DOI: 10.1002/chem.200500787

Scope and Mechanism of the Pd^{II}-Catalyzed Arylation/Carboalkoxylation of Unactivated Olefins with Indoles

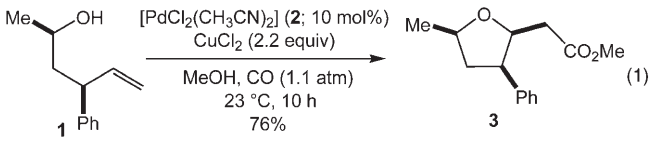
Cong Liu and Ross A. Widenhoefer*[a]

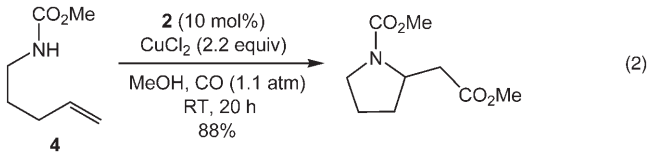
Abstract: Treatment of 1-methyl-2-(4-pentenyl)indole (**5**) with a catalytic amount of $[PdCl_2(MeCN)_2]$ (**2**; 5 mol%) and a stoichiometric amount of $CuCl_2$ (3 equiv) in methanol under CO (1 atm) at room temperature for 30 min gives methyl (9-methyl-2,3,4,9-tetrahydro-4-carbazolyl)acetate (**6**), which was isolated in 83% yield. A number of 2- and 3-alkenyl indoles undergo a similar palladium-catalyzed cyclization/carboalkoxylation to give the corresponding polycyclic indole derivatives in moderate to excellent yields with excellent regio- and diastereoselectivity. Under similar conditions, vinyl arenes undergo intermolecular arylation/carboalkoxylation with indoles to give 3-(1-aryl-2-carbomethoxyethyl) indoles in moderate yield with high regioselectivity. Stereochemical analyses of the palladium-catalyzed cyclization/carboalkoxylation of both 2- and 3-alkenyl indoles are in agreement with mechanisms involving outer-sphere attack of the indole on a palladium–olefin complex followed by α-migratory insertion of CO and methanolysis of the resulting acyl palladium intermediate. $CuCl_2$ functions as the terminal oxidant in this palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles and also significantly increases the rate of reaction of **2** with the alkenyl indole to form the corresponding acyl palladium complex. Spectroscopic studies are in agreement with the intermediacy of a heterobimetallic Pd/Cu complex as the active catalyst in this reaction.

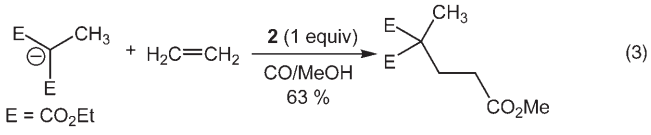
Keywords: C–C coupling · cyclization · homogeneous catalysis · indoles · palladium

Introduction

The palladium(II)-catalyzed addition of a heteroatom nucleophile and an alkoxycarbonyl group across the C=C bond of an unactivated olefin is an effective method for the synthesis of functionalized heterocycles.[1] As an example, treatment of γ-hydroxy olefin **1** with a catalytic amount of $[PdCl_2(CH_3CN)_2]$ (**2**) and a stoichiometric amount of $CuCl_2$ in methanol under CO leads to intramolecular alkoxylation/carboalkoxylation and formation of the substituted tetrahydrofuran **3** [Eq. (1)].[2] Similarly, 4-pentenyl carbamates such as **4** undergo palladium-catalyzed intramolecular amination/carboalkoxylation to form substituted pyrrolidine derivatives [Eq. (2)].[3] Although the addition of a stabilized carbanion and an alkoxycarbonyl group across the C=C bond of an unactivated olefin has been achieved in the presence of a stoichiometric amount of palladium [Eq. (3)], this reaction has not been achieved catalytically due to the incompatibility of the carbon nucleophile with the stoichiometric oxidant and/or Pd^{II} complex.[4]







[a] C. Liu, Prof. R. A. Widenhoefer
P. M. Gross Chemical Laboratory, Duke University
Durham, NC 27708-0346 (USA)
Fax: (+1) 919-660-1605
E-mail: ross.widenhoefer@duke.edu

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. General experimental methods and techniques, experimental procedures, analytical, spectroscopic, and structural data for new compounds.

We have developed effective procedures for the palladium-catalyzed hydroalkylation and oxidative alkylation of unactivated olefins with activated methylene compounds.[5] For example, treatment of 8-nonene-2,4-dione with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$ (2.5 equiv) at room temperature for 3 h leads to the isolation of 2-acetyl-3-methyl-2-cyclohexenone in 80% yield [Eq. (4)]. Unfortunately, our efforts to extend this protocol to include the palladium-catalyzed alkylation/carboalkoxylation of alkenyl β-diketones proved unsuccessful. However, recent reports describing the effective palladium-catalyzed oxidative cyclization of alkenyl indoles[6,7] prompted us to explore the palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles. Here we provide a full account of the development, scope, and mechanistic investigation of the palladium-catalyzed arylation/carboalkoxylation of unactivated olefins with indoles and related nucleophiles.[8] These transformations represent the first examples of the catalytic addition of a carbon nucleophile and an alkoxycarbonyl group across the C=C bond of an unactivated olefin.

(4)

Results and Discussion

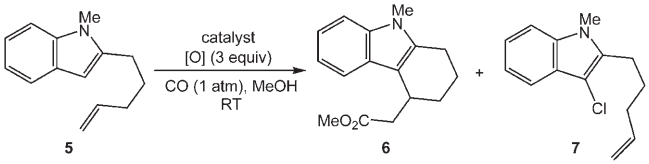
Development and scope

Palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles: The conditions that proved effective for the addition of a heteroatom nucleophile and an alkoxycarbonyl group across the C=C bond of an unactivated olefin also proved effective for the cyclization/carboalkoxylation of 2-alkenyl indoles. For example, treatment of 2-alkenyl indole **5** with a catalytic amount of **2** (10 mol%) and a stoichiometric amount of $CuCl_2$ (3 equiv) in methanol under CO (1 atm) at room temperature for 30 min gave tetrahydrocarbazole **6** in 94% yield by GC analysis (Table 1, entry 1). Whereas a catalyst loading of 5 mol% led to no significant decrease in the efficiency of the reaction, a further decrease to 2 mol% led to a decrease in the yield of **6** (Table 1, entries 2 and 3). The use of $[PdCl_2(PPh_3)_2]$, $Pd(OAc)_2$, $[Pd_2(dba)_3]$ (dba = *trans*,*trans*-dibenzylideneacetone), or $[PtCl_2(H_2C{=}CH_2)]_2$ as the catalyst led to diminished yields of **6** and concomitant formation of 3-chloro-1-methyl-2-(4-pentenyl)indole (**7**; (Table 1, entries 4–7, respectively). $CuBr_2$ proved less effective than $CuCl_2$ as a stoichiometric oxidant, while $Cu(OAc)_2$ or *p*-benzoquinone led to no detectable formation of either **6** or **7** (Table 1, entries 8–10).

Guided by the experiments outlined in the preceding paragraph, a preparative-scale reaction of **5** (0.1 M) with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$ (3 equiv) in methanol under CO (1 atm) led to isolation of **6** in 83% yield (Table 2, entry 1). Palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles displays good generality and good functional-group tolerance. Thus, unprotected, electron-rich, and electron-poor 2-(4-pentenyl)indoles undergo palladium-catalyzed cyclization/carboalkoxylation to form the corresponding tetrahydrocarbazoles in good yield (Table 2, entries 2–4). Similarly, the reaction tolerates substitution at the C(1), C(2), and C(3) carbon atoms of the 4-pentenyl chain and at the *cis*-terminal olefinic position (Table 2, entries 5–10); 2-(4-alkenyl) indoles substituted at the *trans*-terminal olefinic position do not undergo this reaction efficiently. Palladium-catalyzed cyclization/carboalkoxylation can also be applied to the synthesis of functionalized tetrahydro-β-carbolinones (Table 2, entry 7).

2-(3-Alkenyl)- and 2-(5-alkenyl) indoles also undergo efficient palladium-catalyzed cyclization/carboalkoxylation (Table 2, entries 11–14). For example, the reaction with (*E*)-2-(1,1-dimethyl-3-hexenyl)indole [(*E*)-**11**] leads to 6-*endo* cyclization to give the tetrahydrocarbazole *trans*-**12** as the only isomer in 84% yield (Table 2, entry 12). The palladium-catalyzed cyclization/carboalkoxylation of 2-(3-alkenyl) indoles is stereospecific, and cyclization of (*Z*)-**11** gives *cis*-**12** in 92% yield as the only isomer (Table 2, entry 13). In comparison, 2-(5-hexenyl)-1-methylindole (**13**) undergoes palladium-catalyzed 7-*exo*-trig cyclization to form **14** in 74% yield (Table 2, entry 14). It is noteworthy that significant amounts of a chlorinated intermediate,[9] presumably 3-chloro-2-(5-hexenyl)-1-methylindole (**15**), are generated early in the palladium-catalyzed cyclization of **13**; compound **15** is then converted slowly into **14**. More specifically, after 15 min at room temperature 63% of **13** had been con-

Table 1. Effect of Pd^{II} source and terminal oxidant on the palladium-catalyzed cyclization/carboalkoxylation of **5**.

