C–H Bond Functionalization

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Aerobic Palladium(II)-Catalyzed 5-*endo-trig* Cyclization: An Entry into the Diastereoselective C-2 Alkenylation of Indoles with Tri- and Tetrasubstituted Double Bonds**

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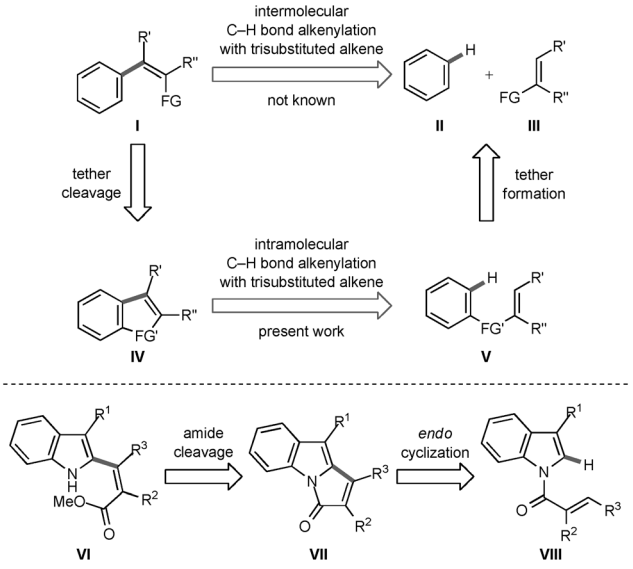
The Mizoroki–Heck reaction, that is the palladium(0)-catalyzed alkenylation of prefunctionalized arenes (or alkenes),[1] is now rivaled by oxidative palladium(II)-catalyzed processes (also referred to as Fujiwara–Moritani reactions) that involve C–H bond activation.[2] These related palladium catalyses proceed through the same C–C bond-forming step, the migratory insertion of a C–C double bond into the intermediate C(sp^2)–Pd^{II} bond. Intermolecular coupling reactions are, however, limited to unhindered alkenes. If not functionalized with a directing group,[3] di- or even trisubstituted alkenes are usually not sufficiently reactive,[4,5] and the few successful oxidative coupling reactions are associated with selectivity problems[5] (**I**⇒**II** and **III**, Scheme 1, upper). This situation changes in the intramolecular variant, in which those alkenes participate indeed in C–C couplings.[1,6] We therefore had the idea to temporarily tether a trisubstituted alkene **III** with a synthetically useful functional group to an arene **II** (**V**⇒**II** and **III**, Scheme 1, upper). Intramolecular coupling (**IV**⇒**V**, Scheme 1, upper) would then be followed by the cleavage of the tether (**I**⇒**IV**, Scheme 1, upper). The net outcome of this three-step sequence is a C–H bond alkenylation with complete control of the double bond geometry in the fully substituted alkene. For this, the planned ring closure onto the trigonal carbon atom would have to occur with *endo* selectivity, which is still the exception in oxidative palladium(II) catalysis.[7–9]

With our experience in intramolecular alkenylation (*exo* mode)[10,11] of indole C–H bonds and *exo* cyclization of α,β-unsaturated amides,[12] we designed indole **VIII** with an alkene tethered to the indole nitrogen atom by an amide group (Scheme 1, lower). Its unprecedented *endo* ring closure[9] would give the rare motif of 3*H*-pyrrolo[1,2-*a*]indole-3-ones[13] (**VII**⇒**VIII**, Scheme 1, lower). Subsequent ring-opening by cleavage of the amide linkage would provide a diastereocontrolled access to C-2 alkenylated indoles, which are hitherto not accessible by direct C–H coupling with the requisite trisubstituted α,β-unsaturated acceptors (**VII**⇒**VI**, Scheme 1, lower).[5c,d,14] Herein, we show the realization of this strategy for several alkene substitution patterns and also for functionalized indole building blocks, for example, tryptophan und tryptamine.



Scheme 1. Strategy for the diastereocontrolled formation of tetrasubstituted double bonds by "indirect" C–H bond alkenylation of trisubstituted alkenes: Application to the C-2 alkenylation of indoles (FG and FG′ = functional groups).

