Indole Synthesis

DOI: 10.1002/ange.201204633

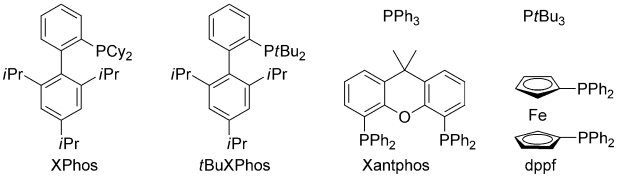
Multicomponent Assembly of Highly Substituted Indoles by Dual Palladium-Catalyzed Coupling Reactions**

*John M. Knapp, Jie S. Zhu, Dean J. Tantillo, and Mark J. Kurth**

The development of new methods for the synthesis of heterocycles[1] continues to be an important area of chemical research, and new organometallic catalytic methods[2] are providing synthetic routes to important targets previously unavailable to the synthetic chemist. As indoles are ubiquitous in pharmaceuticals and in natural products,[3]dozens of methods for their construction have been developed.[4] The search for straightforward, diversity-oriented routes to indoles is of importance to both synthetic and biological researchers.[5] Some of these synthetic strategies have involved the use of palladium catalysis and there are reports of indole syntheses using Heck and Buchwald–Hartwig assemblies.[6] There are also reports of multicomponent reactions to form indoles.[7] We report herein a general palladium-catalyzed multicomponent assemblies for indole synthesis that incorporates both a Buchwald–Hartwig[8] reaction and an arene–alkene coupling[9] reaction and requires a single catalyst/ligand system. This method involves three components and allows for easy diversification from readily available starting materials. Multicomponent reactions are advantageous in that they provide expedient methods for the construction of complex structures, minimize synthetic steps, and use relatively simple starting materials.[10] The overall one-pot three-step multicomponent assembly reported herein is illustrated in Scheme 1.

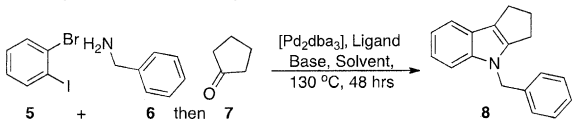
Reaction optimization established that the use of the dppf ligand (1,1′-bis(diphenylphosphanyl)ferrocene; Scheme 2) and Cs_2CO_3 as base (Table 1, entry 4) gave the best yields. When Xphos, *t*BuXphos, and Xantphos (entries 1, 2, and 3, respectively) were used the product was obtained, albeit in lower yields, whereas PPh_3 (entry 5) and P*t*Bu$_3$ (entry 6) did not promote the reaction. When KO*t*Bu was used the yields were lower (entry 7), possibly because of enolate formation from the ketone or aldehyde, thus reducing the likelihood of an amine–carbonyl condensation. No product was obtained when K_3PO_4 was used (entry 8). The addition of $MgSO_4$ favors enamine formation by effectively excluding water from the carbonyl + amine ⇄ enamine + H_2O equilibrium. Attempts at using a palladium(II) catalyst as a source of palladium(0) resulted in no product (entry 11); this result may indicate that reduction of Pd^{II} to Pd^0 is too slow for the Pd^{II} species to be an effective precatalyst for this process.

Our optimized reaction conditions work effectively with an array of substrates (Scheme 3) and proceed with a catalyst loading of 2 mol% of [$Pd_2(dba)_3$] (4% Pd).[11] A wide range of carbonyl compounds are suitable as substrates for this process. Cyclic and acyclic ketones were used and both gave the indole products (cyclic: **8**, **14**, **17**, **18**, **21**; acyclic: **15**, **20, 22**)



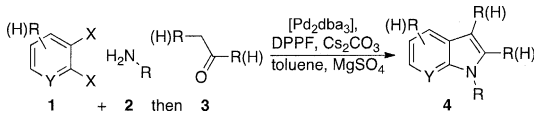
Scheme 2. Ligands.

Table 1: Optimization of one-pot reaction conditions.



