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Diastereoselective Synthesis of Dibenzoazepines through Chelation on Palladium(IV) Intermediates

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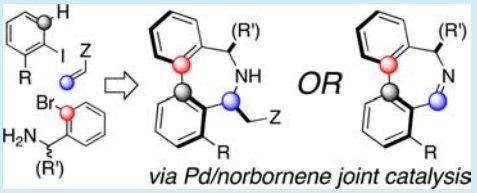
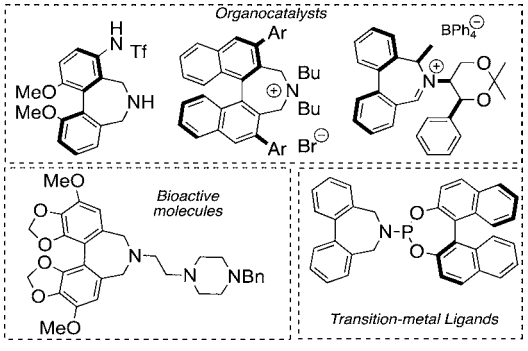
Supporting Information

ABSTRACT: Joint palladium/norbornene organometallic catalysis allows for straightforward access to dibenzo[*c*,*e*]azepines. These synthetically challenging polycyclic frameworks form in one pot via a three-component coupling of an aryl iodide, a bromobenzylamine, and an olefin. A key, atroposelective aryl−aryl coupling from chelated Pd(IV) intermediates dictates the outcome of the cascade. DFT modeling sheds light on the complex mechanism that allows the complete diasteroselectivity to be observed.



Palladium catalysis is a powerful synthetic tool for the synthesis of complex nitrogen-containing polycyclic frameworks from readily available precursors.[1] A broad domain of applications has indeed stimulated the development of a variety of methods to create 5- and 6-membered (poly)heterocycles. Sequences affording the 7-membered azepine ring are far less developed.[2] Beside their renowned biological properties,[3] dibenzo[*c*,*e*]azepines in particular are at the heart of versatile organocatalysts and ligands (Scheme 1).[4] Their preparation

Scheme 1. Applications of Dibenzo[*c*,*e*]azepines

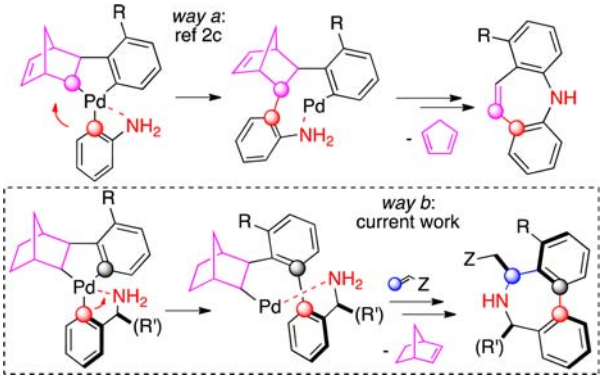


requires multistep syntheses, and access to functionalized frameworks is often costly. This affects the readily accessible pool of structures and thus ultimately limits the development of novel ligands, organocatalysts, and bioactive molecules incorporating this core.

The association of palladium and norbonene forms a unique dual organometallic catalytic system able to deliver complex polycyclic structures from simple precursors. Its versatility has led to numerous synthetic applications in the last 20 years, mainly reported by the group of Catellani and Lautens.[5,6]

We present herein the first catalytic method for the diastereoselective one-pot synthesis of dibenzo[*c*,*e*]azepines from commercially available precursors by exploiting the properties of chelation[5b,c] on in situ generated Pd(IV) intermediates. Previous studies have revealed that a suitable chelating group can control the chemoselectivity of Pd(IV) reductive elimination (Scheme 2, way *a*).[2c] Herein we used

Scheme 2. Pd(IV) Strategies to Dibenzoazepines



chelation as a relay to induce an atroposelective aryl−aryl coupling and then prevent rotation around the biaryl axis until a Heck reaction occurred, paving the way for a stereospecific aza-Michael cyclization that eventually delivered target azepines (Scheme 2, way *b*).

