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Advancing Palladium-Catalyzed C−N Bond Formation: Bisindoline Construction from Successive Amide Transfer to Internal Alkenes

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Aminopalladation of alkenes[1] has emerged as a versatile method for the synthesis of alkyl nitrogen bonds. In contrast, alternative palladium catalysis for the direct installment of C−N bonds from alkyl−palladium η^1-amido complexes remains a challenging task.[2] The sequential combination of both approaches enables stepwise oxidative diamination of alkenes and offers new synthetic methodology toward the important class of vicinal diamines.[3] Such a sequence was recently realized for palladium(II) catalysis using ureas as tethered nitrogen sources under intramolecular reaction control.[4,5] This chemistry relies on the use of iodosobenzene diacetate as oxidant and may be understood on the basis of a high oxidation state metal intermediate.[4b,6,7] This work now presents the first examples for catalytic diamination of *internal alkenes* employing Pd catalysis. Its approach relies on simple amido groups as nitrogen source and, within an operationally convenient oxidation reaction, allows for the construction of bisindoline, bipyrrolidine, and annelated indoline heterocycles containing vicinal diamine moieties.

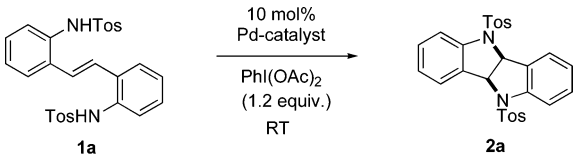
After an extensive screening of candidates for catalytic diamination with simple amides,[8] it was discovered that a precursor **1a** undergoes a highly selective diamination to form protected bisindoline **2a** (Table 1). Optimized reaction conditions for the oxidative diamination employ $PhI(OAc)_2$ as oxidant. Acetate base is required for high rate, and the combination of NMe_4Cl and NaOAc was found to be most convenient. DMF represents the optimum solvent for complete solubility of the starting material. Less polar solvents such as dichloromethane require longer reaction times due to low solubility. A quantity of 10 mol % of catalyst allowed for complete conversion during 14 h reaction time, although the reaction proceeds at lower catalyst loading as well.

It is noteworthy that the reaction is not influenced by steric or electronic factors (Table 2, eq 1). For example, sterically congested di(2,4,6-tri-*iso*-propylphenyl) derivative **1e** underwent clean diamination to yield a single isomer **2e** in 93% isolated yield, and the nosyl substitution in **1d** was similarly tolerated. The reaction is highly stereospecific and furnishes chiral C_2-symmetric products from *E*-configured alkene precursors. This stereochemistry was unambiguously confirmed by X-ray analysis of product **2a**.

The high efficiency of precursors that require formal *endo*-amination can be understood on the basis of the ligand-free, coordinatively unsaturated palladium catalyst. Palladium−tosylamide precoordination as initial step was recently established for catalytic diamination with ureas.[4b] In the present case, similar nitrogen−palladium interaction[9] is assumed to pose the path for selective *anti*-aminopalladation by the second amido group. At this state, *syn*-aminopalladation[1,5b,9,10] cannot proceed for geometrical reasons. *anti*-Aminopalladation leads to a chelation-controlled state **B**, which inhibits potential β-hydride elimination pathways in aliphatic substrates (eq 3). This complex **B** then undergoes oxidation to palladium(IV),[7] amide dissociation, and selective *anti*-amination/depalladation.[4b,11] This final step is in complete agreement with recent detailed work on a related platinum(IV) complex[12] and again proceeds with complete stereochemical selectivity. Furthermore, it constitutes the first general examples of secondary C_{sp3}−N bond formation in palladium catalysis.[10,13]

These reactions are noteworthy for the fact that the palladium catalyst exercises a remarkable flexibility throughout the course of

Table 1. Optimization of Reaction Conditions

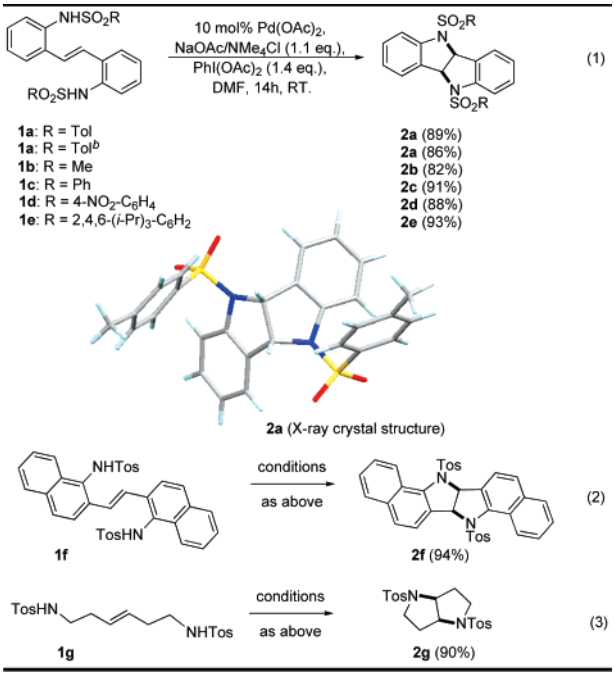


1a **2a**

entry	catalyst	solvent	base (1.1 equiv)	time (h)	yield[a] (%)
1	$Pd(OAc)_2$	CH_2Cl_2	NaOAc/Me_4NCl	36	79
2	$Pd(OAc)_2$	CH_2Cl_2/DMF	NaOAc/Me_4NCl	36	88
3	$Pd(OAc)_2$	DMF	Me_4NOAc	14	88
4	**$Pd(OAc)_2$**	**DMF**	**NaOAc/Me_4NCl**	**14**	**89**
5	$Pd(OAc)_2$[b]	DMF	NaOAc/Me_4NCl	24	74

[a] Isolated product after reductive workup and column chromatography. [b] 5 mol % catalyst loading.