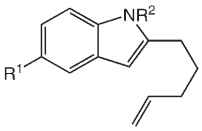
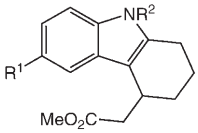
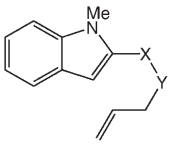
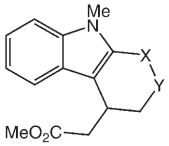
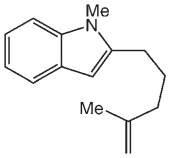
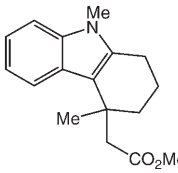
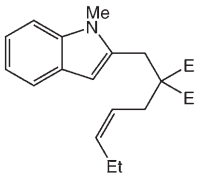
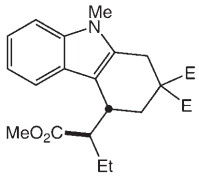
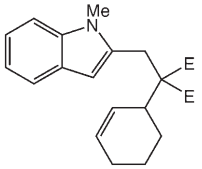
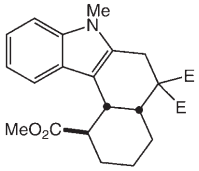
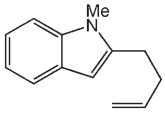
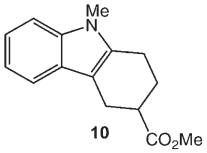
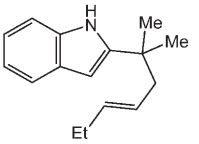
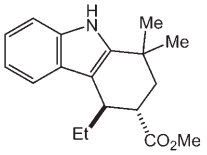
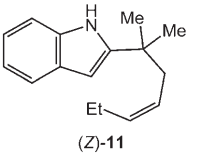
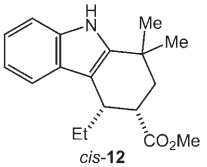


5 6 7

Entry	Catalyst	Cat. loading [%]	[O]	Yield of **6** [%][a]	Yield of **7** [%][a]
1	**2**	10	$CuCl_2$	94	<2
2	**2**	5	$CuCl_2$	92	<2
3	**2**	2	$CuCl_2$	63	6
4	$[PdCl_2(PPh_3)_2]$	10	$CuCl_2$	15	34
5	$Pd(OAc)_2$	10	$CuCl_2$	18[b]	9
6	$[Pd_2(dba)_3]$	5	$CuCl_2$	68	10
7	$[PtCl_2(CH_2{=}CH_2)]_2$	10	$CuCl_2$	<2[c]	33
8	**2**	10	$CuBr_2$	60[d]	–[e]
9	**2**	10	$Cu(OAc)_2$	<2[f]	<2
10	**2**	10	*p*-benzoquinone	<2[c]	<2

[a] GC yield with respect to internal standard. [b] 32% conversion after 5 min. [c] An unidentified by-product was obtained. [d] Yield after 24 h. [e] 3-Bromo-2-(4-pentenyl)indole was formed in 6% yield. [f] Compound **5** was recovered.

Table 2. Cyclization/carboalkoxylation of alkenyl indoles catalyzed by $[PdCl_2(CH_3CN)_2]$ (**2**) (5 mol%) in the presence of $CuCl_2$ (3 equiv) in methanol at room temperature.

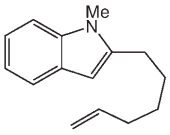
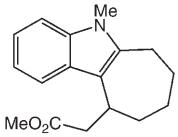
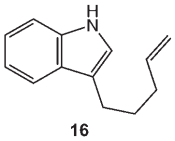
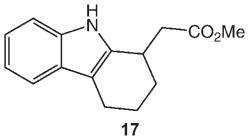
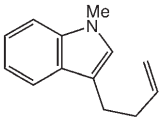
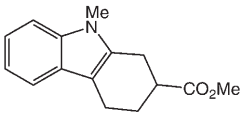
Entry	Alkenyl indole	Product	Time [h]	Yield [%][a]
				
1	$R^1=H$, $R^2=Me$ (**5**)	**6**	0.5	83
2	$R^1=H$, $R^2=H$ (**8**)	**9**	0.5	83
3	$R^1=OMe$, $R^2=Me$		0.5	86
4	$R^1=F$, $R^2=H$		0.5	74
				
5	$X=CMe_2$, $Y=CH_2$		0.5	84
6	$X=CH_2$, $Y=C(CO_2Me)_2$		0.5	87
7	$X=CO$, $Y=NMe$		12	91
8			2.5	87
9			3.5	62 ($\geq$50:1)
10			24	45 ($\geq$50:1)[b]
11			0.5	76
12	 (*E*)-**11**	 *trans*-**12**	3	84 ($\geq$50:1)
13	 (*Z*)-**11**	 *cis*-**12**	3	92 ($\geq$50:1)

sumed to form a 9:1 mixture of **15** and **14**, which together account for 82% of the reaction products.[10] After 8 h at room temperature 92% of **13** had been consumed to form a 1:7 mixture of **15** and **14**, which together account for more than 95% of the reaction products.

Although indoles tend to react with electrophiles at the C(3) carbon atom, the indole C(2) carbon atom is also nucleophilic and, for this reason, we explored the palladium-catalyzed cyclization/carboalkoxylation of 3-alkenyl indoles.[11] Thus, 3-(4-pentenyl)indole (**16**) undergoes palladium-catalyzed 6-*exo* cyclization to form tetrahydrocarbazole **17**, which was isolated in 85% yield (Table 2, entry 15). Similarly, 1-methyl-3-(3-butenyl)indole (**18**) undergoes palladium-catalyzed 6-*endo* cyclization at room temperature over 42 h to form **19**, which was similarly isolated in 58% yield (Table 2, entry 16).

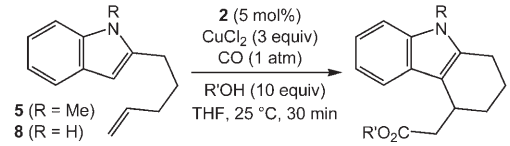
Cyclization/carboalkoxylation of alkenyl indoles in THF: The effective palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles does not require methanol as solvent. For example, treatment of 2-(4-pentenyl)indole (**8**) with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$ (3 equiv) in THF containing methanol (10 equiv) gives tetrahydrocarbazole **9** in 83% yield (Table 3, entry 1). This yield is comparable to that obtained when employing methanol as solvent (Table 2, entry 2). A number of other primary and secondary alcohols, including ethanol, *n*-octanol, isopropanol, and cyclohexanol, were also successfully employed in the palladium-catalyzed cyclization/carboalkoxylation of **8** to form tetrahydrocarbazoles **20**–**24** in good yield (Table 3, entries 2–5). Howev-

Table 2. (Continued)

Entry	Alkenyl indole	Product	Time [h]	Yield [%][a]
14	 **13**	 **14**	24	74
15	 **16**	 **17**	3	85
16	 **18**	 **19**	42	58

[a] Material isolated with greater than 95% purity. [b] 10 mol% of **2** employed.

Table 3. Cyclization/carboalkoxylation of alkenyl indoles catalyzed by $[PdCl_2(CH_3CN)_2]$ (**2**; 5 mol%) in the presence of $CuCl_2$ (3 equiv) in THF at room temperature.



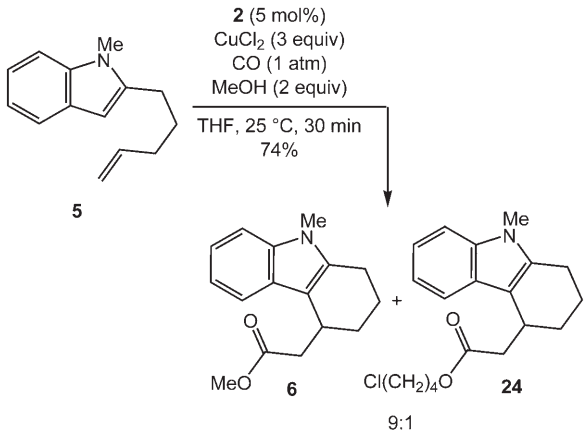
Entry	R	R′	Product	Yield [%][a]
1	H	Me	**9**	83
2	H	Et	**20**	73
3	H	*n*-octyl	**21**	73
4	H	*i*Pr	**22**	82
5	H	Cy	**23**	74
6	Me	$(CH_2)_4Cl$	**24**	65

[a] Material isolated with greater than 95% purity.

er, tertiary alcohols are not effective reagents for the palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles in THF.

