Tandem Reactions

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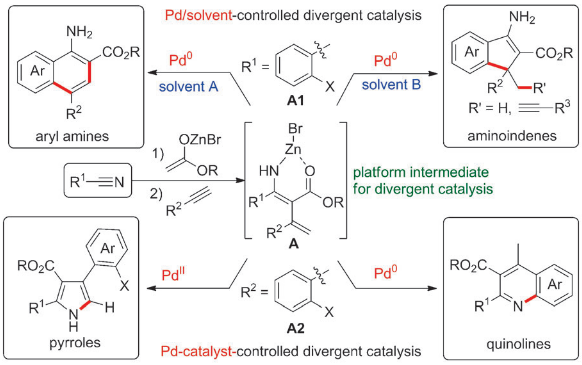
Formation of Four Different Aromatic Scaffolds from Nitriles through Tandem Divergent Catalysis**

*Ju Hyun Kim, Jean Bouffard, and Sang-gi Lee**

Abstract: *A zinc bromide complex, formed by the sequential reaction of nitriles with a Reformatsky reagent and terminal alkynes, is used as an intermediate for divergent palladium-catalyzed reactions. The reaction pathway of the intermediate is precisely controlled by the choice of the reaction solvent or the palladium catalyst to quickly form four different aromatic scaffolds—arylamines, aminoindenes, pyrroles, and quinolines—starting from readily available nitriles.*

Divergent catalytic reactions provide quick access to structurally different compounds from a common precursor through controlled reaction pathways, and are highly attractive tools in the discovery of drugs and functional materials.[1,2] A more promising, yet challenging strategy that remains largely unexplored is tandem divergent catalysis, which combines the key advantages inherent to both tandem reactions[3] and divergent catalysis to provide a rapid access to different structures from the same simple reagents while minimizing the generation of waste. In the course of our studies on the tandem use of the Blaise reaction in catalysis,[4] we envisoned that the zinc bromide complex **A**, formed by the sequential reaction of nitriles with a Reformatsky reagent and 1-alkynes,[5] may serve as a viable intermediate for divergent catalysis involving selective C–C and C–N bond-forming reactions. Herein, we report a strategy based on divergent palladium catalysis that provides four distinct compound classes—arylamines, aminoindenes, pyrroles, and quinolines—from simple nitriles (Scheme 1).[6]

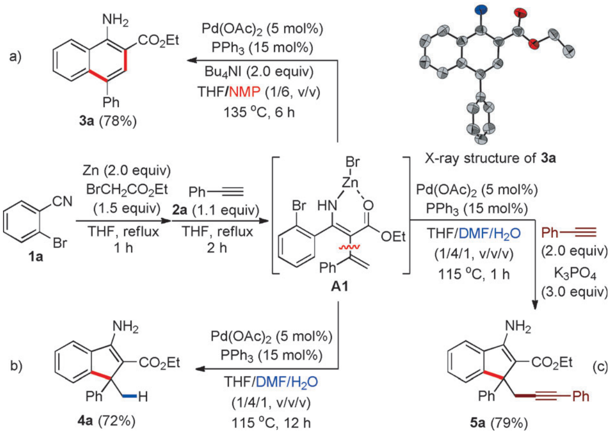
Our investigations began with the Pd-catalyzed intramolecular C–C bond-forming reactions of **A1** ($R^1 = o\text{-}C_6H_4Br$, $R^2 = Ph$), formed by the sequential reaction of 2-bromobenzonitrile, a Reformatsky reagent, and 1-phenylacetylene. When the intermediate **A1** was reacted in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ in DMF, 1-aminonaphthalene **3a** was isolated in 22% yield (entry 1, Table S1).[7,8] A cursory inspection of the skeletal framework of intermediate **A1** and 1-aminonaphthalene **3a** showed that an unusual 1,2 migration of a C–C bond had occurred.