Entry	Ligand	Base	Solvent	Yield [%]
1	Xphos	Cs_2CO_3	toluene	55
2	*t*BuXphos	Cs_2CO_3	toluene	49
3	Xantphos	Cs_2CO_3	toluene	61
4	dppf	Cs_2CO_3	toluene	68
5	PPh_3	Cs_2CO_3	toluene	0
6	P*t*Bu$_3$	Cs_2CO_3	toluene	0
7	dppf	KO*t*Bu	toluene	51
8	dppf	K_3PO_4	toluene	0
9	dppf	Cs_2CO_3	dioxane	trace
10	dppf	Cs_2CO_3	DMF	14
11[a]	dppf	Cs_2CO_3	toluene	0

[a] $Pd(OAc)_2$ was used in place of [Pd_2dba_3]. DMF = *N*,*N*-dimethylformamide.

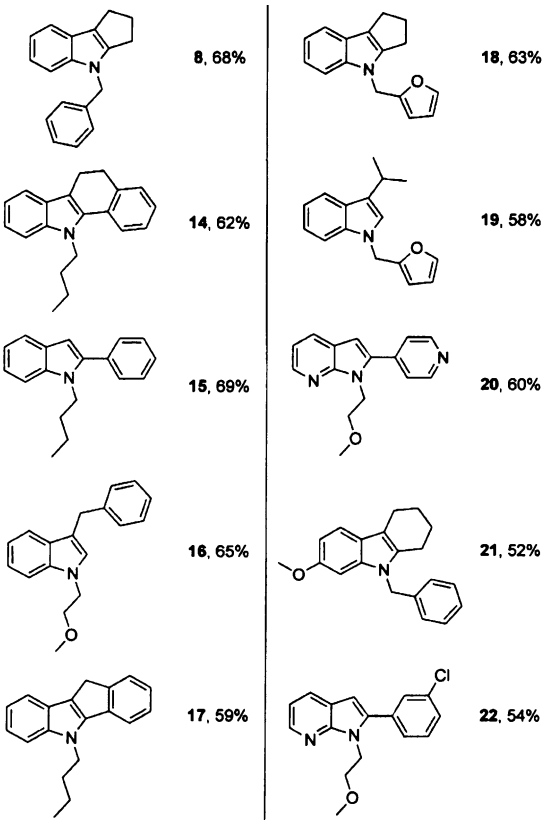


Scheme 1. A one-pot, three-reactant palladium-catalyzed indole synthesis. dba = dibenzylideneacetone.

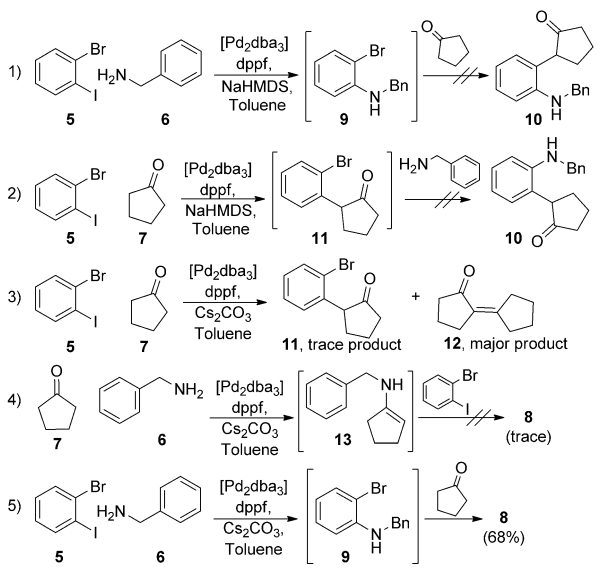
[*] J. M. Knapp, J. S. Zhu, Prof. D. J. Tantillo, Prof. M. J. Kurth
Department of Chemistry, University of California Davis
1 Shields Ave., Davis, CA 95616 (USA)
E-mail: mjkurth@ucdavis.edu

[**] We thank the National Institute of Health (GM089153), the National Science Foundation (CHE-0910870 and CHE-030089 with the Pittsburgh Supercomputer Center) for their generous financial support. We also thank Prof. Annaliese Franz (UC Davis) and Prof. Tomislav Rovis (Colorado State) for helpful discussions.

Supporting information (including experimental, spectral and computational data) for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204633.



Scheme 3. Three-component indole products and yields. Reaction conditions: *o*-bromoiodoarene (1 mmol), primary amine (1 mmol), ketone/aldehyde (3 mmol), [Pd_2dba_3] (2 mol%), dppf (5 mol%), Cs_2CO_3 (2.2 mmol), $MgSO_4$ (10 mmol), toluene (0.5 M), 130°C. Yields are of the isolated product after purification by column chromatography.