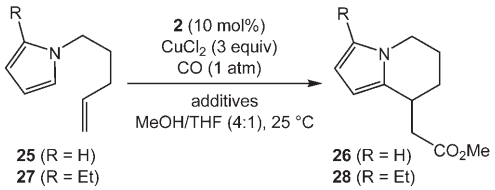
The use of fewer than ten equivalents of alcohol in the palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles in THF led to formation of both the desired ester and the corresponding 4-chlorobutyl ester, presumably formed by ring-opening and incorporation of THF. For example, treatment of **5** with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$ (3 equiv) in THF containing only two equivalents of methanol gave an approximately 9:1 mixture of **6** and the 4-chlorobutyl ester **24** in 74% combined yield (Scheme 1). Compound **24** was independently synthesized in 65% yield by the palladium-catalyzed reaction of **5** and 4-chloro-1-butanol (10 equiv) in THF (Table 3, entry 6).

Cyclization/carboalkoxylation of 1-(4-pentenyl)pyrroles: We also explored the use of pyrroles as nucleophiles in the palladium-catalyzed arylation/carboalkoxylation of unactivated olefins. Because the C(2) carbon of a pyrrole is more nucleophilic than the C(3) carbon atom,[12] we targeted *N*-alkenyl pyrroles as substrates for palladium-catalyzed cyclization/carboalkoxylation. Treatment of *N*-(4-pentenyl)pyrrole (**25**) under the conditions optimized for the cyclization/carboalkoxylation of alkenyl indoles led to complete consumption of **25** and isolation of tetrahydroindolizine **26** in 14% yield as the only product detected upon GC analysis of the crude reaction mixture (Table 4, entry 1). Because HCl is formed as a



Scheme 1.

Table 4. Palladium-catalyzed intramolecular cyclization/carboalkoxylation of 1-(4-pentenyl)pyrroles.



Entry	R	Additives[a]	Time [min]	Conv. [%]	Yield [%][b]
1	H	none	60	–	(14)
2	H	4-Å MS	30	71	66
			60	86	56
3	H	4-Å MS, DTBP (2 equiv)	15	4	2
4	H	4-Å MS, DTBP (2 equiv)[c]	60	98	84(70)
5	Et	4-Å MS, DTBP (2 equiv)[c]	60	–	(56)

[a] DTBP = 2,6-di-*tert*-butylpyridine. [b] GC yield with respect to internal standard; isolated yields in parentheses. [c] DTBP added over 30 min.

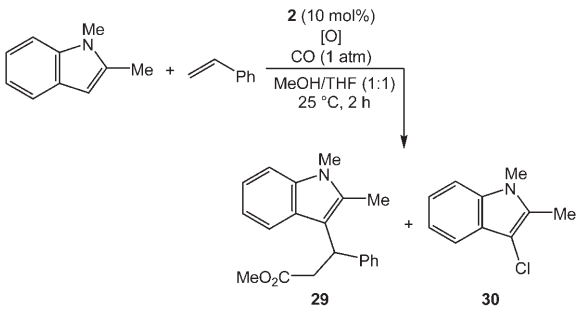
by-product of cyclization/carboalkoxylation, and because pyrroles polymerize rapidly under acidic conditions,[11] we reasoned that the low yield of **26** is due to competitive polymerization of **25** and/or **26** during the course of the reaction. In agreement with this hypothesis, addition of 4-Å molecular sieves to the reaction mixture increased the yield of **26** to 66% (by GC) after 30 min. However, longer reaction times led to diminished yields of **26**, pointing to the inefficient removal of HCl from the reaction mixture (Table 4, entry 2).[13]

Although addition of a Brønsted base to the palladium-catalyzed cyclization/carboalkoxylation of **25** would certainly consume the HCl formed in the conversion of **25** to **26**, Pd^{II} complexes are reduced to Pd^0 in the presence of methanol and base. It was therefore not surprising that addition of 2,6-di-*tert*-butylpyridine (DTBP, 2 equiv) to the palladium-catalyzed reaction of **25** led to a significant decrease in both conversion and product yield (Table 4, entry 3). We therefore considered that slow addition of the base to the reaction mixture might sequester the HCl without leading to the reduction of **2**. In an optimized procedure, slow addition of DTBP (2 equiv) over 30 min to a mixture of **25**, **2** (10 mol%), $CuCl_2$ (3 equiv), and 4-Å molecular sieves in methanol/THF (4:1) under CO (1 atm) gave **26**, which was isolated in 70% yield (84% by GC; Table 4, entry 4). This protocol was also applied to the cyclization/carboalkoxylation of 2-ethyl-1-(4-pentenyl)pyrrole (**27**) to form tetrahydroindolizine **28** in moderate yield (Table 4, entry 5).

Intermolecular arylation/carboalkoxylation of vinyl arenes with indoles: The palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles was extended to include the intermolecular arylation/carboalkoxylation of vinyl arenes with indoles. In an initial experiment, treatment of a mixture of 1,2-dimethylindole (1 equiv) and styrene (3 equiv, 0.60 M) with a catalytic amount of **2** (10 mol%) and a stoichiometric amount of $CuCl_2$ (2.5 equiv) in methanol/THF under CO (1 atm) at room temperature for 2 h led to formation of a 2:1 mixture of 1,2-dimethyl-3-(1-phenyl-2-carbomethoxyethyl)indole (**29**) and 3-chloro-1,2-dimethylindole (**30**) in 90% combined yield (by GC; Table 5, entry 1). Work-up and chromatography led to isolation of **29** and **30** in 55% and 20% yield, respectively.

A number of experiments were performed to improve the selectivity for **29** in the reaction of 1,2-dimethylindole with styrene. Increasing the amount of styrene to six equivalents did little to improve the production of **29** (Table 5, entry 2). Employment of $Cu(OAc)_2$ or *p*-benzoquinone as the stoichiometric oxidant led to no formation of **29**, while decreasing the amount of $CuCl_2$ by employing a mixture of $CuCl_2$ (1 equiv) and O_2 (1 atm) as the oxidant mixture prevented formation of **30** but also diminished the yield of **29** (Table 5, entries 3–5). Although $FeCl_3$ alone was not effective as a stoichiometric oxidant (Table 5, entry 6), the use of mixtures of $FeCl_3$ and $CuCl_2$ led to increased formation of **29** with significantly diminished formation of **30**. For example, reaction of 1,2-dimethylindole with styrene in the presence of a catalytic amount of **2** and a stoichiometric mixture of $CuCl_2$ (2.5 equiv) and $FeCl_3$ (1 equiv) led to formation of a 36:1 mixture of **29** and **30** in 74% combined yield (GC), from which **29** was isolated in 64% yield (Table 5, entry 7).

Table 5. Effect of reaction conditions on the palladium-catalyzed intermolecular arylation/carboalkoxylation of styrene with 1,2-dimethylindole.



Entry	Equiv styrene	[O] (equiv)	Yield of **29** [%][a]	Yield of **30** [%][a]
1	3	$CuCl_2$ (3)	60(55)	30(20)
2	6	$CuCl_2$ (3)	61	27
3	3	$Cu(OAc)_2$ (3)	<1[b]	<1
4	3	*p*-benzoquinone (3)	<1[c]	<1
5	3	$CuCl_2$ (1)/O_2[b]	43	<1
6	3	$FeCl_3$ (3)	12	<1
7	3	$CuCl_2$ (2.5)/$FeCl_3$ (1)	72(64)	2

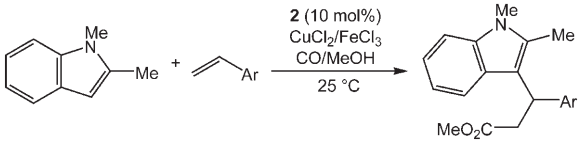
[a] GC yield with isolated yield in parentheses. [b] 1,2-Dimethylindole was recovered unchanged. [c] The predominant species formed was a 1:1 adduct of 1,2-dimethylindole and *p*-benzoquinone (GC/MS analysis).