Scheme 1. A tandem strategy for the divergent conversion of nitriles to arylamines, aminoindenes, pyrroles, and quinolines.

Optimization of the reaction parameters (Table S1) showed that the catalytically active Pd^0 species is best obtained from $Pd(OAc)_2$ (5 mol%) and PPh_3 (15 mol%), and that the outcome of the tandem catalytic reaction is determined by the reaction solvent. Ultimately, the choice of *N*-methyl-2-pyrrolidinone (NMP) in the presence of 2.0 equiv of Bu_4NI at 135 °C for 6 h was optimal for the tandem synthesis of **3a** (78% overall yield, Scheme 2a). A significant finding is the formation of aminoindenene **4a** when the tandem reaction is conducted in DMF/H_2O. Rather than merely accelerating the reduction of $Pd(OAc)_2$ to Pd^0,[9] the tandem catalytic reaction pathways of **A1** in this solvent mixture are redirected to give the hydrodehalogenated aminoindene **4a** in 72% yield (Scheme 2b).[10]

These results point toward a Heck-type 5-*exo*-trig carbopalladation, giving the σ-bonded complex **B** as a second



Scheme 2. Pd/solvent-controlled selective tandem synthesis of 1-aminonaphthalene **3a** and indenes **4a** and **5a** from a common nitrile **1a**.

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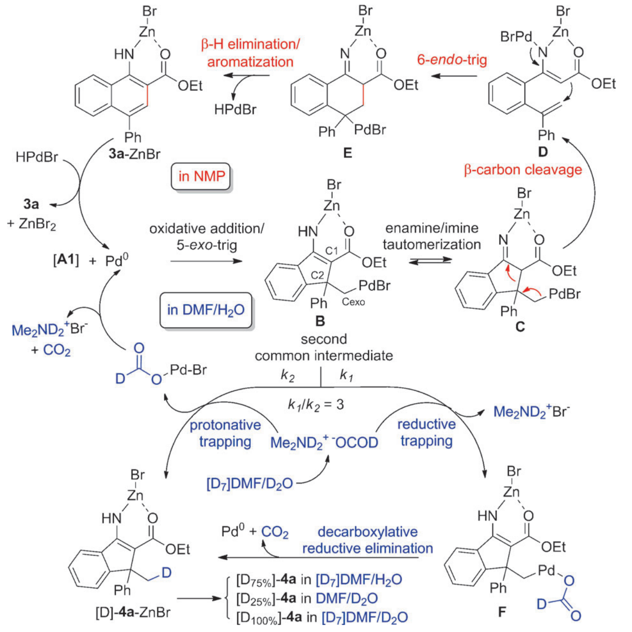


Scheme 3. Proposed reaction pathways for the formation of **3a** in NMP and **4a** in DMF/H$_2$O.