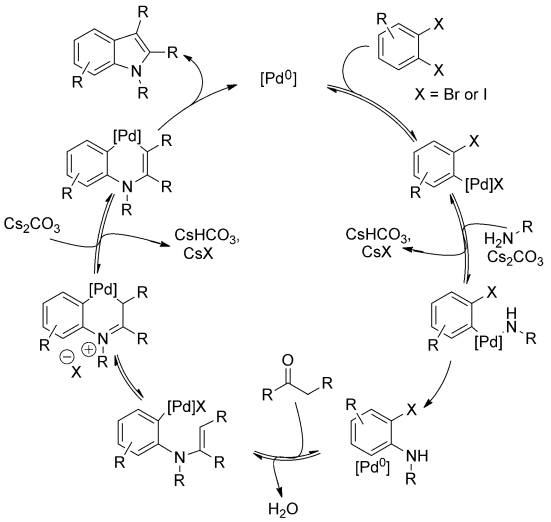


Scheme 4. Examination of the order of events for the reported indole synthesis. NaHMDS = sodium hexamethyldisilazide.

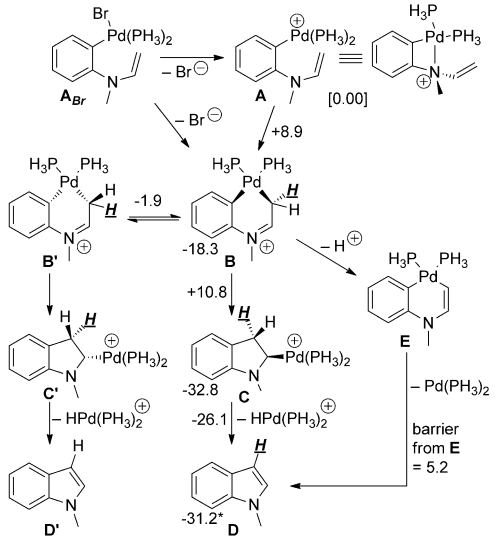
in similar yields. Aldehydes also successfully form indoles (**16** and **19**) under our optimized reaction conditions. A variety of primary amines can be used and the aryl component can be a carbocycle, an anisole, or a pyridine. For all of the indoles prepared, the appropriate *o*-bromoiodo arene was used. A larger scale reaction (5 mmol rather than the typical 1 mmol) was also conducted for the synthesis of **14**. A substantial change in yield was not observed for this larger scale reaction (that is, the yield for the 5 mmol reaction was only a 2% more than that of the 1 mmol reaction). The optimized yield for the synthesis of **8** is 68%, which equates to each of the three steps in our one-pot reaction sequence (Buchwald–Hartwig coupling, condensation, and arene–alkene coupling) proceeding in 88% average yield. Indeed, the yield of our one-pot transformation is comparable to the overall yield recently reported by Urabe and co-workers for their three-step three-pot indole synthesis.[12]

Three bonds are formed in this transformation: an N–aryl bond by a Buchwald-Hartwig coupling, an N–vinyl bond by condensation of a nitrogen nucleophile onto an aldehyde or ketone giving an enamine, and a C–C bond by an arene–alkene coupling. We envisioned that several possible reaction sequences could be used to construct the indole core from these three transformations. As shown in Scheme 4, several experiments were carried out to probe the order of events in our reaction. Experiments 1–3 involve the intermediacy of enolates.[13] In experiment 1, the use of a strong base (NaHMDS) favors enolate formation; although Buchwald–Hartwig coupling occurred (to form **9**), subsequent enolate coupling (to form **10**) failed. In experiment 2, initial enolate generation and coupling occurred but subsequent amine addition did not give the Buchwald–Hartwig product (**10**). For experiment 3 the attempted enolate coupling using optimized reaction conditions (that is, with a weaker base) gave only a trace amount of desired product; the major product (**12**) formed arose from dimerization of cyclopentanone. On the basis of these results, we conclude that enolates do not play a significant role in the transformation described herein. Preformation of the enamine (**13**) yielded only small amounts of product using the optimized conditions, thus indicating that such a process likely does not initiate the catalytic cycle (Scheme 4, experiment 4). Initial Buchwald–Hartwig coupling, followed by addition of the ketone, did produce the indole product in 68% yield (Scheme 4, experiment 5). In light of the results of experiments 1–5, we propose the catalytic cycle shown in Scheme 5.