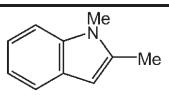
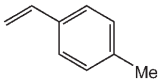
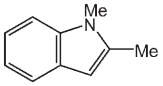
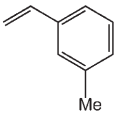
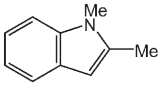
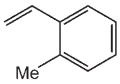
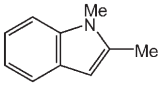
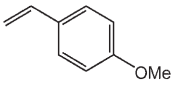
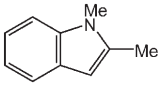
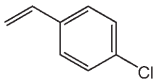
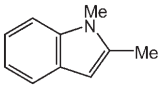
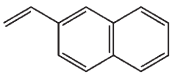
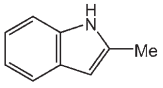
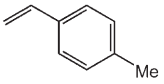
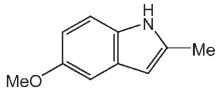
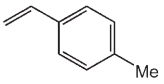
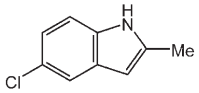
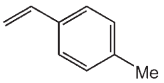
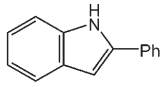
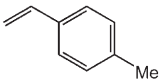
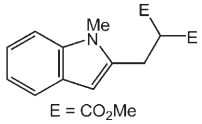
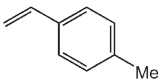
The palladium-catalyzed intermolecular arylation/carboalkoxylation of vinyl arenes with 1,2-dimethylindole tolerates substitution at the *ortho*, *meta*, and *para* positions of the vinyl arene (Table 6, entries 1–3). Similarly, electron-rich and electron-poor vinyl arenes and 2-vinylnaphthalene undergo palladium-catalyzed arylation/carboalkoxylation with 1,2-dimethylindole to afford the corresponding products in modest yield as single regioisomers (Table 6, entries 4–6). Unprotected 2-methylindole, 5-chloro-2-methylindole, and 5-methoxy-2-methylindole also undergo palladium-catalyzed arylation/carboalkoxylation with 4-methylstyrene to give the products in >60% yield. Likewise, indoles that possess either a phenyl group or a 2,2-dicarbomethoxyethyl group at the 2-position of the indole undergo palladium-catalyzed arylation/carboalkoxylation with 4-methylstyrene in good yield (Table 6, entries 7–11). Indoles that do not possess substitution at the C(2) position of the indole failed to undergo efficient arylation/carboalkoxylation.

Mechanism

Stereochemistry and mechanism of C–C bond formation: The stereospecific conversion of (*E*)- and (*Z*)-**11** into *trans*- and *cis*-**12**, respectively (Table 2, entries 12 and 13), confirmed the *anti* addition of the indole and the carbomethoxy group across the C=C bond of the pendant olefin. Because α-migratory insertion of CO into an M–C bond occurs with retention of stereochemistry at the metal-bound carbon

Table 6. Intermolecular arylation/carboalkoxylation of vinyl arenes with indoles catalyzed by $[PdCl_2(CH_3CN)_2]$ (**2**) (10 mol%) in the presence of $CuCl_2$ (2.5 equiv) and $FeCl_3$ (1 equiv) in MeOH at room temperature.

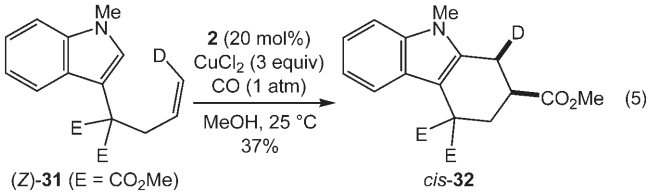


Entry	Indole	Vinyl arene	Time [h]	Yield [%][a]
1			1	78
2			1	76
3			1	44
4			1	40
5			3	50
6			1	58
7			3	71
8			1	63
9			3	65
10			3.5	77
11			23	63

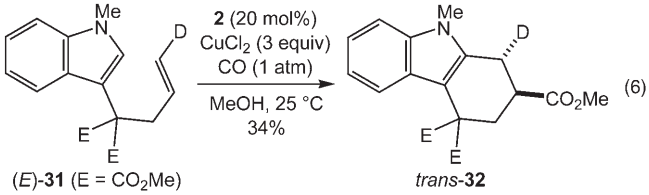
[a] Material isolated with greater than 95% purity.

atom,[14] this stereochemical outcome is in agreement with a mechanism for the palladium-catalyzed cyclization/carboalkoxylation of (*Z*)-**11** that involves outer-sphere attack of the indole on the palladium–olefin complex **I**, which, coupled with loss of HCl, would form the alkylpalladium intermediate **II** (Scheme 2). α-Migratory insertion of CO into the Pd–C bond of **II** with retention of stereochemistry would form the acyl palladium complex **IIIa**, which could undergo methanolysis to release *cis*-**12** and form a palladium(0) complex. Oxidation of this Pd^0 complex with Cu^{II} would then regenerate the active Pd^{II} catalyst (Scheme 2).

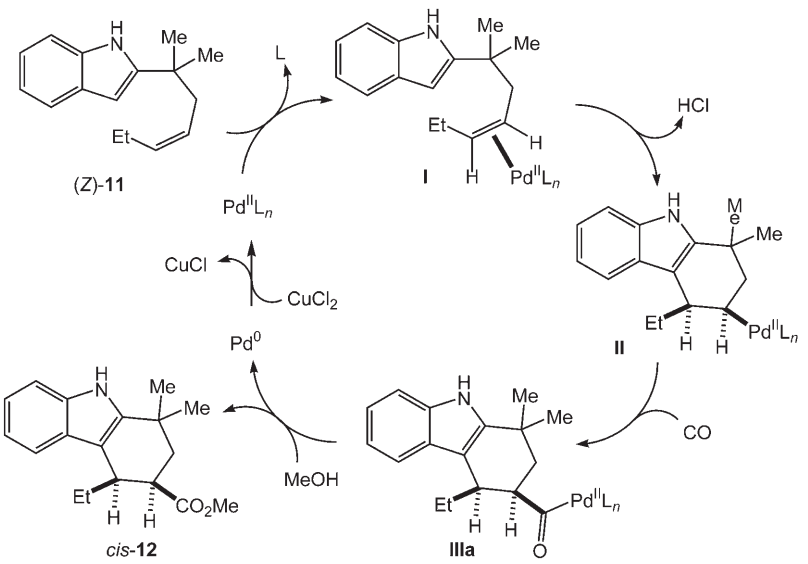
It is noteworthy that the Pd-$(OAc)_2$-catalyzed oxidative cyclization of 3-alkenyl indoles has been shown to occur with net *syn* addition of the indole and palladium across the C–C bond of the olefin.[6] This stereochemical outcome is consistent with a mechanism involving activation of the C(2)–H bond of the indole followed by β-migratory insertion of the olefin into the resulting Pd–C bond.[6] In contrast, the 6-*endo* regioselectivity observed for the conversion of 3-(3-butenyl)indole **18** into **19** in the presence of a catalytic amount of **2** points to an outer-sphere mechanism for C–C bond formation. In an effort to confirm this hypothesis, we investigated the stereochemistry of the palladium-catalyzed cyclization/carboalkoxylation of stereochemically pure 3-(4-deuterio-3-butenyl)indoles. In one experiment, treatment of (*Z*)-3-(4-deuterio-3-butenyl)indole [(*Z*)-**31**] with a catalytic amount of **2** in the presence of $CuCl_2$ gave *cis*-**32**, which was isolated in 37% yield, as a single diastereoisomer [Eq. (5)]. The palladium-catalyzed cyclization/carboalkoxylation of **31** is stereospecific, and palladium-catalyzed cyclization/carboalkoxylation of (*E*)-**31** gives *trans*-**32**, which was isolated in 34% yield, also as a single diastereoisomer [Eq. (6)].



(5)



(6)



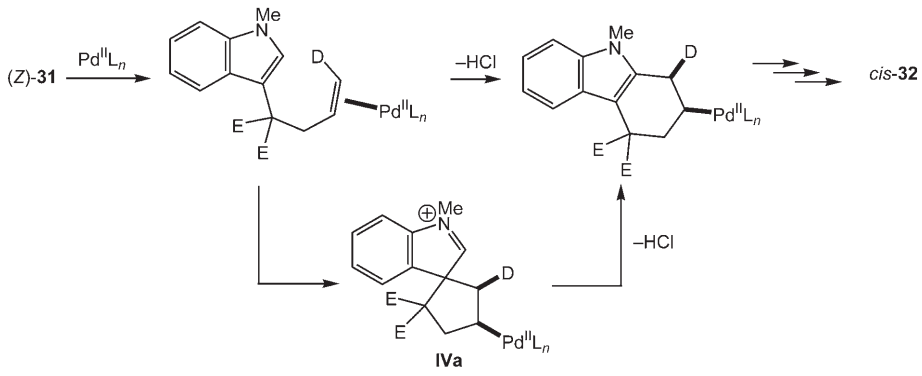
Scheme 2.