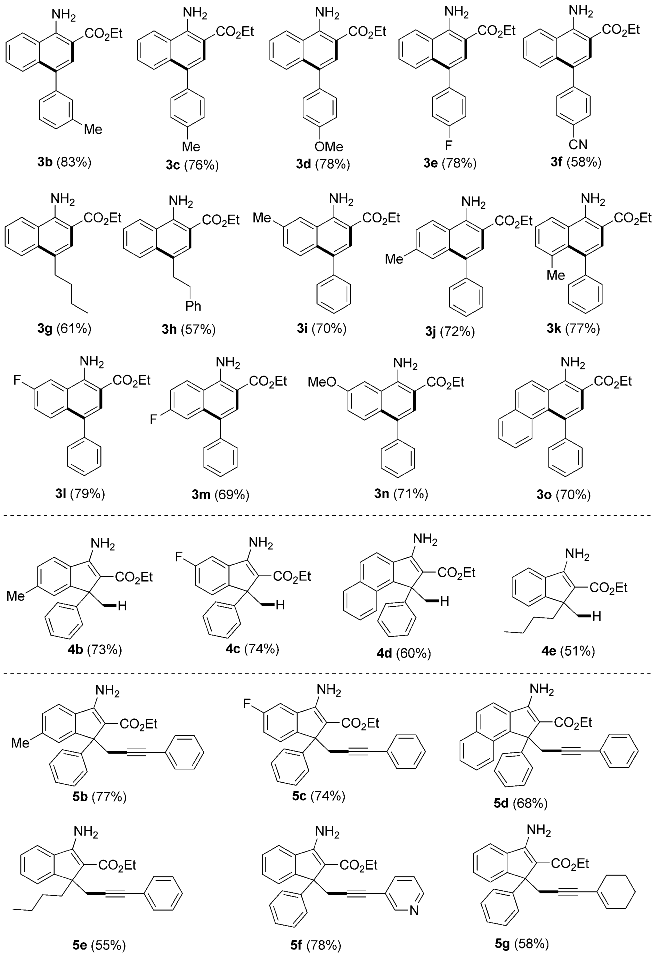
common intermediate,[11] which may be in equilibrium with its imine tautomer **C** (Scheme 3). In the absence of β-hydrogen atoms, a β-carbon cleavage from **C** (C1−C2 bond cleavage), which affords the stabilized palladium enolate, is among plausible reaction pathways.[12–13] The latter would undergo a subsequent 6-*endo* cyclization of **D**, forming the C_{exo}−C1 bond, and β-H elimination/aromatization would afford **3a**-ZnBr and HPdBr. Closure of the catalytic cycle would then occur upon regeneration of Pd^0 and liberation of aminonaphthalene **3a**, as observed in NMP as solvent. The formation of aminoindene **4a** in DMF/H$_2$O is ascribed to the protonative and reductive trappings of alkylpalladium **B**.[14] When the same reaction was conducted in deuterium-labelled [D$_7$]DMF/H$_2$O, 75 % deuterium was incorporated in place of one of the protons in the exocyclic methyl group, implying the intermediacy of a palladium formate such as **F**, which undergoes decarboxylation followed by reductive elimination to afford the deuterium labeled [D$_{75\%}$]-**4a**. Reactions performed in DMF/D$_2$O and [D$_7$]DMF/D$_2$O gave 25 % and 100 % deuterium incorporation, respectively, in **4a**. These labeling experiments suggest that dimethylammonium formate, generated from DMF and H$_2$O, can effect either the protolysis of **B** or its reduction with a rate ratio of $k_1/k_2 = 3$.[15]

The intermediacy of σ-carbopalladate **B** offers an additional opportunity for increasing the diversity of aminoindenes obtained in this tandem reaction if its interception with a suitable carbon nucleophile occurs at a rate competitive with the hydrodehalogenation sequence. To our delight, the tandem Pd-catalyzed reaction of **A1** with 2.0 equivalents of phenylacetylene in the presence of 3.0 equivalents K$_3$PO$_4$ in DMF/H$_2$O satisfied these requirements, affording **5a** in 79 % yield within 1 h (Scheme 2c).

Under these reaction conditions, various kinds of aminonaphthalenes **3**, aminoindenes **4**, and the alkynylated aminoindenes **5** can be selectively synthesized from nitriles (Table 1). The tandem reaction of **A1**, prepared starting from 2-bromobenzonitrile with phenylalkynes that bear either electron-donating or electron-withdrawing groups afforded the corresponding 1-aminonaththalenes **3b**–**3f** in excellent yields. Alkyl alkynes such as 1-hexyne and 4-phenylbutyne were also successfully incorporated to provide 4-alkyl-substituted 1-aminonaphthalenes **3g** and **3h**, albeit with slightly lower yields. Variation of the nitrile moiety enabled the rapid synthesis of polysubstituted arylamines **3i**–**3o** in excellent yields in a tandem one-pot manner. Switching to the conditions optimized for the trapping of **B** gave aminoindenes with methyl (**4a**–**4e**) and phenyl propargyl (**5a**–**5e**) substituents from the same nitriles and alkynes. The incorporation of 3-ethynylpyridine (**5f**) and cyclohexenyne (**5g**) groups highlights the rapid generation of molecular diversity through these tandem one-pot catalytic sequences.