Our investigation began with the identification of suitable reaction conditions for the *endo* cyclization of a representative precursor (**1**→**2**, Table 1). Our previously elaborated aerobic oxidative setup[12] in the presence of pivalic acid[15] using Stoltz's $Pd(OAc)_2$–**L1** combination[11a,c,12,16] afforded fully substituted **2** in reasonable yield[17] (Table 1, entry 1). Variation of acid and solvent was only detrimental (Table 1, entries 2–4), and control experiments showed that all components of the $Pd(OAc)_2$–**L1**–acid system are necessary for the reaction (Table 1, entries 5–7). It is worth mentioning that no exocyclic alkene regioisomer is formed because competing β-hydride elimination pathways (β-H versus β′-H) are an issue in intermolecular coupling reactions of α-methyl-substituted α,β-unsaturated acceptors.[5c,d]

In analogy to the seminal work of Stoltz and co-workers,[11a,c,16a] we also tested several electronically modified pyridines (**L2**–**L7**, Figure 1). It emerged from this screening

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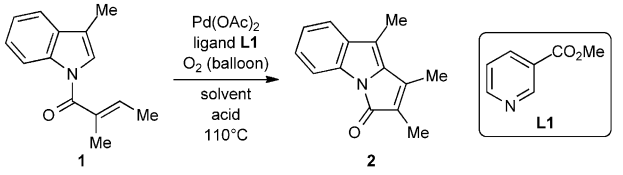
Table 1: Identification of reaction conditions.[a]



Entry	$Pd(OAc)_2$ [mol%]	Ligand **L1** [mol%]	Acid	Solvent	Conv. [%][b]	Yield [%][b]
1	10	40	$tBuCO_2H$	mesitylene	93	48
2	10	40	AcOH	mesitylene	48	12
3	10	40	$tBuCO_2H$	$tAmOH$[c]	85	30
4	10	40	$tBuCO_2H$	pinacolone	87	38
5	10	40	–	mesitylene	47	0
6	10	–	$tBuCO_2H$	mesitylene	99	10
7	–	–	$tBuCO_2H$	mesitylene	60	0

[a] All reactions were conducted by using the indicated amounts of $Pd(OAc)_2$ and **L1** under O_2 atmosphere (balloon) with a substrate concentration of 0.1 M in the indicated solvent with added acid (30 equiv) at 110°C for 12 h. [b] Both conversion and yield were determined by GLC analysis by using *n*-tetracosane as internal standard. [c] 24 h.

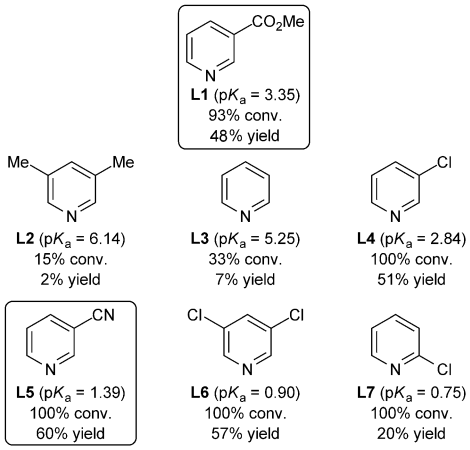
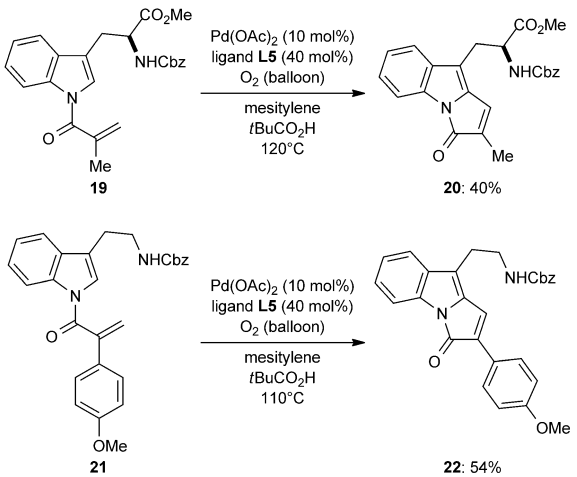


