Urea Ligand-Promoted Chainwalking Heteroannulation for the Synthesis of 6- and 7-membered Azaheterocycles

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Abstract:. Typical approaches to heterocycle construction require significant changes in synthetic strategy even for a change as minor as increasing the ring size. The ability to access multiple heterocyclic scaffolds through a common synthetic approach, simply through trivial modification of one reaction component, would enable facile access to diverse libraries of structural analogues of core scaffolds. Here, we show that urea-derived ligands effectively promote Pd-mediated chainwalking processes to enable remote heteroannulation for the rapid construction of six- and seven-membered azaheterocycles under essentially identical reaction conditions. This method demonstrates good functional group tolerance and effectively engages sterically hindered substrates. In addition, this reaction is applicable to target-oriented synthesis, demonstrated through the formal synthesis of antimalarial alkaloid galipinine.

The ubiquity and importance of nitrogen-containing heterocycles in medicinally relevant, small organic molecules has inspired a plethora of synthetic methods to enable their construction.[1,2] Despite this, some general synthetic challenges remain. Most consequentially, the ability to rapidly generate libraries of structural analogues is hampered by the fact that even a change as simple as increasing the ring size (e.g., indoline to tetrahydroquinoline) typically requires a completely distinct approach, with non-overlapping precursors and synthetic routes (Figure 1A).[3] In addition, the most common approaches to generating aliphatic heterocycles such as indolines, tetrahydroquinolines (THQs), and benzazepines often rely on either modification of a pre-existing heterocyclic core (e.g., reduction of quinoline) or intramolecular cyclization, limiting the potential for efficient diversification of such structures.[4] An alternative strategy, wherein a trivial modification of one substrate in a fragment coupling-based approach, would enable the modular and convergent construction of a range of differently-sized azaheterocycles.

Transition metal-catalyzed heteroannulation of ambiphilic coupling partners with olefins is an attractive transformation for the synthesis of heterocycles.[5] In principle, variation of either one of the starting materials could provide access to a diverse range of heterocyclic products. Although there have been a number of notable methodological developments in the forty years since the reaction was first reported, a limitation to the synthesis of five-membered rings has largely remained. The limited examples of using olefin heteroannulation to access six-membered rings have typically entailed lengthening the backbone of the ambiphile, which encounters the same issue as other common heterocycle synthesis approaches of requiring a distinct synthetic route to the relevant substrate that was described above.[6] Additionally, seven-membered rings are

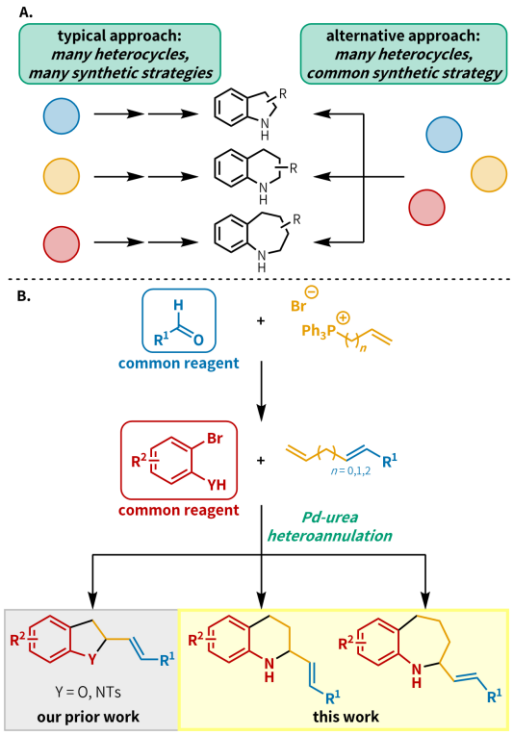

Figure 1. Approaches to heterocycle synthesis. (A) Typical approaches to heterocycle synthesis require distinct synthetic routes for even seemingly subtle changes like ring size; alternatively, a unified synthetic strategy could enable access to diverse heterocycles from common starting materials. (B) Olefin heteroannulation promoted by urea ligands enables rapid construction of 5-, 6-, and 7-membered rings with trivial modifications to one reaction component.

generated in poor yields. An alternative strategy could be achieved by exploiting the tendency of palladium to undergo chainwalking, leading to a more remote η^3-allyl complex that upon ring closure would generate larger rings. This chainwalking strategy has been used to achieve a range of elegant remote functionalization reactions of olefins,[7] most recently through "redox relay" Heck reactions.[8] The key advantage of this chainwalking strategy for heteroannulation is the ability to use common starting materials and a unified methodological approach to access multiple heterocyclic cores.