In an initial experiment (Table 1, entry 1), iodotoluene (1.1 equiv) reacted with bromobenzylamine and acrylonitrile (4 equiv) in the presence of 5 mol % of $Pd(OAc)_2$, 10 mol % of trifurylphosphine, and 60 mol % of norbornene in DMF at 130 °C under argon for 24 h. Azepine **1** was isolated (in a low 5% yield) together with its imino derivative **2** formed via retro-Mannich elimination of acetonitrile (6%, vide infra) and 8% of **3**, the analogue of **1** *N*-alkylated by a second olefin molecule.

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Table 1. Optimization of Reaction Conditions[a]

entry	ligand	yield of **1a** (%)	entry	ligand	yield of **1a** (%)
1[b,c]	P(2-furyl)$_3$	5	4	PEt_3	62
2	P(O-*i*-Pr)$_3$	55	5	P(*i*-Pr)$_3$	75
3	PMe_3	51	6[d]	P(*i*-Pr)$_3$	65

[a]Reaction conditions: $Pd(OAc)_2$ 5 mol %, 0.02 M, ligand 10 mol %, norbornene 60 mol %, Ar–I 0.29 mmol, 1.1 equiv, olefin 2 equiv, K_2CO_3 2.2 equiv in DMF under Ar at 130 °C for 24 h. ^{1}H NMR yield using benzoylnitromethane as internal standard. [b]With 4 equiv of olefin. [c]With Cs_2CO_3. [d]2.5 mol % of Pd for 36 h.

Phosphorus ligands possessing alkyl substituents provided better results (entries 3–5). In particular, the use of 10 mol % of trisisopropylphosphine delivered **1a** in 75% yield (entry 5). Palladium could be reduced to 2.5 mol %, although a longer reaction time slightly favors formation of imine product **2a**, lowering the yield to 65% (entry 6). Conversion of the iodide partner was always complete, direct Heck-type coupling with the olefin being the most concerning side reaction. By way of contrast, unreacted aryl bromide could be recovered at the end of these experiments.

We tested the method toward differently substituted aryl halides and olefins (Figure 1). Gratifyingly, product **1a** could be

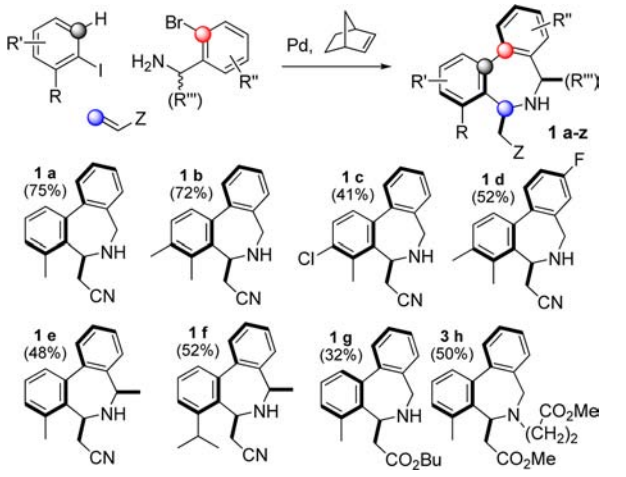

Figure 1. Reaction conditions: as entry 5 of Table 1 for 8–16 h. Isolated yields on average of at least two runs: (a) 1.1 equiv of olefin; (b) 4 equiv of olefin added after full conversion.

isolated in 75% yield, after 8 h, as a single diastereoisomer. Different donor groups, including aliphatic chains or ethers, were tolerated by the sequence and delivered **1** in synthetically useful yields compared to existing multistep procedures. Electron-withdrawing groups were less tolerated on the aryl iodide (**1c**, 41%) than on the bromide partner (**1d**, 52%). We were delighted that the reaction of racemic bromides delivers **1e** and **1f** as a single diastereomer out of the four possible (the unreacted bromide recovered at the end of these reactions did not present any enantiomeric excess).[7] Less volatile acrylates could be used in stoichiometric amounts (**1g**, 32%). Further addition of the olefin, upon full conversion, delivered *N*-alkylated product **3h** in 50% yield. In all of these reactions, minor amounts of **2** and **3** were invariably observed (less than 10% each).

