc (2.0 equiv), air (1 atm), DMSO (0.025 M), 80 °C]^{5,14,15} to **3a** afforded a low yield of

two products **4a** and **2a** resulting from the *N*-demethylation and *N*-de(2-methoxycarbonyl)ethylation, respectively, in a 1/1 ratio (entry 1, Table 1). Because of the weak acidity of the acetic acid in DMSO (pK_a = 12.3),¹⁶ we assumed that base (AcO⁻)-promoted β-elimination of the *N*-[2-(methoxycarbonyl)ethyl] group is at least partly responsible for the formation of **2a**. Therefore, we continued condition screening using Pd(TFA)₂ as a catalyst, reasoning that trifluoroacetate is a much weaker base relative to acetate (pK_a of TFA in DMSO = 3.45).¹⁶ Gratefully, the reaction produced **4a** as a major product using Pd(TFA)₂ as the Pd(II) source under otherwise identical conditions (entries 4 and 5), although the conversion was slightly lower (entries 5 vs 3). Adding TsOH (0.1 equiv) to the reaction mixture further improved the selectivity in favor of the desired product **4a** (entry 6), while addition of 1,10-phenanthroline reduced both the reaction rate and the selectivity (entry 7). Finally, addition of a catalytic amount of Cu(OTf)₂ (0.25 equiv) is highly beneficial to the reaction. Overall, the optimum conditions consisted of performing the intramolecular diamination of **3a** in DMSO (*c* 0.025 M) at 80 °C in the presence of Pd(TFA)₂ (0.1 equiv), Cu(OTf)₂ (0.25 equiv), HOAc (1.0 equiv), and *n*-Bu₄Ni (1.0 equiv). Under these conditions, double cyclization of **3a** took place smoothly to afford the desired product **4a** in 71% isolated yield with almost complete chemoselectivity.

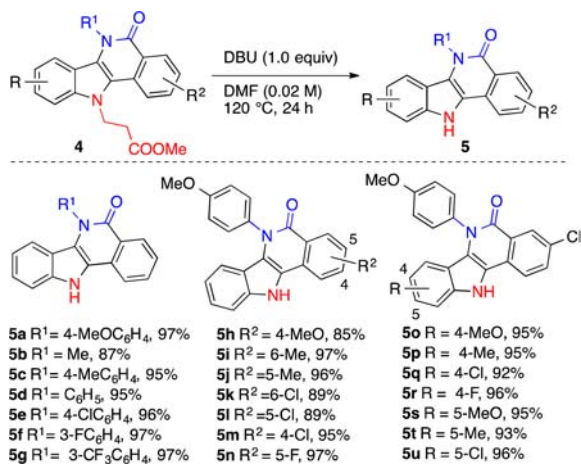
With the optimum conditions in hand, the substrate scope was examined next. Various substituted 2-[(2-aminophenylethynyl)-benzamidines **3** were prepared by a Sonogashira coupling reaction [Pd(PPh₃)₂Cl₂ (3 mol %), CuI (4 mol %), Et₃N (4.0 equiv) in DMF at 80 °C, 2–3 h].¹⁷ The results on the Pd-catalyzed oxidative diamination of these substrates are summarized in Scheme 2. As is seen, no significant electronic effect was observed and a range of substituents at different positions of the aromatic rings were tolerated including the chlorine atom, which provides a handle for further functionalization.

The removal of the *N*-[2-(methoxycarbonyl)ethyl] group by way of the retro-Michael reaction was next investigated. Gratefully, simply heating a DMF solution of **4a** in the presence of DBU (1.0 equiv) at 120 °C afforded the desired *N*-deprotection product **5a** in 97% yield. These conditions were found to be generally applicable to a wide range of substrates as summarized in Scheme 3.

Scheme 2. Synthesis of Tetracycles 4 by Pd-Catalyzed Oxidative Diamination of Alkynes