The stereospecific conversion of (*E*)- and (*Z*)-**31** into *trans*- and *cis*-**32**, respectively [Eqs. (5) and (6)], confirmed the *anti* addition of the indole and the carbomethoxy group across the C=C bond of the olefin and supports a mechanism involving outer-sphere nucleophilic attack of the C(2) position of the indole on a palladium-complexed olefin (Scheme 3). The *anti* stereochemistry of the carbopalladation of an olefin with a π-nucleophile has previously been observed in the Pd^{II}-catalyzed addition of allenes to 1,3-dienes.[15]

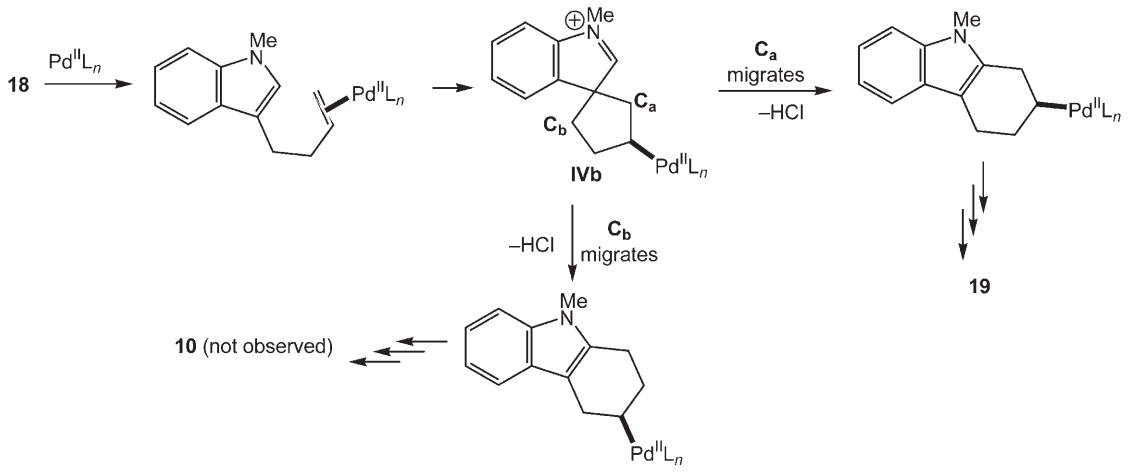
The C(3) position of an indole is more nucleophilic than the C(2) position. For this reason, we also considered a mechanism for the stereospecific cyclization of (*E*)- and (*Z*)-**31** involving outer-sphere attack of the C(3) carbon atom of the indole on a Pd-complexed olefin to form the spirocyclic iminium ion intermediate **IVa**, followed by stereospecific 1,2-migration of the primary alkyl group to the C(2) carbon atom of the indole (Scheme 3).[16] Attack of the C(3) position of an indole on a pendant electrophile to form a 3,3-spirocyclic iminium ion intermediate, followed by alkyl migration, has been observed for the cyclization of 3-(4-tosylbutyl)indole,[17] for the Pictet–Spengler cyclization of *N*-benzylidenetryptamines,[18] and for the BF_3-catalyzed cyclization of 4-(3-indolyl)butanol.[19]

Although we cannot rule out spirocycle **IVa** as an intermediate in the conversion of **31** into **32**, this mechanism appears unlikely because cyclization/carboalkoxylation of **18** forms tetrahydrocarbazole **19** (Table 2, entry 16) without formation of the corresponding regioisomer **10** (Table 2, entry 11). Selective conversion of **18** into **19** via spirocyclic intermediate **IVb** would require selective 1,2-migration of carbon C_a instead of migration of C_b (Scheme 4). In contrast to the alkyl groups bound to the C(3) indole position of spirocyclic intermediate **IVa** [$C(CO_2Me)_2$ and CH_2], the alkyl groups bound to the C(3) indole position of spirocyclic intermediate **IVb** (C_a and C_b) do not appear to be sufficiently different, either electronically or sterically, to account for the selective migration of C_a rather than C_b (Scheme 4).

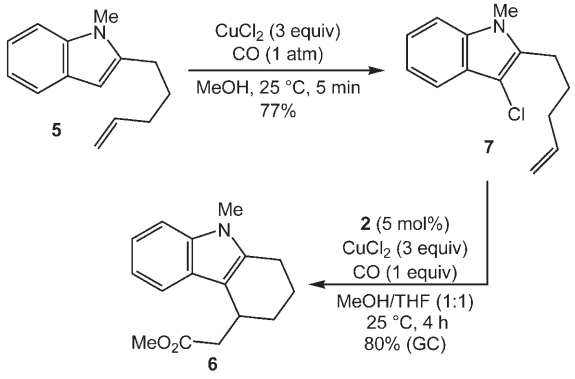
The role of 3-chloroindoles in arylation/carboalkoxylation: Because electron-rich indoles undergo chlorination at the C(3) position in the presence of $CuCl_2$,[20] it is not surprising that 3-chloroindoles are formed as by-products in the palladium-catalyzed, copper-mediated arylation/carboalkoxylation of olefins with indoles. Unexpected, however, was the formation and consumption of chlorinated indole **15** in the palladium-catalyzed conversion of **13** into **14**. This observation suggests that **15** might be an intermediate in this conversion and, likewise, that **7** might be an intermediate in the conversion of **5** into **6**. To better understand the role of 3-chloroindoles in the palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles, several additional experiments were performed. In one experiment, treatment of **5** with $CuCl_2$ (3 equiv) in methanol under CO for 25 min in the absence of **2** led to complete consumption of **5** to form **7** as the exclusive product, as determined by GC analysis; **7** was isolated in 77% yield from a subsequent preparative-scale reaction (Scheme 5). However, when a suspension of **5** and $CuCl_2$ (3 equiv) containing a catalytic amount of **2** (5 mol%) was monitored peri-



Scheme 3.



Scheme 4.

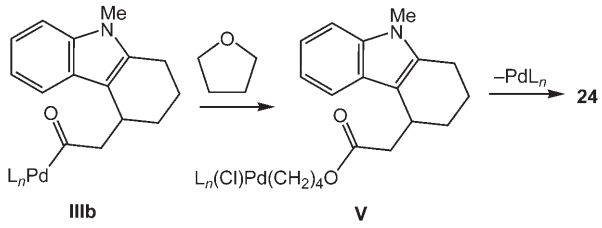


Scheme 5.

odically by GC analysis, no significant amount of **7** ($\leq 2\%$) was observed throughout complete conversion of **5** to **6**. Failure to observe **7** under conditions suggests either that **7** is not formed or that it is formed and consumed rapidly under these reaction conditions. The latter possibility was firmly discounted on account of the slow consumption of **7** under the same conditions. For example, treatment of **7** with a catalytic amount of **2** (5 mol%) and a stoichiometric amount of $CuCl_2$ (3 equiv) under CO (1 atm) at room temperature in methanol for 4 h gave **6** in 80% yield (GC) as the only product (Scheme 5).

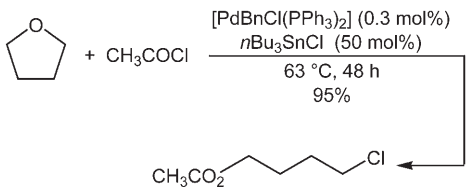
The pathway by which 3-chloroindoles **7** and **15** are converted into tricyclic indoles **6** and **14**, respectively, is unclear. Given the proposed mechanism of palladium-catalyzed cyclization/carboalkoxylation (see above), it appears unlikely that a 3-chloroindole would be sufficiently nucleophilic to undergo outer-sphere attack on a palladium-complexed olefin. An alternative mechanism involving oxidative addition of the C–Cl bond followed by olefin β-migratory insertion also appears unlikely given the strongly oxidizing environment that would render the available concentration of Pd^0 exceedingly low. Furthermore, all our observations regarding the stereochemistry of Pd-catalyzed indole arylation argue against an inner-sphere mechanism for C–C bond formation. For these reasons, it appears most likely that conversion of chlorinated indoles **7** and **15** into **6** and **14**, respectively, occurs by reversion of the 3-chloroindole to the parent 3*H*-indole followed by cyclization/carboalkoxylation. Unfortunately, we have been unable to obtain experimental evidence to support this proposal.

The mechanism of formation of 4-chlorobutyl ester 24: The use of fewer than ten equivalents of alcohol in the palladium-catalyzed cyclization/carboalkoxylation of **5** in THF leads to formation of the 4-chlorobutyl ester **24** as a by-product, presumably by ring-opening and incorporation of THF (Scheme 1). The Pd^{II}-catalyzed ring-opening of THF has been observed previously. For example, refluxing a THF solution of acetyl chloride in the presence of a catalytic mixture of $[(PPh_3)_2Pd(Bn)Cl]$ and tributylchlorostannane gives 4-chlorobutyl acetate in 95% yield [Eq. (7)].[21] This transformation was proposed to occur by initial reduction of Pd^{II} to Pd^0 followed by oxidative addition of the acid chloride to form an acyl palladium(II) complex. Nucleophilic attack of THF on this acyl palladium complex, followed by ring-opening and C–Cl reductive elimination, would then release the 4-chlorobutyl ester.[21] In a similar manner, **24** is presumably formed by attack of THF on the acyl palladium intermediate **IIIb** to form the palladium chloride intermediate **V** (Scheme 6); C–Cl reductive elimination would then form **24**. However, given that reaction of **5** with 4-chlorobutanol also leads to the formation of **24**, we cannot rule out a mechanism involving copper- or palladium-catalyzed ring-



Scheme 6.