By using an enolizable olefin such as methyl vinyl ketone, a retro-Mannich reaction on **1** smoothly occurs under the reaction conditions, selectively delivering **2** and thus off-setting the nitrogen alkylation responsible for the formation of **3** (Figure 2). Electron-donating groups such as alkyl chains,

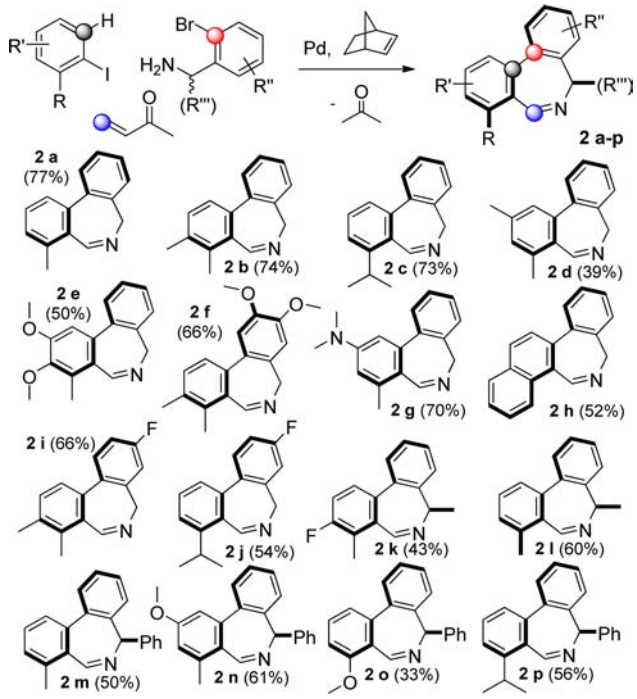

Figure 2. Conditions: as Figure 1, with 4 equiv of olefin for 24 h; isolated yields on the average of at least two runs.

ethers, and amines or a fused aromatic fragment are generally well tolerated on both halides (**2a–h**). Fluorinated bromides react smoothly (**2i,j**), providing higher yields than a fluorine-substituted iodide (**2k**, 43%). Reaction of racemic amines affords the corresponding products **2** as a single diastereomer in synthetically useful yields (**2k–p**).

Previous studies[5,6] and our present DFT-based analysis suggest that the mechanism of Scheme 3 is at work in these sequences. Complex **I** forms, upon Ar–I oxidative addition and subsequent insertion of norbornene, intermediate **II**. C–H activation readily occurs in the basic environment,[8] and electron-rich metallacycle **III** can thus undergo a second oxidative addition to chelated Pd(IV) complex **IV**.[2c,5] Chemoselective, nonreversible sp^2–sp^2 coupling provides **V**. Nitrogen chelation is retained and prevents rotation of the biaryl axis. This key feature is kept in **VI** that forms by steric congestion-driven extrusion of norbornene. A careful tuning of the reaction conditions then allowed us to offset the *intramolecular* Buchwald–Hartwig coupling previously exploited to synthesize dihydrophenanthrines using these coupling partners.[9] An *intermolecular* Heck reaction can instead occur and generate **4**.[10] The relative conformation of the biaryl is responsible for the stereoselectivity of the aza-Michael cyclization and eventually delivers **1** as a single diastereomer. Release of the *syn*-pentane steric strain in **1** could induce a retro-Mannich reaction in the basic media leading to **2**. While chelation has been already used as a relay to induce atroposelective formation