Our group recently reported that ligands derived from urea could promote the Pd-catalyzed heteroannulation of 2-

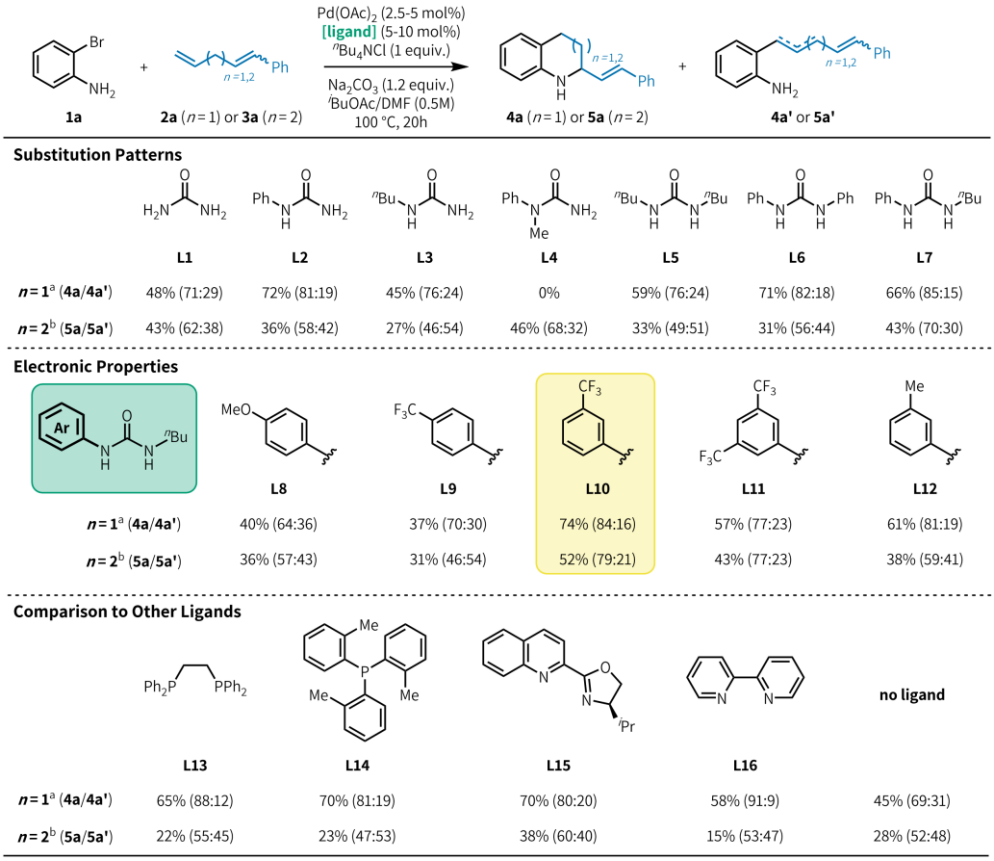

Figure 2. Ligand investigations. Yields determined by GC using dodecane as an internal standard and are an average of three runs. Reported yields are of products **4a** or **5a**, respectively. Reaction conditions: **1a** (0.500 mmol), **2a** or **3a** (1.00 mmol), $Pd(OAc)_2$, ligand, $^nBu_4NCl$ (0.500 mmol), Na_2CO_3 (0.600 mmol), ^{t}BuOAc/DMF (0.5M), 100 °C, 20h. [a] 2.5 mol% $Pd(OAc)_2$, 5 mol% ligand, 9:1 ^{t}BuOAc/DMF. [b] 5 mol% $Pd(OAc)_2$, 10 mol% ligand, 1:3 ^{t}BuOAc/DMF.