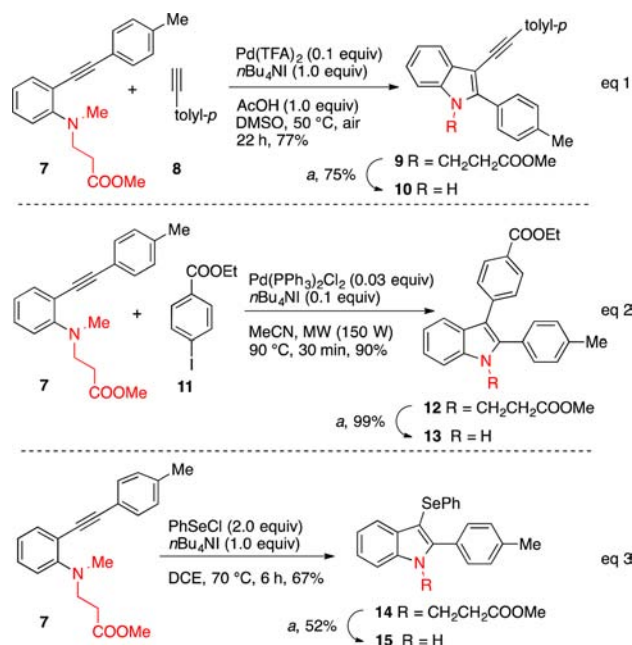


^aConditions: Pd(TFA)₂ (0.1 equiv), Cu(OTf)₂ (0.25 equiv), *n*Bu₄NI (1.0 equiv), HOAc (1.0 equiv), DMSO (0.025 M), air, 80 °C, 14 h.

Scheme 3. *N*-Deprotection of Tetracycles 4 by the Retro-Aza-Michael Addition

To demonstrate the utility of this *N*-protecting group in heterocycle syntheses, other cyclizations reported in the literature were examined. Reaction of 7 with terminal alkyne 8 under optimized conditions afforded indole 9 in 77% isolated yield.^{8a} Heating a DMF solution of 9 in the presence of DBU provided the 2,3-disubstituted indole 10 in 75% yield (eq 1, Scheme 4). Reaction of 7 with methyl 4-iodobenzoate 11 under slightly modified Larock's conditions^{7d} afforded indole 12 resulting from the chemoselective removal of the *N*-Me group. DBU-mediated *N*-deprotection furnished the indole 13 in almost quantitative yield. Finally, 2-phenylselenenyl-substituted indole 14, prepared from 7 following Larock's standard procedure,^{11d} was converted to NH-indole 15 in 52% yield, together with its deselenylated product (20%).

Many aniline-based syntheses of heterocycles require the use of *N,N*-dialkylated derivatives for effective cyclization, leading therefore inevitably to *N*-alkylated products.⁷⁻¹¹ Removal of the *N*-alkyl group, particularly the *N*-methyl group, is a daunting task making access to free NH heterocycles difficult. Finding a suitable *N*-alkyl group that is easily introduced to starting

Scheme 4. *N*-(2-Methoxycarbonyl)ethyl as a Removable Protecting Group in Other Transformations

^aDBU (1.0 equiv), DMF (0.02 M), 120 °C.