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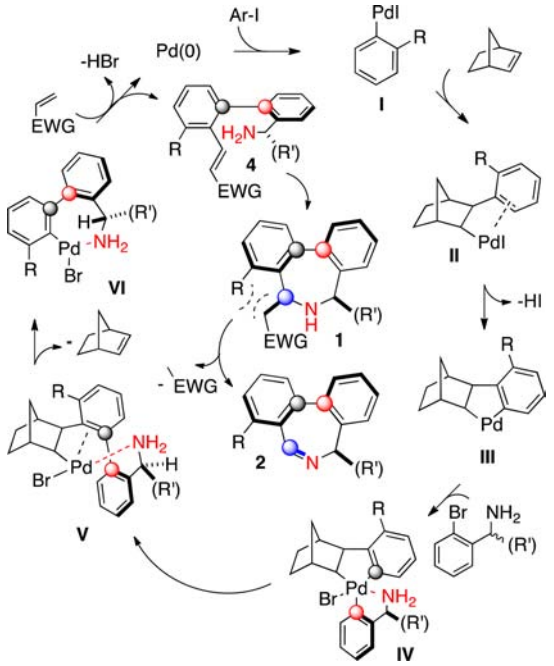
Scheme 3. Proposed Mechanistic Rationale



of biaryls,[11] to the very best of our knowledge this would be the first application of this strategy in Pd(IV) sequences. Indeed, Pd/norbornene-cocatalyzed cascades are reported to afford products as mixture of diastereoisomers in the absence of a chelating group on substrates.[12]

Among modeled pathways, most relevant mechanistic features are highlighted hereafter with full details provided in the Supporing Information. Formation of **1** as a single out of four possible diastereomers employing racemic bromides relies on discrimination in energetic barriers before the nonreversible C−C bond formation of the Pd(IV) reductive elimination. Figure 3 shows calculated pathways for the (*R*)- and (*S*)-bromide on the enantiomer of the Pd(II)metallacycle **III**. Lower energy intermediates from **III** are those in which both its

