

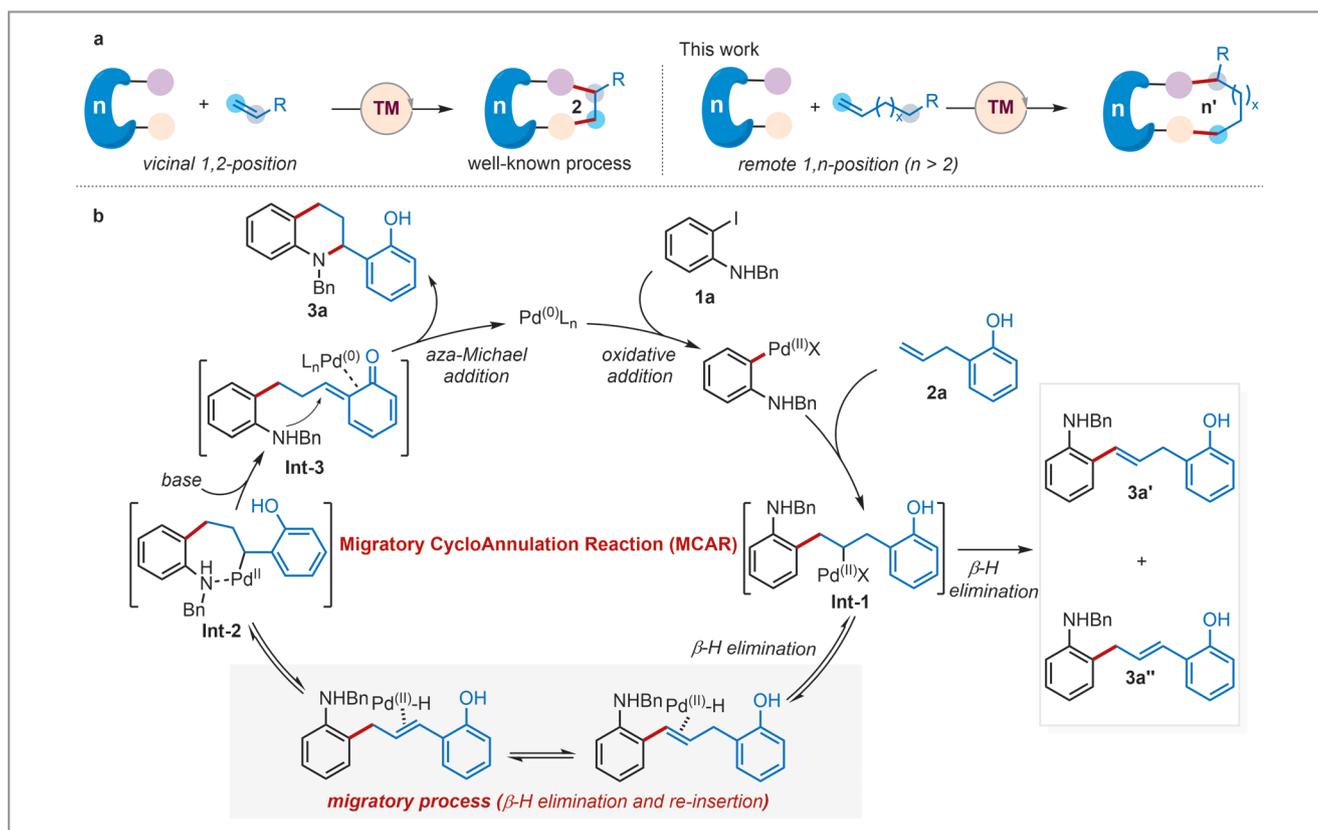
Construction of Azaheterocycles via Pd-Catalyzed Migratory Cycloannulation Reaction of Unactivated Alkenes