bromoanilines and 2-bromophenols with 1,3-dienes to access indoline and dihydrobenzofuran products (Figure 1B).[9] The most notable feature of this urea-enabled heteroannulation methodology was the ability to engage functionally and structurally diverse coupling partners, most notably with a unique tolerance for sterically-demanding substrates. We hypothesized that these urea ligands, which upon coordination in the presence of base generate an anionic Pd complex, would be effective at promoting chainwalking processes, allowing us to engage nonconjugated dienes in heteroannulation reactions. Here, we describe the successful implementation of this strategy, demonstrating that 1,4- and 1,5-dienes can be engaged in heteroannulation reactions, providing rapid access to functionalized THQs and benzazepines, the latter of which are particularly challenging to construct using any existing synthetic approaches.

Using 2-bromoaniline **1a** and either 1-phenyl-1,4-pentadiene **2a** or 1-phenyl-1,5-hexadiene **3a** as model substrates for chainwalking heteroannulation, we examined the effects of urea ligand structure on the desired reactivity (Figure 2). The reaction was most sensitive to the degree of substitution on the urea. While monosubstituted arylureas (**L2**) were effective for the synthesis of THQ **4a**, the more challenging benzazepine product **5a** was obtained in much lower yield and poor chemoselectivity; neither electronic nor steric modifications to this ligand class led to improved yields of desired product (**L3**, **L4**). 1,3-dialkyl- and arylureas (**L5**, **L6**) led to modest product yields and poor chemoselectivity, but aryl-alkylurea **L7** showed promising results for generating both **4a** and **5a**. Electron-rich urea **L8** afforded products in modest yield and poor chemoselectivity; switching to electron-poor *para*-trifluoromethyl substitution did not lead to any improvements (**L9**), but *meta*-trifluoromethyl-substituted urea **L10** was effective for both THQ and benzazepine synthesis, affording products **4a** and **5a** in good yields and reasonable chemoselectivity over undesired elimination products **4a'** and **5a'**. Adding a second trifluoromethyl group (**L11**) did not lead to further improvement in product yield, and the poorer performance with *meta*-tolyl urea **L12** suggests the effect is electronic and not steric.

As described above, there have been decades of development of Pd-catalyzed reactions that involve chainwalking processes to enable remote functionalizations of olefins.[7,8] We compared our urea-enabled methodology to several distinct ligand classes that have been highly effective in previously reported chainwalking processes. All these ligands (**L13-L16**) are comparable to urea ligand **L10** for the synthesis of THQs for both product yield and chemoselectivity. However, for the more challenging benzazepines they are unable to