Several mechanisms for indole ring formation from an *N*-arylenamine were examined using density functional theory calculations (at the B3LYP/6-31G(d)[C,H,N],LANL2DZ [Pd] levels with the simplified model system shown in Scheme 6).[14] No transition-state structures corresponding to the alkene insertion step of a traditional Heck reaction were found. Instead, a two-step alkene insertion process via an intermediate metallacycle (**A**→**B**→**C**) was located. Simple insertion (that is, **A**→**C**, as in the Heck reaction) is likely disfavored owing to the strain associated with *endo* cyclization and the fact that intermediate cation **B** is stabilized by imine resonance. Formation of **B** can be formulated as the attack of an enamine on an electrophilic metal center (with or without prior Br^- loss). Intermediate **C**, which displays a significant agostic interaction (Pd—H distance of 2.0 Å



Scheme 5. Proposed catalytic multicomponent-assembly mechanism. The dppf ligand is omitted for clarity.



Scheme 6. Computed mechanisms for arene–alkene coupling. Computed relative free energies (B3LYP/6-31G(d)[C,H,N], LANL2DZ[Pd], all relative to the energy of **A**, except for the **E**→**D** barrier) for structures involved in indole ring formation. Energies of minima are shown next to each structure; energies of transition-state structures are shown over arrows.[14] *Energy for $[HPd(PH_3)_2$-*N*-methylindole$]^+$ complex.

and elongated C–H distance of 1.15 Å), can readily undergo β-hydride elimination to form indole **D**. Although this elimination requires a *cis* Pd and H relationship, either methylene hydrogen can be removed, as **B** can undergo a conformational change (from one half-chair to another) with a low barrier (**B**→**B′**, Scheme 6); note that this would, in principle, allow β-hydride elimination to occur for any substrate with at least one hydrogen at the nucleophilic enamine carbon, regardless of alkene configuration.

An alternative to this "interrupted Heck" reaction was also examined. Deprotonation of one of the acidic methylene protons of **B** would lead to **E**, which can undergo reductive elimination to form indole **D** with a low predicted barrier ($\approx$5 kcal mol^{-1}). Although both mechanisms (**A**→**B**/**B′**→**C**/**C′**→**D**/**D′** and **A**→**B**→**E**→**D**) are consistent with our experimental results, we favor the latter on energetic grounds, assuming the reaction conditions allow for rapid deprotonation of **B**.[14] This mechanistic proposal differs from the traditional Heck mechanism proposed (or implied) in previous studies on *N*-arylenamine cyclizations of this type.[6c,d,15]

In conclusion, we have developed a versatile one-pot three-step multicomponent assembly route to highly substituted indoles using a palladium-catalyzed reaction involving three independent components. Indole formation can be accomplished using suitable reaction conditions that favor in situ generation of an aniline, condensation to an arylenamine, and a subsequent arene–alkene coupling reaction to close the ring. A single palladium catalyst/ligand system mediates both coupling reactions. We have also presented a detailed mechanism for the palladium-catalyzed ring-closing step. The mechanism described herein is supported by quantum chemical calculations and offers an alternative to direct Heck coupling as previously suggested. This work significantly extends indole construction and diversification strategies.

Received: August 21, 2012
Published online: September 24, 2012

Keywords: homogeneous catalysis · nitrogen heterocycles · multicomponent reactions · palladium · synthetic methods

[1] For recent examples, see: a) S. Kramer, T. Skrydstrup, *Angew. Chem.* **2012**, *124*, 4759–4762; *Angew. Chem. Int. Ed.* **2012**, *51*, 4681–4684; b) B. Yao, Q. Wang, J. Zhu, *Angew. Chem.* **2012**, *124*, 5260–5264; *Angew. Chem. Int. Ed.* **2012**, *51*, 5170–5174; c) C. J. Ball, J. Gilmore, M. C. Willis, *Angew. Chem.* **2012**, *124*, 5816–5820; *Angew. Chem. Int. Ed.* **2012**, *51*, 5718–5722; d) W. Gati, M. M. Rammah, M. B. Rammah, F. Couty, G. Evano, *J. Am. Chem. Soc.* **2012**, *134*, 9078–9081.