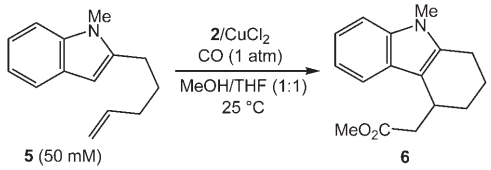
opening of THF followed by attack of 4-chlorobutanol on **IIIb**.



(7)

The effect of $CuCl_2$ on arylation/carboalkoxylation: We noted with interest that $CuCl_2$ is significantly more effective as a stoichiometric oxidant for the palladium-catalyzed arylation/carboalkoxylation of unactivated olefins with indoles than other oxidants (Tables 1 and 5). For this reason, we considered that $CuCl_2$ might play an active role in this reaction in addition to serving as the stoichiometric oxidant. An analysis of the effect of $CuCl_2$ on the rate of reaction of **5** with **2** strongly supported this contention. Reaction of **5** (50 mM) with a catalytic amount of **2** (5 mol%, 2.5 mM) in the presence of $CuCl_2$ (3 equiv) at room temperature for 5 min led to 62% consumption of **5** to form **6** in 58% yield (GC analysis versus internal standard; Table 7, entry 1).

Table 7. Effect of **2** and $CuCl_2$ on the cyclization/carboalkoxylation of **5** in MeOH/THF at room temperature.



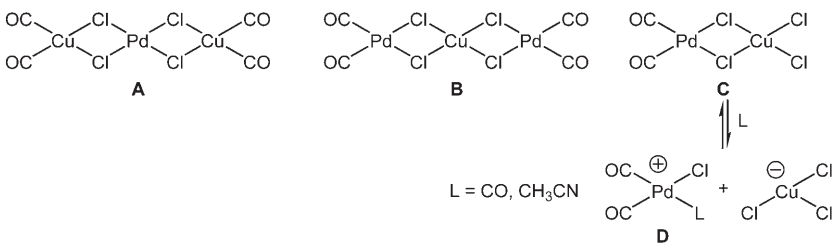
Entry	**2** (equiv)	$CuCl_2$ (equiv)	Time [min]	Conv. [%]	Yield of **6** (by GC, %)[a]
1	0.05	3.0	5	62	58
			25	98	95
2	1.0	0	240	72	53
3	1.0	1.5	5	98	37
			180	98	97

[a] No significant (ca. 2%) amounts of **7** were observed in these transformations.

After 25 min, 98% of **5** had been consumed to form **6** in 95% yield (GC). Conversely, reaction of equimolar amounts of **5** (50 mM) and **2** in the absence of $CuCl_2$ at room temperature for 4 h led to only 72% consumption of **5** to form **6** in 53% yield (Table 7, entry 2). In a third experiment, reaction of **5** with a stoichiometric amount of both **2** (1 equiv, 50 mM) and $CuCl_2$ (1.5 equiv) at room temperature for 5 min led to 98% consumption of **5** with formation of **6** in 37% yield as the sole product detected by GC analysis; after 180 min, **6** accounted for 97% of the reaction mixture (by GC analysis; Table 7, entry 3).

The nature of the palladium catalyst: The experiments described in the preceding paragraph established that $CuCl_2$ significantly increases the rate of reaction of **5** with **2**. Also noteworthy is the large discrepancy between the amount of **5** consumed and the amount of **6** formed in the initial stages of the stoichiometric reaction of **5** with **2** and $CuCl_2$ (Table 7, entry 3). In an effort to gain insight into the manner in which $CuCl_2$ affects the reactivity of **2** toward **5**, several additional experiments were performed. In one experiment, treatment of a solution of **2** in [D_4]methanol with CO (1 atm) for 5 min led to complete displacement of acetonitrile and formation of the known chloride-bridged carbonylpalladium dimer $[Pd(CO)(Cl)(\mu\text{-}Cl)]_2$ (**33**), which was characterized by IR spectroscopy [$\nu_{CO} = 2166\ cm^{-1}$ ($CHCl_3$)] and by ^{13}C NMR analysis of the corresponding ^{13}C isotopomer $[Pd(^{13}CO)(Cl)(\mu\text{-}Cl)]_2$ [**33**-$(^{13}CO)_2$; $\delta = 165.5$ ppm].[22] Addition of $CuCl_2$ to a suspension of **33**-$(^{13}CO)_2$ in [D_4]methanol led to rapid (<1 min) formation of a green solution that displays an approximate 4:1 ratio of resonances at $\delta = 165.5$ and 173.8 ppm in the ^{13}C NMR spectrum.[23] The IR spectrum of the green solution generated from reaction of **33** and $CuCl_2$ in chloroform [$\nu_{CO} = 2168\ cm^{-1}$ ($CHCl_3$)] does not differ significantly from that of **33**.

The presence of a peak at $\delta = 173.8$ ppm in the ^{13}C NMR spectrum of a solution of **33**-$(^{13}CO)_2$ and $CuCl_2$ points to the equilibrium formation of a new complex, which we suggest is a chloride-bridged, heterobimetallic Cu/Pd carbonyl complex.[24] Activation of a Pd^{II} catalyst by Cu^{II} through the formation of a heterobimetallic palladium/copper complex has been proposed in a number of catalytic transformations. In one case, Fenton and Steinwand proposed that an unspecified palladium/copper bimetallic complex functions as the active catalyst in the Pd^{II}/Cu^{II}-catalyzed oxidative carbonylation of ethanol to form diethyl oxalate.[25] Hosokawa and coworkers have also proposed a bimetallic palladium/copper complex that contains bridging acetate and peroxo ligands as the active catalyst in the Pd^{II}-catalyzed oxidative cyclization of 2-allylphenols in the presence of $Cu(OAc)_2$ and oxygen,[26] and Alper and Zargarian have suggested palladium/copper bimetallic complexes **A** and **B** as possible structures for the active catalyst in the palladium(II)-catalyzed dicarbonylation of terminal alkynes (Scheme 7).[27] In support of this contention, the stoichiometric reaction of $PdCl_2$,

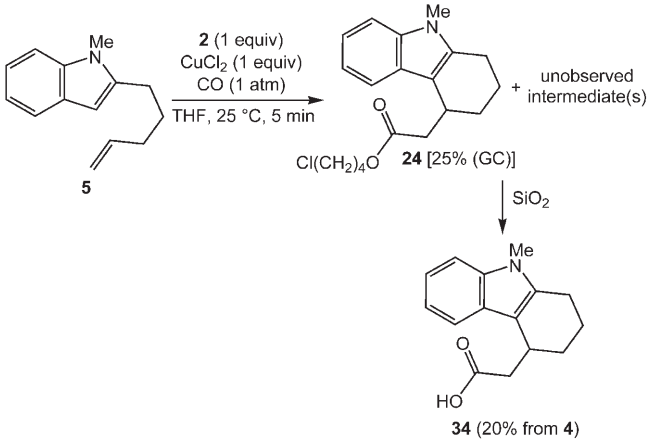


Scheme 7.

$CuCl_2$, and CO led to formation of a catalytically active, unstable, yellow complex that displays an IR stretch at 1985 cm^{-1} (nujol). Given the close similarity between our system and Alper's, it appears likely that a similar palladium/copper species (**A**, **B**, or **C**) is the active catalyst in both cases (Scheme 7)

We considered that a bimetallic Pd/Cu complex such as **B** or **C** might derive its high activity for the cyclization/carboalkoxylation of alkenyl indoles by generating an equilibrium concentration of a highly activated cationic carbonylpalladium complex such as **D** (Scheme 7). However, treatment of **5** with a stoichiometric 1:1 mixture of **2** and AgOTf in methanol under CO (1 atm) at room temperature for 48 h led to only 50% conversion of **5** into **6**. This observation argues against a cationic palladium complex such as **D** as the active catalyst in the palladium-catalyzed, copper-mediated cyclization/carboalkoxylation of alkenyl indoles.

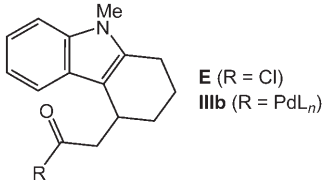
Because no by-products or intermediates were observed by GC analysis during the conversion of **5** into **6** in the presence of a stoichiometric mixture of **2** and $CuCl_2$ (Table 7, entry 3), the large discrepancy between the amount of **5** consumed and the amount of **6** formed early in the reaction points to the rapid conversion of **5** into a GC-silent intermediate that is slowly converted into **6**. The presence of such an intermediate in the conversion of **5** and **2** into **6** was more firmly established in the following experiment. When a 1:1:1 mixture of **5**, **2**, and $CuCl_2$ was stirred in THF under CO at room temperature for 5 min in the absence of methanol, **5** was completely consumed to form the 4-chlorobutyl ester **24** in about 25% yield as the only product observed by GC analysis (Scheme 8). However, subsequent silica gel



Scheme 8.

chromatography of the reaction mixture led to isolation of carboxylic acid **34** in 20% yield.[28] Because **24** is stable to chromatography (see above), we conclude that **34** is formed by hydrolysis of an unobserved intermediate.