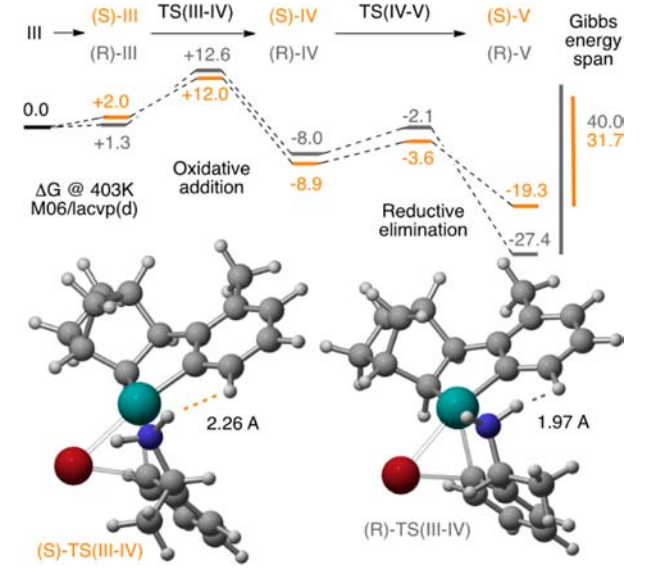


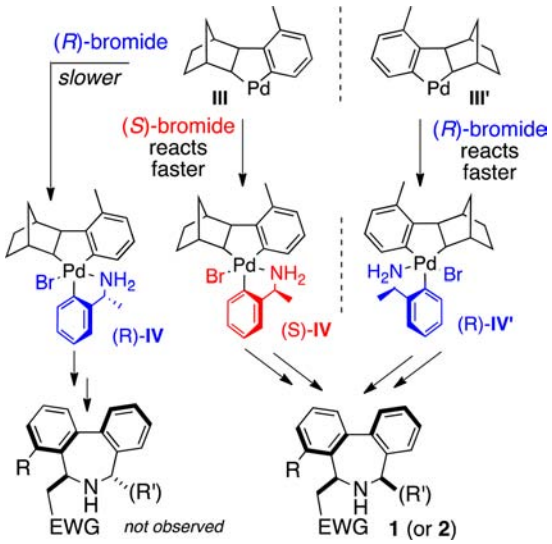
Figure 3. Calculated pathways for the reaction of (*R*)- and (*S*)-methyl-2-bromobenzylamine with palladacycle **III**.

equatorial ligands are displaced by the substrate, providing square-planar complexes **(S)-III** and **(R)-III** (trimethylphospine used in calculation). Oxidative addition slightly favors the reactivity of the (*S*)-bromide (orange pathway, $\Delta\Delta G$ of −0.6 kcal/mol between the two transition states), delivering Y-distorted, trigonal bipyramidal Pd(IV) complex **(S)-IV**. Pentacoordinated high-valent palladium complexes are often more reactive than their octahedral counterparts.[5a,13]

The subsequent reductive elimination is also easier (by 1.5 kcal/mol in ΔG). Furthermore, intermediate **(S)-V** is less stable than its **(R)-V** diastereomer by 8.1 kcal/mol. All these features contribute to a lower energy span for the orange pathway over the grey one (by 8.3 kcal/mol in ΔG), and thus, the turnover frequency of the former outpaces its peer.[14] Steric reasons are responsible for these energetic differences, as shown by short contacts highlighted for two competing oxidative addition transition states on **III** (0.29 Å longer in the favored TS, left).

This situation is reversed for the enantiomer of complex **III**, on which the (*R*)-bromide reacts faster instead (**III′**, Scheme 4). The mechanism thus resembles a parallel kinetic

Scheme 4. Parallel Kinetic Resolution of Racemic Bromides



resolution[15] in which each enantiomer of a racemic substrate reacts faster with a particular enantiomer of the in situ generated Pd(II) metallacycle. A similar outcome in Pd(IV) sequences has not been reported yet.

Metal chelation is then retained up to the release of **4**. Indeed, both norbornene extrusion from **V** and the subsequent Heck coupling on **VI** are more favorable pathways than the corresponding biaryl rotations that require the release of nitrogen coordination. This is consistent with the experimentally observed diastereoselectivity, as rotation of the benzylamine fragment would ultimately deliver a mixture of diastereoisomers, observed in similar cascades employing nonchelating halides.[12] The most favorable rotation barrier is expectedly found examining **4**, which is the least sterically hindered intermediate. Its calculated transition state is nevertheless energy demanding (+27.6 kcal/mol in ΔG) and easily outmatched by a base-mediated aza-Michael cyclization (ΔG +3.9 kcal/mol), which locks the configuration of products to prevent the formation of diastereomers.

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In summary, we have developed a one-pot catalytic method for the synthesis of dibenzo[*c*,*e*]azepines and their imine analogues via palladium/norbornene joint organometallic catalysis. The complete distereoselectivity observed originates from a chelated Pd(IV) complex via atroposelective aryl−aryl coupling. This behavior is coupled with a parallel kinetic resolution-like mechanism that employs racemic bromides and exerts the same remarkable selectivity. We hope that these findings will benefit the future design of (dia)stereoselective Pd/norbornene arylation cascades and contribute to spreading further the applications of dibenzo[*c*,*e*]azepines.

■ ASSOCIATED CONTENT

Supporting Information

X-ray of **2i** (CIF), detailed computational studies, experimental procedures, and spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) A 1:1 mixture of diastereomers was instead obtained employing L-menthyl acrylate with an aryl iodide and either bromobenzylamine or a substituted, racemic one. For an in-depth DFT-based rationalization, vide infra, see the Supporting Information.

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