[2] For recent examples, see: a) C. Huang, A. G. Doyle, *J. Am. Chem. Soc.* **2012**, *134*, 9541–9544; b) J. F. Brazeau, S. Zhang, I. Colomer, B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 2742–2749; c) B. Li, H. Wang, Q. Zhu, Z. Shi, *Angew. Chem.* **2012**, *124*, 4014–4018; *Angew. Chem. Int. Ed.* **2012**, *51*, 3948–3952; d) Y. Chen, M. Chen, Y. Liu, *Angew. Chem.* **2012**, *124*, 6599–6603; *Angew. Chem. Int. Ed.* **2012**, *51*, 6493–6497.

[3] a) J. S. Mason, I. Morize, P. R. Menard, D. L. Cheney, C. Hulme, R. F. Labaudiniere, *J. Med. Chem.* **1999**, *42*, 3251–3264; b) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953; c) U. Pindur, T. Lemster, *Curr. Med. Chem.* **2001**, *8*, 1681–1698; d) H. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303–4427; e) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; f) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195–7210.

[4] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–2245; b) E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559–568; c) G. Bartoli, R. Leardini, A. Medici, G. Rosini, *J. Chem. Soc.* **1978**, 692–696; d) G. Bartoli, F. Palmieri, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.* **1989**, *30*, 2129–2132; e) G.

Bartoli, M. Bosco, R. Dalpozzo, *J. Chem. Soc.* **1991**, 2757 – 2761; f) W. Madelung, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 1128 – 1134; g) C. D. Nenitzescu, *Bull. Soc. Chim. Romania* **1929**, *11*, 37 – 43; h) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689 – 6690.

[5] M. Shiri, *Chem. Rev.* **2012**, *112*, 3508 – 3549.

[6] a) M. C. Willis, G. N. Brace, I. P. Holmes, *Angew. Chem.* **2005**, *117*, 407 – 410; *Angew. Chem. Int. Ed.* **2005**, *44*, 403 – 406; b) T. Jensen, H. Pedersen, B. Bang-Andersen, R. Madsen, M. Jørgensen, *Angew. Chem.* **2008**, *120*, 902 – 904; *Angew. Chem. Int. Ed.* **2008**, *47*, 888 – 890; c) M. Nazaré, C. Schneider, A. Lindenschmidt, D. W. Will, *Angew. Chem.* **2004**, *116*, 4626 – 4629; *Angew. Chem. Int. Ed.* **2004**, *43*, 4526 – 4528; d) C. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, *62*, 2676 – 2677; e) S. G. Newman, M. Lautens, *J. Am. Chem. Soc.* **2010**, *132*, 11416 – 11417; f) Y. Jia, J. Zhu, *J. Org. Chem.* **2006**, *71*, 7826 – 7834; g) Y. Fang, M. Lautens, *Org. Lett.* **2005**, *7*, 3549 – 3552; h) A. Fayol, Y. Fang, M. Lautens, *Org. Lett.* **2006**, *8*, 4203 – 4206; i) S. D. Edmondson, A. Mastracchio, E. M. Parmee, *Org. Lett.* **2000**, *2*, 1109 – 1112; j) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 10251 – 10263; k) Z. Shi, F. Glorius, *Angew. Chem.* **2012**, *124*, 9354 – 9356; *Angew. Chem.* Int. Ed. **2012**, *51*, 9220 – 9222; l) Y. Wei, I. Deb, W. Yoshikai, *J. Am. Chem. Soc.* **2012**, *134*, 9098 – 9101.

[7] a) B. Z. Lu, W. Zhao, H. Wei, M. Dufour, V. Farina, C. H. Senanayake, *Org. Lett.* **2006**, *8*, 3271 – 3274; b) Y. Ohta, H. Chiba, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2009**, *74*, 7052 – 7058; c) L. T. Kaspar, L. Ackermann, *Tetrahedron* **2005**, *61*, 11311 – 11316; d) O. Leogane, H. Lebel, *Angew. Chem.* **2008**, *120*, 356 – 358; *Angew. Chem. Int. Ed.* **2008**, *47*, 350 – 352; e) J. Barluenga, A. Jimenez-Aquino, C. Valdes, F. Aznar, *Angew. Chem.* **2007**, *119*, 1551 – 1554; *Angew. Chem. Int. Ed.* **2007**, *46*, 1529 – 1532; f) J. Barluenga, A. Jimenez-Aquino, F. Aznar, C. Valdes, *J. Am. Chem. Soc.* **2009**, *131*, 4031 – 4041; g) D. Bouyssi, N. Monteiro, G. Balme, *Beilstein J. Org. Chem.* **2011**, *7*, 1387 – 1406.