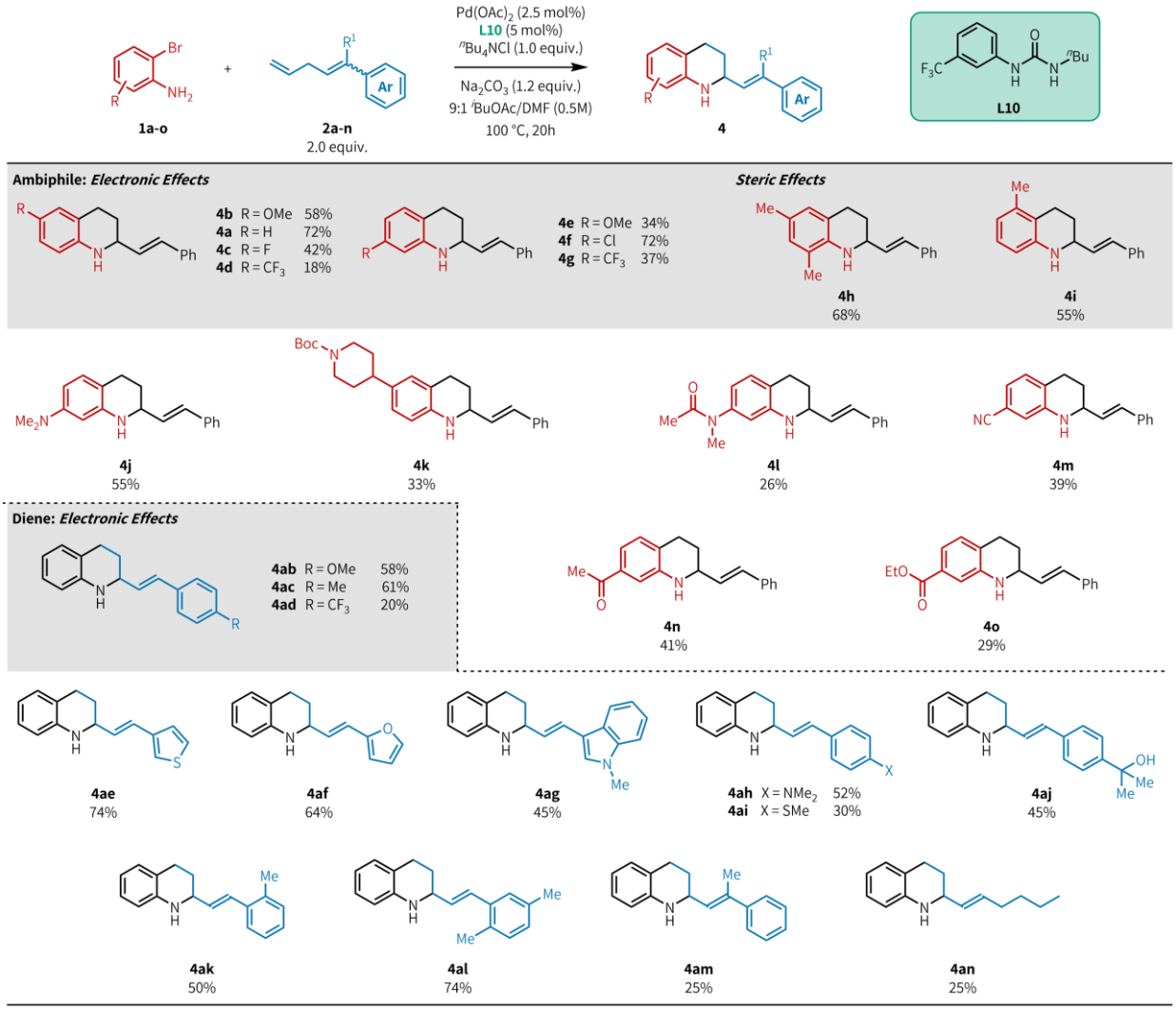

Figure 3. Substrate scope for tetrahydroquinoline (THQ) synthesis. Yields correspond to isolated products and are an average of three runs. Reaction conditions: **1** (0.500 mmol), **2** (1.00 mmol), $Pd(OAc)_2$ (0.0125 mmol), **L10** (0.025 mmol), $^nBu_4NCl$ (0.500 mmol), Na_2CO_3 (0.600 mmol), 9:1 ^{t}BuOAc/DMF (0.5M), 100 °C, 20h. [a] 5 mol% $Pd(OAc)_2$, 10 mol% ligand.

maintain useful levels of desired heteroannulation reactivity, with particularly poor chemoselectivity, while urea ligand **L10** showed minimal loss of chemoselectivity.