We also anticipated that the intermediate **A2**, generated using 2-chloroaryl alkynes, may serve as a common precursor for catalyst-controlled selective C−N bond-forming reactions to provide both pyrroles **6** and quinolines **7** selectively,

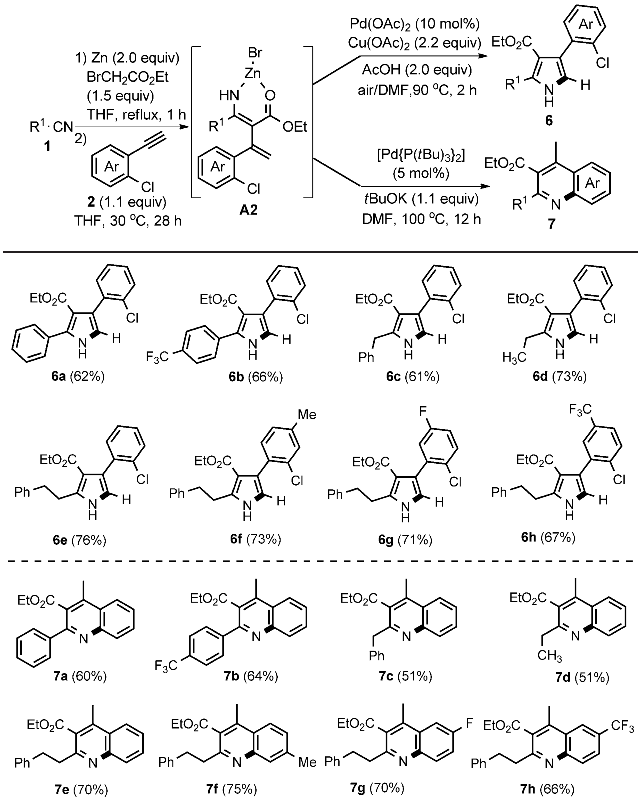
Table 1: Tandem synthesis of arylamines and aminoindenes from nitriles.[a]



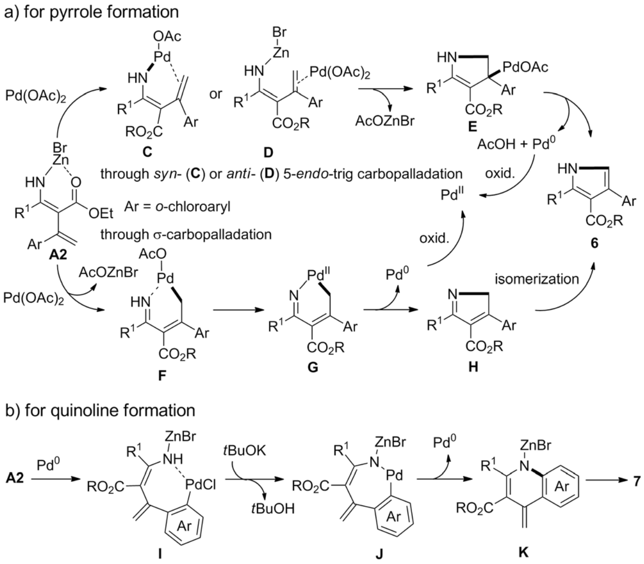
[a] For details on the reaction conditions, see the Supporting Information. Yields of isolated products are given.