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Azaheterocycles, which are among the most prominent structural units in medicinal chemistry, are prevalent in small molecule drugs and bioactive compounds.¹ Therefore, methodologies for the efficient construction of azaheterocycle-containing molecules are in high demand. Among the reported synthetic methods to access these compounds, the Larock annulation – which exploits the cycloannulation of ambiphilic arylhalides with carbon–carbon double bonds – is one of the most widely used and promising strategies. “For now, development of the synthesis of 5- or 6-membered azaheterocycles from highly reactive styrenes, 1,3-dienes, allenes, or strained cyclic alkenes via $[n+2]$ processes, in which the cyclization occurs at the vicinal 1,2-position of those alkenes, dominates the literature,”^{2–4} said Professor Peng Wang, from the Shanghai

Institute of Organic Chemistry (P. R. of China), whose research group has recently introduced the concept of the Pd-catalyzed migratory cycloannulation strategy as a novel approach for building up a range of diverse sizes of azaheterocycles (Scheme 1a). “This protocol breaks through the limitation of the transition-metal-catalyzed $[n+2]$ cyclization, which has normally been achieved with the vicinal 1,2-functionalization of alkenes, leading to the diverse construction of a series of 6-, 7- and 8-membered azaheterocycles,” added Professor Wang.

Professor Wang continued: “One of our group’s research interests is to develop remote difunctionalization of unactivated alkenes by employing transition-metal chain-walking. Recently, we reported a nickel-catalyzed formal hydroarylation of unactivated alkenes.⁵ The mechanistic study revealed



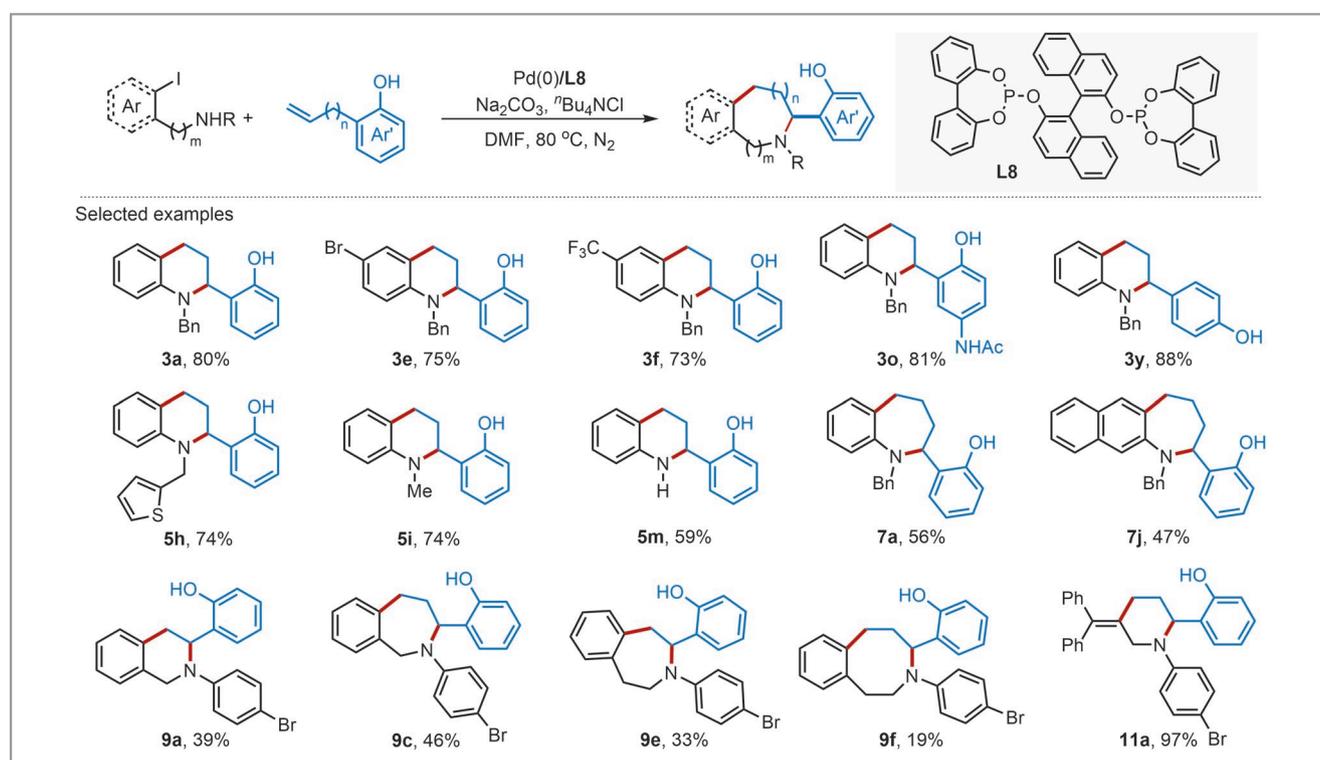
Scheme 1 Pd-Catalyzed migratory cycloannulation reaction