We next investigated the scope of this methodology, starting with 2-bromoaniline substrates (Figure 3). Notably, we found that unprotected bromoanilines are most effective in the chainwalking heteroannulation reaction, thus obviating the requirement for pre-installing a protecting group on nitrogen. Under optimized conditions, diene **2a** and 2-bromoaniline **1a** cyclize to form the desired model THQ in 72% yield. Electron-neutral to electron-rich bromoanilines were typically the most effective (**4a-c**, **4e**), while electron-poor substrates gave lower product yields (**4d**, **4g**); the reaction was particularly sensitive to electron-withdrawing groups placed para to the aniline (**4d**). Sterically-hindered bromoanilines are good substrates for this reaction (**4h**, **4i**), consistent with our previous urea-enabled heteroannulation reports[9] and in contrast to prior methodologies, which were inhibited by substitution placed ortho to either the halide or nucleophile.[6,7] The reaction also displayed good functional group tolerance (**4j-4o**), particularly for substrates bearing electron-donating functionality like dimethylamino groups (**4j**, 55%). A substrate bearing an *N*-Boc-piperidine afforded product in modest yield (**4k**, 33%). While product yields were generally modest with various carbonyl groups (**4l-4o**), this is attributed primarily to the reaction's sensitivity to electron-withdrawing functionality, as the product yields in these cases are comparable to substrates bearing trifluoromethyl substitution (**4d**, **4g**). Unsubstituted amides were not well tolerated in this method (see Supporting Information).

One important feature of this methodology is that E/Z mixtures of diene are tolerated. The 1,4-diene scope showed a similar sensitivity to the electronic properties of the substrate, with electron-rich aryl dienes (**4ab**, **4ac**) affording product in higher yields than electron-poor dienes (**4ad**). Among aryl dienes, the reaction tolerates a range of functional groups, including heterocycles (**4ae-4ag**), tertiary amines (**4ah**), thioethers (**4ai**), and unprotected alcohols (**4aj**). Similar to the bromoanilines, steric hindrance is well-tolerated in the diene component (**4ak**, **4al**). Even branched dienes afford product in

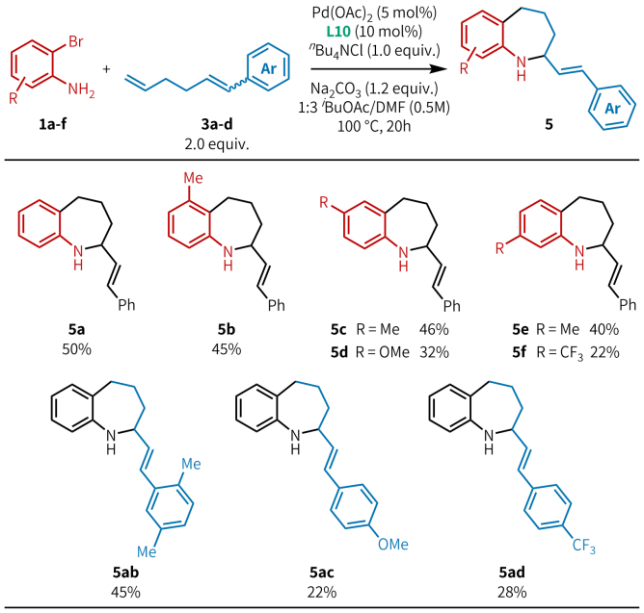

Figure 4. Substrate scope for benzazepine synthesis. Yields correspond to isolated products and are an average of three runs. Reaction conditions: **1** (0.500 mmol), **3** (1.00 mmol), $Pd(OAc)_2$ (0.025 mmol), **L10** (0.050 mmol), $^nBu_4NCl$ (0.500 mmol), Na_2CO_3 (0.600 mmol), 1:3 ^{t}BuOAc/DMF (0.5M), 100 °C, 20h.