Figure 1. Screening of pyridine ligands and pK_a values of pyridines.[18]

that the basicity of the pyridine nitrogen atom has to be well-balanced. On the one hand, the palladium(II) atom coordinated by pyridine must retain its electrophilicity, which is the case for less Lewis basic pyridines, that is, those with low pK_a values (**L4**–**L7**, Figure 1). On the other hand, if the pyridine is too electron-deficient, the nitrogen atom will not be able to coordinate to the palladium(II) atom (**L7**, Figure 1). That trend is exactly seen in our survey. Yields increase substantially with decreasing pK_a values until a maximum is reached (2% for **L2** with $pK_a = 6.14$ to 60% for **L5** with $pK_a = 1.39$). Lower pK_a values afford poorer yields (20% for **L7** with $pK_a = 0.75$). We found a yield of 60% of isolated product after use of ligand **L5** sufficiently promising (Scheme 2 and Table 2).

We continued exploring the scope of the *endo* ring closure with the $Pd(OAc)_2$–**L5**–$tBuCO_2H$ system and found a few trends (**VIII**⇒**VII**, Table 2, columns 1–10). A series of trisubstituted alkene precursors were cyclized in acceptable yields at full conversion (Table 2, entries 1–8).[17] For β-aryl-substituted α,β-unsaturated amides, variation of the electronic nature of the X group in para position from donating to withdrawing resulted in longer reaction times (Table 2, entries 3–8). Yields of isolated products were generally higher with disubstituted alkenes, even at low $Pd(OAc)_2$ loadings (Table 2, entries 9–12). The substituent in the 3 position of indole had a substantial effect on the reaction rate (Me versus Ph), and a higher reaction temperature was required for the arylated indoles (110°C versus 150°C). Several of these cyclizations provide access to 1,2,9-trisubstituted 3*H*-pyrrolo[1,2-*a*]indole-3-ones in good yields.[17]

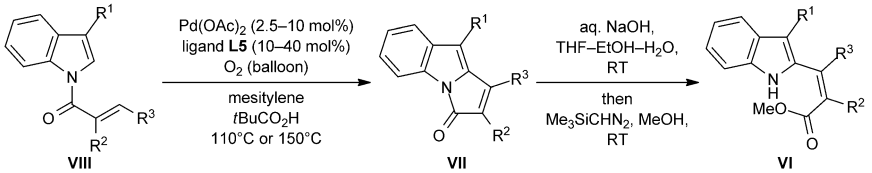
The ring-opening was accomplished by using aqueous NaOH in THF–EtOH–H_2O,[13] and the intermediate carboxylic acid was directly esterified by following a standard procedure[19] (**VII**→**VI**, Table 2, columns 7 and 8 as well as 11–13). The amide cleavage was usually slow (12 h versus 1 h), except for those substrates with an electron-withdrawing X group at the aryl substituent (F and CF_3, Table 2, entries 5 and 6). Recyclization after the esterification step was a minor side reaction but became major for the CF_3-substituted acrylic ester with a more electrophilic carboxy carbon atom (Table 2, entry 6). The geometry of the double bond was retained throughout the sequence, and all C-2 alkenylated indoles were diastereomerically pure (configuration determined by nOe measurements, see the Supporting Information for details). To test the aerobic *endo* cyclization for functionalized indoles, we subjected tryptophan- and tryptamine-derived precursors to the standard protocol (Scheme 2). Yields of isolated products were in the expected range.