We considered that the GC-silent intermediate formed in the stoichiometric reaction of **5**, **2**, and $CuCl_2$ could be either the acid chloride **E** or the acyl palladium complex **IIIb**, both of which would be expected to undergo hydrolysis to form **34**. However, an NMR experiment strongly suggested that this GC-silent intermediate is the acyl palladium complex **IIIb**. Thus, when alkenyl indole **5** was added to a



green solution of **2** and $CuCl_2$ in THF/[D_4]methanol (1:1) under ^{13}CO and analyzed after 2.5 min by ^{13}C NMR spectroscopy, in addition to the resonances at $\delta = 173.8$ and 165.5 ppm, a resonance was observed at $\delta = 210.4$ ppm that is approximately half the intensity of the $\delta = 165$ ppm resonance. The resonance at $\delta = 210.4$ ppm, which is consistent with the carbonyl carbon of an acyl palladium complex,[29] was observed throughout the conversion of **5** into **6** and disappeared only upon complete formation of **6** (ca. 20 min).[30,31] These results are in agreement with the rapid formation of an acyl palladium complex **IIIb** followed by its slow conversion into **6**.

Catalyst resting state: Although acyl palladium complex **IIIb** is formed more rapidly than it is consumed in the stoichiometric reaction of **5**, **2**, and $CuCl_2$, it does not appear that conversion of **IIIb** into **6** is the turnover-limiting step under catalytic conditions. When the reaction of **5** with a catalytic amount of **2** and a stoichiometric amount of $CuCl_2$ in [D_4]methanol under ^{13}CO was monitored periodically by ^{13}C NMR spectroscopy, resonances at $\delta = 173.5$ and 164.5 ppm were observed during the entire reaction, with no detection of a resonance at $\delta = 210.4$ ppm. This observation suggests that cyclization of **5** into **IIIb** rather than conversion of **IIIb** into **6** is the turnover-limiting step in the palladium-catalyzed, copper-mediated conversion of **5** into **6**. The rapid formation of **IIIb** under stoichiometric, but not catalytic, conditions can be attributed to the significantly lower concentration of **2** present under catalytic conditions.

Conclusion

We have developed a mild and effective palladium(II)-catalyzed, copper(II)-mediated protocol for the arylation/carboalkoxylation of unactivated olefins with indoles. Both 2- and 3-alkenyl indoles undergo this palladium-catalyzed cyclization/carboalkoxylation in the presence of a stoichiometric amount of $CuCl_2$ to form polycyclic indoles in good yield with excellent regio- and diastereoselectivity. 1-(4-Pentenyl)-pyrroles also undergo palladium-catalyzed cyclization/carboalkoxylation although the efficiency of these reactions is compromised by competitive polymerization of the pyrrole. Vinyl arenes undergo palladium-catalyzed intermolecular ar-

ylation/carboalkoxylation with indoles in the presence of a stoichiometric mixture of $CuCl_2$ and $FeCl_3$ to form the corresponding 3-(1-aryl-2-carbomethoxyethyl) indoles in moderate to good yield with high regioselectivity. Stereochemical analysis of the palladium-catalyzed cyclization/carboalkoxylation of both 2-(3-alkenyl)- and 3-(3-alkenyl) indoles has established the *anti* addition of the indole and carbomethoxy group across the C=C bond of the pendant olefin. This stereochemical outcome is in agreement with a mechanism involving outer-sphere attack of the indole moiety on a palladium-complexed olefin followed by CO insertion and methanolysis of the resulting acyl palladium intermediate. Kinetic experiments have revealed that $CuCl_2$ significantly increases the rate at which alkenyl indole **5** reacts with **2** to form acyl palladium complex **IIIb**, and NMR experiments have suggested that the increased rate of reaction of **5** with **2** in the presence of $CuCl_2$ is due to formation of a highly active Pd/Cu heterobimetallic carbonyl complex.

Experimental Section

Methyl (9-methyl-2,3,4,9-tetrahydro-4-carbazolyl)acetate (6): Methanol (4 mL) and a solution of **5** (99 mg, 0.50 mmol) in methanol (1.0 mL) were added sequentially to a flask containing $[PdCl_2(CH_3CN)_2]$ (**2**; 6.5 mg, 2.5×10^{-2} mmol) and $CuCl_2$ (200 mg, 1.5 mmol) that had been twice evacuated (12 mmHg) and refilled with CO (1 atm). The resulting suspension was stirred for 30 min and concentrated under vacuum. Column chromatography of the residue (SiO_2; hexanes/EtOAc, 5:1) gave **6** (106 mg, 83%) as a pale-yellow oil. TLC (hexanes/EtOAc, 5:1): R_f=0.27. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ=7.57 (d, $^3J_{H,H}$=8.4 Hz, 1H; CH), 7.29 (d, $^3J_{H,H}$=8.2 Hz, 1H; CH), 7.20 (t, $^3J_{H,H}$=7.6 Hz, 1H; CH), 7.11 (t, $^3J_{H,H}$=7.6 Hz, 1H; CH), 3.76 (s, 3H; CH_3), 3.63 (s, 3H; CH_3), 3.63–3.58 (m, 1H; CH), 3.04 (dd, $^3J_{H,H}$=4.0, $^2J_{H,H}$=15.2 Hz, 1H; CH_2), 2.79–2.64 (m, 2H), 2.47 (dd, $^3J_{H,H}$=10.4, $^2J_{H,H}$=14.8 Hz, 1H; CH_2), 2.02–1.92 (m, 3H), 1.87–1.79 ppm (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C): δ=173.9, 137.2, 136.4, 126.5, 120.9, 119.1, 118.3, 111.5, 109.0, 51.9, 40.2, 29.4, 29.0, 28.6, 22.4, 19.5 ppm; IR (neat): $\tilde{\nu}$=2934, 1731, 1470, 1434, 1416, 1379, 1281, 1166, 1080, 1014, 739 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{19}NO_2$: C 74.68, H 7.44; found: C 74.95, H 7.47.

All remaining polycyclic indoles in Table 2 were isolated from the corresponding alkenyl indoles by following a procedure similar to that described above unless noted otherwise.

Cyclization of 8 in THF: THF (4 mL), methanol (180 μL, 5.0 mmol), and a solution of **8** (99 mg, 0.50 mmol) in THF (1.0 mL) were added sequentially to a flask containing **2** (6.5 mg, 2.5×10^{-2} mmol) and $CuCl_2$ (200 mg, 1.5 mmol) under CO (1 atm). The resulting suspension was stirred for 30 min and then concentrated under vacuum. Column chromatography of the residue (SiO_2; hexanes/EtOAc, 5:1) gave **9** (106 mg, 83%) as a pale yellow oil.

All remaining tricyclic indole derivatives depicted in Table 3 were synthesized following a similar procedure.

Methyl 2-(5,6,7,8-tetrahydroindolizin-8-yl)acetate (26):[32] Methanol (1.0 mL) was added to a flask containing **2** (13.0 mg, 0.050 mmol), $CuCl_2$ (200 mg, 1.5 mmol), and 4-Å molecular sieves (200 mg) under CO (1 atm) and the resulting mixture was stirred at room temperature for 10 min. A solution of **25** (67 mg, 0.50 mmol) in methanol (0.5 mL) was added to the resulting mixture in one portion and a solution of 2,6-di-*tert*-butylpyridine (191 mg, 1.0 mmol) in methanol/THF (1:1, 1 mL) was then added with a syringe pump over 30 min. The resulting mixture was stirred for an additional 30 min and concentrated under vacuum. Column chromatography of the residue (SiO_2; hexanes/EtOAc, 5:1) gave **26** (67 mg, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ=6.53 (s, 1H; CH), 6.13 (d, $^3J_{H,H}$=3.2 Hz, 1H; CH), 5.88 (d, $^3J_{H,H}$=3.2 Hz, 1H; CH), 4.02–3.96 (m, 1H; CH), 3.91–3.84 (m, 1H; CH), 3.72 (s, 3H; CH_3), 3.35–3.29 (m, 1H; CH), 2.85 (dd, $^3J_{H,H}$=5.2, $^2J_{H,H}$=15.6 Hz, 1H; CH_2), 2.47 (dd, $^3J_{H,H}$=9.0, $^2J_{H,H}$=15.6 Hz, 1H; CH_2), 2.12–1.91 (m, 3H), 1.47 ppm (q, $^3J_{H,H}$=10.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C): δ=173.1, 132.0, 119.4, 107.9, 103.8, 51.8, 45.5, 40.5, 31.5, 27.9, 22.7 ppm.

Compound **28** was synthesized employing a procedure similar to that described for the synthesis of **26**.