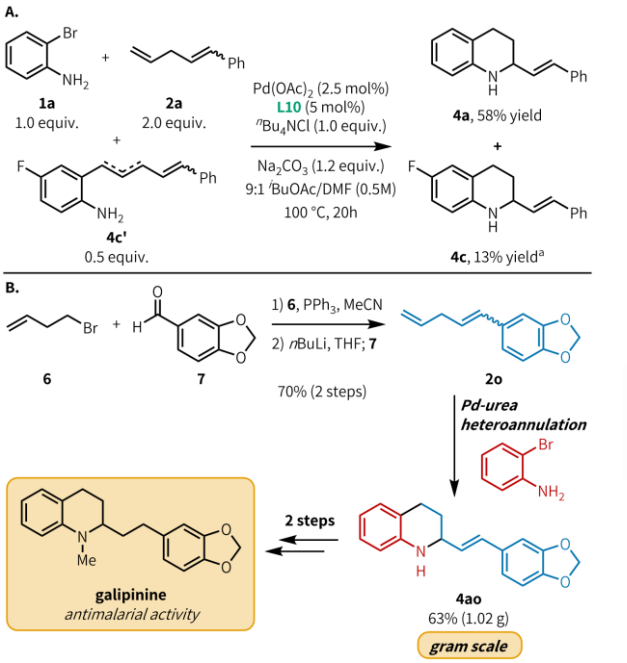

Figure 5. Crossover study and synthetic applications. (A) Crossover experiment with **1a**, **2a**, and elimination byproduct **4c'**. (B) Formal synthesis of galipinine via urea-enabled heteroannulation. See Supporting Information for full experimental details. [a] yield calculated relative to starting amount of **4c'**.

modest yields (**4am**, 25% yield). Alkyl 1,4-dienes are not as effective as aryl dienes, with diene **2n** affording the THQ **4an** in 25% yield.

Although benzazepines are interesting and potentially medicinally valuable core scaffolds, there are very limited methods to access these cores.[10] Moreover, the only example of olefin heteroannulation involving seven-membered ring synthesis gave poor product yields (<20%).[6d] Through our urea-enabled chainwalking approach, we are able to access benzazepines in reasonable yields using 1,5-dienes as coupling partners. Similarly to the synthesis of THQs, E/Z mixtures of diene can be used, increasing the utility of this method. Under our current conditions, electron-neutral substrates are the most effective (**5a**, **5c**, **5e**); the reaction is not sensitive to steric bulk (e.g., **5b**, **5ab**), but electronic variation leads to poorer product yields (**5d**, **5f**, **5ac**, **5ad**). While more reaction development is needed to broaden the scope of benzazepines, the ability to access multiple heterocyclic scaffolds under essentially identical reaction conditions – by varying only the diene – is a notable advance.

As described above (Figure 2), we observe minor byproducts resulting from undesired elimination (**4'/5'**) in the chainwalking heteroannulation reaction. We questioned whether these byproducts were competent intermediates in the reaction or resulted from an off-cycle pathway. To answer this question, we subjected a mixture of fluorinated elimination products (**4c'**) to the heteroannulation reaction in the presence of model substrates **1a** and **2a** (Figure 5A). We observed formation of fluorinated THQ **4c** in 13% yield while model THQ **4a** was generated in 58% yield. These results indicate that **4c'** is indeed a competent intermediate in the heteroannulation reaction. It should be noted that a palladium hydride ([Pd]–H) species must be generated via β-hydride elimination in order for the chainwalking to occur, so observing reactivity of **4c'** in the presence of our model substrates suggests that the [Pd]–H species can dissociate from the alkene, in contrast to some notable prior studies on Pd-catalyzed chainwalking processes.[11] The isolation of elimination byproducts **4'/5'** at the end of the reaction may be due to dissociation of [Pd]–H and then the subsequent decomposition of [Pd]–H outcompeting desired chainwalking and cyclization. Future work will focus on identifying reaction conditions that can better stabilize the [Pd]–H/olefin intermediate complex to expand the scope of benzazepines and other challenging substrates that can be engaged in this reaction.

Lastly, we sought to demonstrate that our method is applicable to the synthesis of natural product targets. Galipinine is a member of the Hancock alkaloid family and is isolated from the plant *galipea officinalis*. Originally used by the indigenous peoples of Venezuela for its general medicinal properties, this compound is effective against malaria and other parasitic infections.[12] Prior synthetic approaches to this molecule typically relied on either reduction and elaboration of a pre-existing heterocyclic core[13] or construction of a tethered substrate for cyclization.[14] In contrast, olefin heteroannulation allows for a fragment-coupling based approach that is well-suited for rapid diversification of the core structure (Figure 5B). Diene component **2** was accessed through a two-step Wittig sequence involving 4-bromo-1-butene **6** and piperonal **7** (70% yield over two steps). The key step, olefin heteroannulation, was conducted at gram scale under our standard reaction conditions, affording THQ **4ao** in 63% yield (1.02 g isolated), the same yield as at standard reaction scale (0.5 mmol). Prior reports have shown that this intermediate can be efficiently transformed into galipinine through *N*-methylation and alkene hydrogenation.[14c] Through this synthetic approach, any one of the starting material fragments can be readily modified to enable rapid access to a diverse library of functional and structural analogues of galipinine to optimize for desired properties.