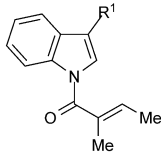
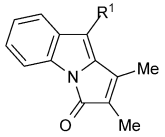
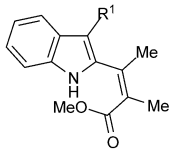
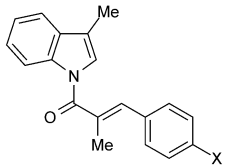
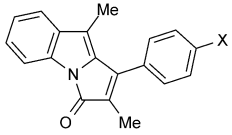
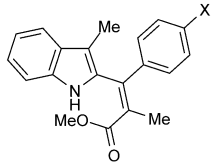
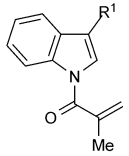
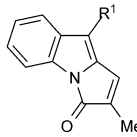
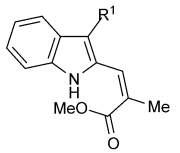
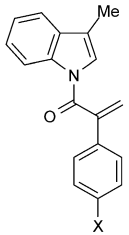
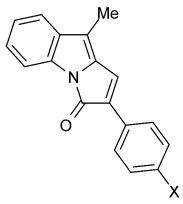
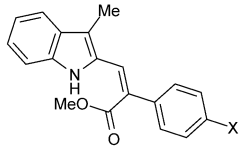


Scheme 2. Aerobic palladium(II)-catalyzed *endo* cyclizations of functionalized precursors. Cbz = benzyloxycarbonyl.

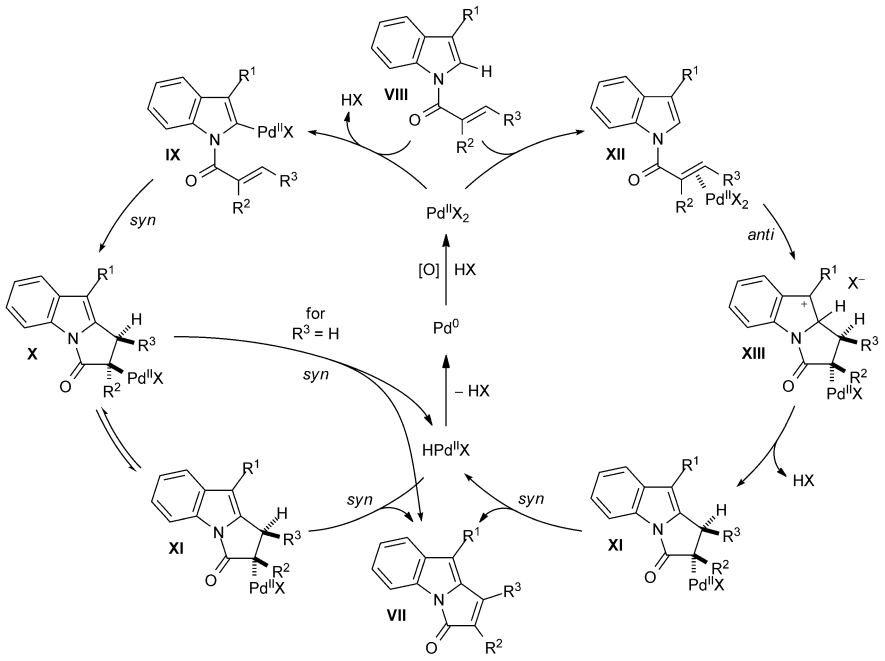
Regarding the mechanism, an in-depth investigation remains to be conducted. A useful clue as to whether C–H bond (**VIII**→**IX**, left cycle, Scheme 3) or alkene activation (**VIII**→**XII**, right cycle, Scheme 3) is involved might however be gained from a stereochemical analysis of the ring closures of those precursors with a defined double bond geometry. Both catalytic cycles are likely to proceed through stereospe-

Table 2: Aerobic palladium(II)-catalyzed *endo* cyclization and subsequent amide cleavage/ester formation.[a,b]