the metal-walking process occurred after the migratory insertion of unactivated alkenes with aryl-metal species. In addition to pursuing the three-component remote difunctionalization of unactivated alkenes, we also came up with a strategy, called transition-metal-catalyzed Migratory Cycloannulation Reaction (MCAR), for the efficient construction of cyclic compounds. This *Nature Communications* paper is a proof-of-concept work on MCAR using a Pd catalyst for the efficient construction of diverse azaheterocycles with unactivated alkenes and the ambiphilic coupling partners.”

Jin-Ping Wang, the first author of the title article and a PhD candidate in the Wang laboratory, pointed out: “The key to accessing the target azaheterocycles by this strategy is identifying the suitable unactivated alkenes.” After screening various unactivated alkenes in this intermolecular cycloannulation with *N*-benzyl-2-iodoaniline, the target product was observed when a hydroxyl group was introduced. “The use of a hydroxyl group will help to render the reactivity of the unactivated alkenes and to control the ring size. Later, the reaction was proven to go through a quinone methide intermediate after the metal migratory process,” Ms. Wang explained, adding: “The mechanistic studies revealed that the reaction might undergo a catalytic cycle involving, sequentially, an oxidative addition

of *N*-benzyl-2-iodoaniline with Pd(0), a migratory insertion to the alkene, the chain-walking process, and an intramolecular aza-Michael addition to the quinone methide intermediate (Scheme 1b).”

“Several challenges were predicted when we started this project, such as the low reactivity of the unactivated nonconjugated alkenes and the difficulty in controlling the cyclization position and in inhibiting any side reactions,” recalled Professor Wang, revealing that, in fact, a large amount of byproducts, including isomerized alkenes and oxidative Heck-type products, were detected in the initial study. After systematically evaluating the reaction parameters, the group finally obtained the best efficiency by utilization of BINOL-derived bisphosphate ligand. “Under optimal conditions, differently sized azaheterocycles were constructed, including tetrahydroquinoline, tetrahydroisoquinoline, tetrahydrobenzo[*b*]azepine, tetrahydrobenzo[*c*]azepine, tetrahydrobenzo[*d*]azepine, hexahydrobenzo[*d*]azocine, and piperidine (Scheme 2). Moreover, we developed the efficient synthesis of a potential selective estrogen receptor modulator (SERM) in four steps, compared with seven steps in the known synthetic route,” said Professor Wang, who concluded: “This Pd-catalyzed migratory cycloannulation strategy is efficient in constructing a wide



Scheme 2 Selected products of the Pd-catalyzed MCAR

range of azaheterocycles from the corresponding unactivated aliphatic alkenes. The *ortho*-hydroxyl group, introduced as a 'locating group' in this chemistry, favors the formation of quinone methide intermediates, which also controls the ring-size of the azaheterocycles. We are currently applying this design principle to achieve transition-metal-catalyzed MCARs with other coupling partners."

Mattias Fanek

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