Ureas are effective pro-ligands for promoting chainwalking in Pd-catalyzed heteroannulation reactions. This strategy allows for rapid access to diverse heterocyclic scaffolds through a unified synthetic strategy and facile modification of

common starting materials. This urea-enabled method is tolerant of a range of functional groups and heterocyclic substituents, as well as sterically-hindered substrates. In addition, both 1,4- and 1,5-dienes can be engaged under the same reaction conditions to construct THQ and benzazepine products, respectively. We have demonstrated the applicability of our urea-enabled methodology to the rapid construction of medicinally relevant scaffolds. Continuing studies are focused on broadening the diversity of heterocyclic cores that can be accessed through this methodological approach.

Experimental Section

General Procedure for the synthesis of tetrahydroquinolines **4** from 1,4-dienes **2** and 2-bromoanilines **1**: All reactions were performed at 0.500 mmol scale. (**L10**) (6.5 mg, 0.0250 mmol, 5.00 mol%), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 2.50 mol%), 90:10 isobutyl acetate/DMF (1.00 mL, 0.5 M), were added to a flame-dried 2 dram vial and backfilled with N_2. 2-bromoaniline **1** (0.500 mmol, 1.00 equiv), 1,4-diene **2** (1.00 mmol, 2.0 equiv) and TBACl (139 mg, 0.500 mmol, 1.00 equiv) were added. Finally, Na_2CO_3 (63.6 mg, 0.550 mmol, 1.2 equiv) was added and the reaction was allowed to stir vigorously at 100°C in an aluminum block with 2-dram slots over a heated stir plate and thermocouple for 20h. Upon reaction completion, the solution was cooled to rt, filtered through celite with EtOAc, and concentrated under reduced pressure. The crude material was then purified by flash column chromatography on SiO_2.

General Procedure for the synthesis of 2,3,4,5-tetrahydro-1*H*-benzo[b]azepines **5** from 1,5-dienes **3** and 2-bromoanilines **1**: All reactions were performed at 0.500 mmol scale. (**L10**) (13.0 mg, 0.050 mmol, 10.0 mol%), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.00 mol%), 90:10 isobutyl acetate/DMF (1.00 mL, 0.5 M), were added to a flame-dried 2 dram vial and backfilled with N_2. 2-bromoaniline **1** (0.500 mmol, 1.00 equiv), 1,5-diene **3** (1.00 mmol, 2.0 equiv) and TBACl (139 mg, 0.500 mmol, 1.00 equiv) were added. Finally, Na_2CO_3 (63.6 mg, 0.550 mmol, 1.2 equiv) was added and the reaction was allowed to stir vigorously at 100°C in an aluminum block with 2-dram slots over a heated stir plate and thermocouple for 20h. Upon reaction completion, the solution was cooled to rt, filtered through celite with EtOAc, and concentrated under reduced pressure. The crude material was then purified by flash column chromatography on SiO_2.

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article.

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Keywords: heterocycle synthesis • palladium catalysis • synthetic method development • heteroannulation • chainwalking

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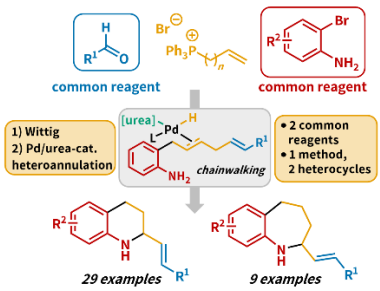

Urea ligands promote chainwalking heteroannulation reactions for the synthesis of 6- and 7-membered azaheterocycles from a common set of precursors. In this reaction, ureas outperform established ligands for Pd-catalyzed chainwalking processes, particularly for more challenging substrates such as 1,5-dienes.