Methyl 3-(1,2-dimethyl-3-indolyl)-3-phenylpropanate (29): A suspension of 1,2-dimethylindole (0.14 g, 1.0 mmol), styrene (0.31 g, 3.0 mmol), **2** (26 mg, 0.10 mmol), $CuCl_2$ (0.33 g, 2.5 mmol), and $FeCl_3$ (0.16 g, 1.0 mmol) in methanol/THF (1:1, 5 mL) under CO (1 atm) was stirred at room temperature for 1 h and concentrated under vacuum. Column chromatography of the residue (SiO_2; hexanes/EtOAc, 10:1→5:1) gave **29** (0.20 g, 64%) as a white solid. TLC (hexanes/EtOAc, 5:1): R_f = 0.35. M.p. 115–117°C. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ=7.48 (br. d, $^3J_{H,H}$=8.0 Hz, 1H; CH), 7.35 (br. d, $^3J_{H,H}$=8.0 Hz, 2H; 2CH), 7.26 (t, $^3J_{H,H}$=7.8 Hz, 2H; 2CH), 7.24 (d, $^3J_{H,H}$=8.0 Hz, 1H; CH), 7.18–7.11 (m, 2H), 7.01 (dd, $^3J_{H,H}$=7.0, 8.0 Hz, 1H; CH), 4.91 (t, $^3J_{H,H}$=7.6 Hz, 1H; CH), 3.63 (s, 3H; CH_3), 3.58 (s, 3H; CH_3), 3.37 (dd, $^3J_{H,H}$=7.2, $^2J_{H,H}$=15.6 Hz, 1H; CH_2), 3.23 (dd, $^3J_{H,H}$=8.6, $^2J_{H,H}$=15.8 Hz, 1H; CH_2), 2.43 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 25°C): δ=173.3, 144.2, 137.1, 133.8, 128.6, 127.6, 126.7, 126.3, 120.6, 119.4, 119.1, 112.8, 109.0, 51.8, 39.7, 38.4, 29.8, 10.9 ppm; IR (neat): $\tilde{\nu}$=2953, 1731, 1470, 1254, 1161, 701 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{21}NO_2$: C 78.15, H 6.89; found: C 78.23, H 6.87. The regiochemistry of **29** was established by combined COSY, HMQC, and HMBC spectroscopy (see Supporting Information).

All remaining 3-(1-aryl-2-carbomethoxyethyl)indoles depicted in Table 6 were synthesized employing a similar procedure to that used to synthesize **29**.

Acknowledgments

We are grateful to the NSF (CHE-03-04994) for support of this research. R.W. thanks the Camille and Henry Dreyfus Foundation for additional financial assistance.

[1] L. S. Hegedus, *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Sausalito, CA, **1999**.
[2] a) M. F. Semmelhack, C. Bodurow, *J. Am. Chem. Soc.* **1984**, *106*, 1496; b) M. F. Semmelhack, J. J. Bozell, T. Sato, W. Wulff, E. Spiess, A. Zask, *J. Am. Chem. Soc.* **1982**, *104*, 5850; c) J. Boukouvalas, G. Fortier, I.-I. Radu, *J. Org. Chem.* **1998**, *63*, 916.
[3] a) H. Harayama, A. Abe, T. Sakado, M. Kimura, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1997**, *62*, 2113; b) Y. Tamaru, M. Hojo, Z. Yoshida, *J. Org. Chem.* **1988**, *53*, 5731.
[4] a) L. S. Hegedus, W. H. Darlington, *J. Am. Chem. Soc.* **1980**, *102*, 4980–4983; b) G. M. Wieber, L. S. Hegedus, B. Åkermark, E. T. Michalson, *J. Org. Chem.* **1989**, *54*, 4649.
[5] a) R. A. Widenhoefer, *Pure Appl. Chem.* **2004**, *76*, 671, and references therein; b) C. Liu, X. Wang, T. Pei, R. A. Widenhoefer, *Chem. Eur. J.* **2004**, *10*, 6343; c) X. Han, X. Wang, T. Pei, R. A. Widenhoefer, *Chem. Eur. J.* **2004**, *10*, 6333; d) H. Qian, T. Pei, R. A. Widenhoefer, *Organometallics* **2005**, *24*, 287.
[6] E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578.
[7] G. Abbiati, E. M. Beccalli, G. Broggini, C. Zoni, *J. Org. Chem.* **2003**, *68*, 7625.
[8] A preliminary account of these results has been published: C. Liu, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 10250.
[9] Compound **15** was characterized on the basis of its molecular weight (*m*/*z* 253) as determined by GC/MS analysis of the crude reaction mixture. Efforts to isolate **15** in pure form were unsuccessful.

[10] This observation suggests that additional, uncharacterized intermediates are formed in the reaction of **13** with **2** and $CuCl_2$ in methanol under CO that also react under these conditions to ultimately form **14**.
[11] W. A. Remers, R. K. Brown, in *Indoles* (Ed.: W. J. Houlihan), Wiley-Interscience, New York, NY, **1972**, vol. 25, pp. 70–71.
[12] *Pyrroles* (Ed.: A. R. Jones), Wiley, New York, NY, **1990–1992**, vol. 48.
[13] a) J. R. Katzer, *Molecular sieves II: [program papers]/ACS symposium series, 40*, American Chemical Society, Washington, **1977**, pp. 16–17; b) C. K. Hersh, *Molecular Sieves*, Reinhold Pub. Corp., New York, **1961**, pp. 50–51.
[14] T. C. Flood, in *Topics in Stereochemistry, vol. 12*, (Ed.: G. L. Geoffroy), Wiley, New York, **1981**, p. 83.
[15] a) I. Dorange, J. Löfstedt, K. Närhi, J. Franzén, J.-E. Bäckvall, *Chem. Eur. J.* **2003**, *9*, 3445; b) A. M. Castaño, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1995**, *117*, 560.
[16] We thank a reviewer for suggesting this alternative mechanism.
[17] A. H. Jackson, P. P. Lynch, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1215.
[18] a) J. R. Williams, L. R. Unger, *J. Chem. Soc. D* **1970**, 1605; b) A. H. Jackson, A. E. Smith, *Tetrahedron* **1968**, *24*, 403.
[19] a) A. H. Jackson, P. Smith, *Chem. Commun. (London)* **1967**, 260; b) A. H. Jackson, B. Naidoo, P. Smith, *Tetrahedron* **1968**, *24*, 6199.
[20] E. Balogh-Hergovich, G. Speier, *J. Chem. Soc. Perkin Trans. 1* **1986**, 2305.
[21] I. Pri-Bar, J. K. Stille, *J. Org. Chem.* **1982**, *47*, 1215.
[22] a) F. Calderazzo, D. B. Dell′Amico, *Inorg. Chem.* **1981**, *20*, 1310; b) D. B. Dell′Amico, F. Calderazzo, N. Zandona, *Inorg. Chem.* **1984**, *23*, 137.
[23] In a control experiment, treatment of a suspension of $CuCl_2$ in methanol with ^{13}CO led to no detectable resonance in the ^{13}C NMR spectrum.
[24] Although **7** could be confidently discounted as an intermediate in the palladium-catalyzed conversion of **5** into **6**, we considered the possibility that an intermediate formed in the conversion of **5** into **7** might undergo rapid cyclization in the presence of **2** to form **6**. Chlorination of an indole with $CuCl_2$ is believed to occur by single electron transfer from the indole to $CuCl_2$ to form an indolyl radical cation that reacts with a second molecule of $CuCl_2$ to form the 3-chloroindole.[17] Given the mechanism of palladium-catalyzed cyclization/carboalkoxylation, it appears unlikely that an electron-deficient indolyl radical cation would undergo nucleophilic attack on palladium-complexed olefin **I** faster than a neutral indole would.
[25] D. M. Fenton, P. Steinwand, *J. Org. Chem.* **1974**, *39*, 701.
[26] T. Hosokawa, T. Uno, S. Inui, S.-I. Murahashi, *J. Am. Chem. Soc.* **1981**, *103*, 2318.
[27] D. Zargarian, H. Alper, *Organometallics* **1991**, *10*, 2914.
[28] No attempt was made to isolate **24** from this reaction mixture.
[29] a) Y.-S. Lin, A. Yamamoto, *Organometallics* **1998**, *17*, 3466; b) Y.-S. Lin, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 723.
[30] Further characterization of **IIIb** by electrospray mass spectrometry was unsuccessful.
[31] It is also noteworthy that the resonance at $\delta = 173.8$ ppm broadens considerably upon addition of **5** to the reaction mixture. Because broadening of this resonance occurs at the same time as the appearance of the resonance at $\delta = 210.4$ ppm, this broadening suggests both that acyl complex **IIIb** is a Pd/Cu heterobimetallic carbonyl complex and that the chemical shift of the carbonyl ligand(s) of this complex differs only slightly from the chemical shift of the carbonyl ligand(s) of the complex formed upon reaction of **2** with $CuCl_2$ at $\delta = 173.8$ ppm.
[32] M. G. Banwell, D. A. S. Beck, J. A. Smith, *Org. Biomol. Chem.* **2004**, *2*, 157.

Received: July 7, 2005
Revised: November 7, 2005
Published online: January 17, 2006