Table 2. Pd-Catalyzed Bisindoline and Bipyrrolidine Synthesis[a]



[a] Yields refer to isolated material after column chromatography or crystallization and are average from at least two independent reactions (0.5 mmol scale). [b] Reaction on 5 mmol scale. Yield refers to crystallized product.

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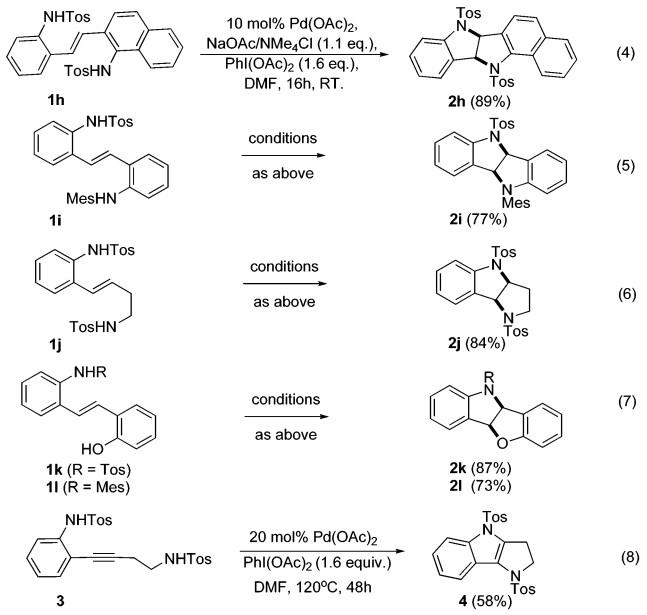
Table 3. Catalytic Oxidation of Unsymmetrical Internal Alkenes **1h**−**l** and Alkyne **3**[a]



[a] Yields refer to isolated material after column chromatography and are average from two independent reactions.

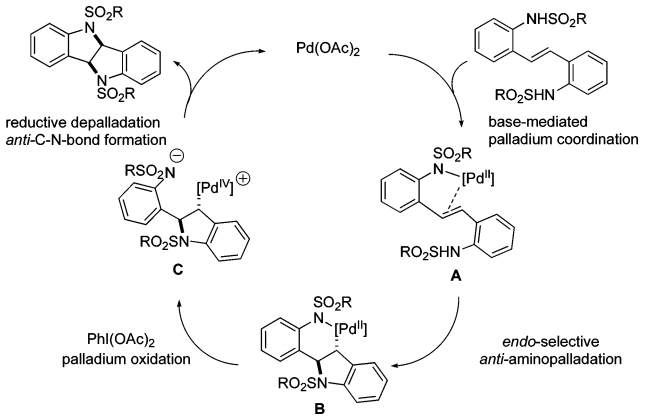


Figure 1. Proposed catalytic cycle for Pd-catalyzed diamination of **1**.

the reaction. It first catalyzes a regioselective amination of an sp^2-carbon within the initial alkene aminopalladation. Next, it installs the second C_{sp3}−N bond within a completely stereospecific amination, employing a nitrogen source of the same electronic nature. From a synthetic point, this overall sequence represents a convenient approach to heterocyclic cores such as bisindolines **2a**−**f** and bipyrrolidine **2g**.

The reaction scope can be further extended to unsymmetrically substituted stilbene derivatives and aliphatic amides (Table 3, eqs 4−6). For these cases, the product conformation again displayed the expected *syn*-positioning of the vicinal hydrogen atoms of the former alkene as deduced from the coupling constants of **2h**−**j**.[8] The application of amide−palladium interaction for alkene activation allows for the reaction of further nucleophiles within the initial step of alkene functionalization. For example, phenol derivatives **1k,l** led to clean overall aminoalkoxylation.[14,15] Finally, the idea of amide−palladium precoordination[16] was employed in the first Pd-catalyzed diamination of an alkyne (eq 8). This reaction broadens the synthetic potential of the stepwise diamination of unsaturated C−C bonds to generate annelated indole **4**.[17] Although overall related in mechanism to the alkene diamination, the reaction required significantly higher temperature. For the second C−N bond formation, this observation can be rationalized on the basis of a thermal reductive elimination from within the Pd coordination sphere[18] instead of the S_N2-type mechanism in the final step of alkene diamination (state **C**, Figure 1).

In summary, the sequential catalytic transfer of two sulfonamides to internal alkenes was shown to afford the construction of vicinal diamines. The reaction consists of two different palladium-catalyzed C−N bond formation reactions and provides convenient access to heterocyclic structures such as bisindolines, annelated indolines, and bipyrrolidines.

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Supporting Information Available: Discussion on the reaction scope, detailed experimental procedures, data for new products, and spectral characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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