materials, compatible with the desired transformations but readily removed after cyclization, is therefore of great importance. We found that the very simple *N*-[2-(methoxycarbonyl)ethyl] group satisfied these criteria. Indeed, 1,2-diarylethyne bearing an *N*-methyl-*N*-[2-(methoxycarbonyl)ethyl]amino and a carboxamide group at the *ortho* positions of the two aromatic rings underwent Pd(II)-catalyzed double cyclization to afford the tetracycles in good to excellent yields. The 2-(methoxycarbonyl)ethyl group attached to the indolyl nitrogen is readily removed under basic conditions (DBU, DMF, 120 °C) to afford the corresponding tetracycles with a free indolyl nitrogen in excellent yields. The two-step sequence has been successfully applied to Larock's indole synthesis demonstrating therefore the generality of this approach.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization data, ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (c) Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *11*, 1147. (d) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365. (e) Iglesias, A.; Pérez, E. G.; Muñiz, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8109. Conjugated dienes: (f) Bar, G. L.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308. (g) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (h) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 3523.
- (2) Reviews on Pd-catalyzed difunctionalization of alkenes: (a) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (b) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (c) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (d) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351. (e) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736. (f) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. *Acc. Chem. Res.* **2014**, *47*, 3665. (g) Kocovsky, P.; Bäckvall, J.-E. *Chem.—Eur. J.* **2015**, *21*, 36.
- (3) In their seminal paper, Muñiz included one example of the diamination of an internal alkyne under their Pd(II)/Pd(IV) catalytic cycle, see ref 1b.
- (4) (a) Jagtap, P. G.; Baloglu, E.; Southan, G.; Williams, W.; Roy, A.; Nivorozhkin, A.; Landrau, N.; Desisto, K.; Salzman, A. L.; Szabó, C. *Org. Lett.* **2005**, *7*, 1753. (b) Li, L.; Chua, W. K. S. *Tetrahedron Lett.* **2011**, *52*, 1574.
- (5) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5170.
- (6) See also: (a) Zheng, J.; Tan, Y. J.; Leow, M. L.; Liu, X.-W. *Org. Lett.* **2012**, *14*, 4386. For Cu-catalyzed oxidative diamination of terminal alkynes, see: (b) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820. (c) Wang, W.; Shen, Y.; Meng, X.; Zhao, M.; Chen, Y.; Chen, B. *Org. Lett.* **2011**, *13*, 4514. (d) Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752.
- (7) Pd(0)-catalyzed: (a) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardiá, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587. (b) Solé, D.; Serrano, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 7270. (c) Solé, D.; Serrano, O. *J. Org. Chem.* **2008**, *73*, 2476. (d) Chen, Y.; Markina, N. A.; Larock, R. C. *Tetrahedron* **2009**, *65*, 8908. (e) Geng, W.; Zhang, W.-X.; Hao, W.; Xi, Z. *J. Am. Chem. Soc.* **2012**, *134*, 20230. (f) Pan, X.; Luo, Y.; Kuang, Y.; Li, G. *Org. Biomol. Chem.* **2014**, *12*, 5861. (g) Hao, W.; Geng, W.; Zhang, W.-X.; Xi, Z. *Chem.—Eur. J.* **2014**, *20*, 2605. (h) Hao, W.; Wei, J.; Geng, W.; Zhang, W.-X.; Xi, Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 14533.
- (8) Pd(II)-catalyzed: (a) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 12311. (b) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12992. (c) Han, X.; Lu, X. *Org. Lett.* **2010**, *12*, 3336. (d) Chin, C. C.; Chin, L.-Y.; Yang, S.-C.; Wu, M.-J. *Org. Lett.* **2010**, *12*, 5652. (e) Álvarez, R.; Martínez, C.; Madich, Y.; Denis, J. G.; Aurrecoechea, J. M.; De Lera, Á. R. *Chem.—Eur. J.* **2010**, *16*, 12746. (f) Xia, X.-F.; Wang, N.; Zhang, L.-L.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2012**, *77*, 9163. (g) Hu, Z.; Liang, D.; Zhao, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 7371. (h) Qiu, G.; Chen, C.; Yao, L.; Wu, J. *Adv. Synth. Catal.* **2013**, *355*, 1579. (i) Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4818. (j) Sheng, J.; Li, S.; Wu, J. *Chem. Commun.* **2014**, *50*, 578.
- (9) Rh(I)-catalyzed: (a) Saito, A.; Kanno, A.; Hanzawa, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3931. (b) Saito, A.; Oda, S.; Fukuya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 1517.
- (10) Pt-catalyzed: Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881.
- (11) Halonium-catalyzed: (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62. (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243. (d) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173. (e) Du, H.-A.; Tang, R.-Y.; Deng, C.-L.; Liu, Y.; Li, J.-H.; Zhang, X.-G. *Adv. Synth. Catal.* **2011**, *353*, 2739. (f) Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 3274. Friedel–Crafts-type cyclization: (g) Moody, C. J.; Swann, E. *Synlett* **1998**, 135.
- (12) Yao, B.; Wang, Q.; Zhu, J. *Chem.—Eur. J.* **2014**, *20*, 12255.
- (13) The 2-(phenylsulfonyl)ethyl group has been used as an indole nitrogen protecting group and can be removed under basic conditions via retro-Michael reaction; see: (a) Gonzalez, C.; Greenhouse, R.; Tallabs, R. *Can. J. Chem.* **1983**, *61*, 1697. (b) Vedejs, E.; Piotrowski, D. W.; Tucci, F. C. *J. Org. Chem.* **2000**, *65*, 5498. (c) Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J. *Tetrahedron Lett.* **2002**, *43*, 135. (d) Dastrup, D. M.; Yap, A. H.; Weinreb, S. M.; Henry, J. R.; Lechleiter, A. J. *Tetrahedron* **2004**, *60*, 901.
- (14) For seminal work on the difunctionalization of alkenes using the Pd(OAc)₂/DMSO/O₂ system, see: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (b) Van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *Chem. Commun.* **1994**, 357.
- (15) For seminal work on the difunctionalization of alkenes using the Pd(OAc)₂/sulfoxide/quinone system, see: Bäckvall, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4959.
- (16) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
- (17) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1999.