through oxidative intramolecular olefin amination[16] and redox-neutral arylamination reactions,[17] respectively. After screening different reaction conditions (see Table S2), we found that the treatment of intermediate **A2**, generated from benzonitrile and *o*-chlorophenylacetylene, with 10 mol% Pd(OAc)$_2$ in the presence of Cu(OAc)$_2$ (2.0 equiv) and AcOH (2.0 equiv) in DMF at 90°C for 2 h afforded pyrrole **6a** selectively in 62% yield.[18,19] The catalytic reaction pathway of **A2** can be redirected by using a Pd^0 catalyst ligated with a sterically hindered electron-rich phosphine, [Pd{P(*t*Bu$_3$)}$_2$] (5 mol%), and *t*BuOK (1.1 equiv) at 100°C in DMF to afford quinoline **7a** in 60% yield.[20] With a set of optimized reaction conditions in hand for the selective synthesis of pyrroles **6** and quinolines **7**, several pairs of these heterocycles were successfully synthesized through tandem reactions of the intermediate **A2**, generated from various nitriles **1**, a Reformatsky reagent, and 2-chloro arylacetylene **2** (Table 2).

Table 2: Tandem Pd-catalyst-controlled divergent conversion of common nitriles to pyrroles **6** and quinolines **7**.[a]



[a] For details on the reaction conditions, see the Supporting Information. Yields of isolated products are given.



Scheme 4. Proposed mechanisms for the formation of a) pyrroles **6**, and b) quinolines **7**.

Mechanistic proposals for the formation of pyrroles **6** and quinolines **7** are outlined in Scheme 4. For the formation of pyrrole **6** (Scheme 4a), the transformation begins with a ligand substitution with Pd(OAc)$_2$, resulting in aminopalladate complex **C**. A 5-*endo*-trig cyclization[21] through either a *syn* or *anti* aminopalladation of **D** gives the intermediate **E**, and subsequent β-H elimination affords pyrroles **6**. The Pd^{II} species can be regenerated by oxidation of Pd^0 with Cu(OAc)$_2$ and O$_2$/AcOH.[22] Nucleophilic substitution pathways forming the γ-C-palladate **F**, followed by nucleophilic substitution, reductive elimination, and isomerization in sequence cannot be ruled out at present. For the formation of quinoline through a typical Buchwald–Hartwig catalytic cycle (Scheme 4b), oxidative addition of Pd^0 to Ar-Cl first affords **I**. Deprotonation of the amine with *t*BuOK forms **J**, which leads to Pd^0 and N-arylated **K** through reductive elimination. Finally, the latter undergoes aromatization to produce the targeted quinoline **7**.

In summary, we have developed tandem divergent catalytic methods for the selective conversion of simple nitriles to four distinct classes of aromatic compounds. The zinc bromide complexes of β-enaminoesters, generated by the sequential reaction of nitriles with a Reformatsky reagent and 1-alkynes, are used as common intermediates. The catalytic reaction pathways of the intermediates are precisely controlled by a simple change of the reaction solvents or palladium catalysts to selectively afford arylamines, aminoindenes, pyrroles, and quinolines. This tandem divergent catalytic approach is shown to be particularly useful to rapidly elaborate simple molecules into different complex structures.

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Communications

Tandem Reactions

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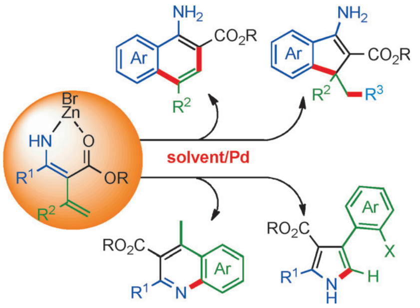
Formation of Four Different Aromatic Scaffolds from Nitriles through Tandem Divergent Catalysis



Four roads diverged: A zinc bromide complex, generated by the sequential reaction of nitriles with a Reformatsky reagent and 1-alkynes, is used as an intermediate for divergent palladium-catalyzed reactions. The reaction pathway depends on the choice of reaction solvents and palladium catalysts. The method provides a simple and efficient approach to four different frameworks starting from readily available nitriles.