Entry	Cyclization precursor **VIII**	No.	$Pd(OAc)_2$ [mol%]	Ligand **L5** [mol%]	*T* [°C]	Annulated indole **VII**	No.	Conv. [%][c]	Yield [%][d,e]	Alkenylated indole **VI**	No.	Yield [%][d,f]
1		**1** (R^1 = Me)	5.0	20	110		**2**	100	60 (60)		**3**	75 (10)
2		**4** (R^1 = Ph)	10	40	150		**5**	94	41		**6**	77 (13)
3		**7a** (X = H)	5.0	20	110		**8a**	100	58 (65)		**9a**	93 (1)
4		**7b** (X = OMe)	5.0	20	110		**8b**	100	61 (69)		**9b**	93 (3)
5		**7c** (X = F)	10	40	110		**8c**	100	60		**9c**	81 (1)
6		**7d** ($X = CF_3$)	10	40	110		**8d**	97	52		**9d**	30 (61)
7		**7e** ($X = NO_2$)	10	40	110		**8e**	99	41		**9e**	—
8		**7f** (X = CN)	10	40	110		**8f**	99	40		**9f**	—
9		**10** (R^1 = Me)	2.5	10	110		**11**	100	64 (64)		**12**	80 (0)
10		**13** (R^1 = Ph)	10	40	150		**14**	99	40		**15**	76 (0)
11		**16a** (X = H)	2.5	10	110		**17a**	100	70 (74)		**18a**	66 (0)
12		**16b** (X = OMe)	2.5	10	110		**17b**	100	66 (73)		**18b**	52 (1)

[a] All cyclizations were conducted by using the indicated amount of $Pd(OAc)_2$:**L5** (1:4 ratio) under O_2 atmosphere (balloon) with a substrate concentration of 0.125 M in mesitylene with added $tBuCO_2H$ (30 equiv) at the indicated temperature overnight. [b] NaOH (30% in H_2O, 3.75 equiv) with a substrate concentration of 0.03 M in THF–EtOH–H_2O = 7:4:1 at room temperature for 12 or 1 h (amide cleavage) then Me_3SiCHN_2 (5.0 equiv) with a substrate concentration of 0.05 M in MeOH at room temperature for 5 to 180 min (esterification). [c] Conversion was determined by GLC analysis using *n*-tetracosane as internal standard. [d] Yields of isolated products after flash chromatography on silica gel. [e] Yield in parentheses refers to catalyst loading with $Pd(OAc)_2$ (10 mol%) and **L5** (40 mol%). [f] Yield in parentheses refers to reisolated annulated indole because of fast cyclization of alkenylated indole.



Scheme 3. Juxtaposition of possible mechanisms: C–H bond versus alkene activation.

cific C–C bond formation and *syn* β-hydride elimination reactions. Migratory insertion is *syn* (**IX**→**X**, left cycle) but nucleophilic addition to the activated alkene is *anti* selective (**XII**→**XIII**, right cycle). In these steps, the decisive alignment of the $C_\alpha(sp^3)$–Pd^{II} and $C_\beta(sp^3)$–H bonds is set, and *syn* elimination is only possible directly from the intermediate formed by alkene activation (**XIII**/**XI**→**VII**, right cycle). Conversely, diastereomeric intermediate **X** formed in the C–H bond-activation catalysis would have to undergo epimerization at C_α via an oxo-π-allylpalladium(II) intermediate to form **XI** prior to β-hydride elimination (**X**→**XI**→**VII**, left cycle).[20] We therefore cannot rule out either mechanism, but alkene activation appears to be a reasonable explanation for this *endo* ring closure.[2a]

Known methods for the palladium(II)-catalyzed C-2 alkenylation of indoles (or arenes) with disubstituted alkenes are often not completely diastereoselective[5,21] and alkene migration is likely to interfere.[5c,d] Our three-step sequence avoids these issues, thus allowing the C–H bond alkenylation of indoles to occur with complete diastereocontrol of the tetrasubstituted double bonds.[22] Separating the net intermolecular coupling into a ring closure and ring opening by employing a cleavable tether might be a promising strategy to access challenging substitution patterns.

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Keywords: C–H activation · cyclization · indoles · oxidative Heck reaction · palladium

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[20] An alternative pathway for $R^2 = Me$ in **X** would be β′-hydride elimination to form an exocyclic double bond (not shown) followed by alkene isomerization to endocyclic **VII**. The exocyclic isomer was however not seen in any of these cyclizations.

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[22] For an amine-catalyzed C-3 alkenylation of indole with β-substituted α,β-unsaturated aldehydes ($E/Z = 82:18 – 96:4$), see: S.-K. Xiang, B. Zhang, L.-H. Zhang, Y. Cui, N. Jiao, *Chem. Commun.* **2011**, *47*, 8097 – 8099.