[8] a) M. Kosugi, M. Kameyama, T. Migita, *Chem. Lett.* **1983**, 927 – 928; b) A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901 – 7902; c) F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969 – 5970; d) J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215 – 7216.

[9] a) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518 – 5526; b) T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; c) R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320 – 2322; d) H. A. Dieck, R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 1133 – 1136.

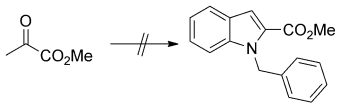
[10] a) D. L. Boger, J. Desharnais, K. Capps, *Angew. Chem.* **2003**, *115*, 4270 – 4309; *Angew. Chem. Int. Ed.* **2003**, *42*, 4138 – 4176; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285 – 307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259 – 281; c) R. Noyori, *Nat. Chem.* **2009**, *1*, 5 – 6; d) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321 – 3329; e) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831 – 844; f) J. E. Biggs-Houck, A. Younai, J. T. Shaw, *Curr. Opin. Chem. Biol.* **2010**, *14*, 371 – 382; g) S. Hardy, S. F. Martin, *Org. Lett.* **2011**, *13*, 3102 – 3105; h) D. M. D'Souza, T. J. J. Mueller, *Chem. Soc. Rev.* **2007**, *36*, 1095 – 1108.

[11] For recent reviews on palladium catalysis in indole synthesis, see: a) S. Patil, J. K. Buolamwini, *Curr. Org. Synth.* **2006**, *3*, 477 – 498; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873 – 2930; c) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873 – 2920.

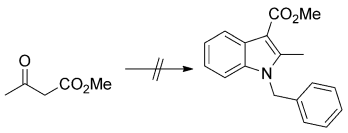
[12] M. Yamagishi, K. Nishigai, A. Ishii, T. Hata, H. Urabe, *Angew. Chem.* **2012**, *124*, 6577 – 6580; *Angew. Chem. Int. Ed.* **2012**, *51*, 6471 – 6474.

[13] For a recent review of enolate coupling, see: D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234 – 245.

[14] a) **A**, the **A**→**B** transition-state structure, **B**, and the **B**→**C** transition-state structure were recomputed for complexes having $P(CH_3)_3$ ligands instead of PH_3 ligands, but no significant mechanistic differences were observed. Energies (kcal mol^{-1}) relative to that of **A**: +5.6 (**A**→**B**), −17.2 (**B**), +14.7 (**B**→**C**). The predicted **E**→**D** barrier for complexes having $P(CH_3)_3$ ligands is 6.0 kcal mol^{-1}. b) **A**, the **A**→**B** transition-state structure, and **B** were recomputed for a reactant with a carbomethoxy group on the internal alkene carbon of the enamine; this is a model of a system that did not work experimentally (that is, which formed only the aryl amine; see below). Energies (kcal mol^{-1}) relative to that of **A**: +11.0 (**A**→**B**), −12.5 (**B**). This larger barrier and smaller exergonicity for the **A**→**B** reaction are consistent with reduced reactivity of a less-nucleophilic enamine.



c) **A**, the **A**→**B** transition-state structure, and **B** were recomputed for a reactant with a carbomethoxy group on the terminal alkene carbon of the enamine and a methyl group on the internal carbon (see below); this is a model of an experimental system that formed the aryl amine as the major product and only trace amounts of the indole product. Energies (kcal mol^{-1}) relative to that of **A**: +6.7 (**A**→**B**), −18.1 (**B**). These results suggest that the problem with this reaction is not an inherent electronic deactivation of the enamine (also borne out by calculations for a compound with an ester group on the terminal alkene carbon of the enamine and no methyl group on the internal carbon; see the Supporting Information); interactions between the ester group and the diphosphine ligand or inherent acidity of the β-ketoester may therefore be responsible for the experimental problems.



[15] a) K. Koerber-Plé, G. Massiot, *Synlett* **1994**, 759 – 760; b) N. Lachance, M. April, M. Joly, *Synthesis* **2005**, 2571 – 2577; c) K. Yamazaki, Y. Nakamura, Y. Kondo, *J. Org. Chem.* **2003**, *68*, 6011 – 6019.

