

THE CATELLANI REACTION

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October 9, 2014

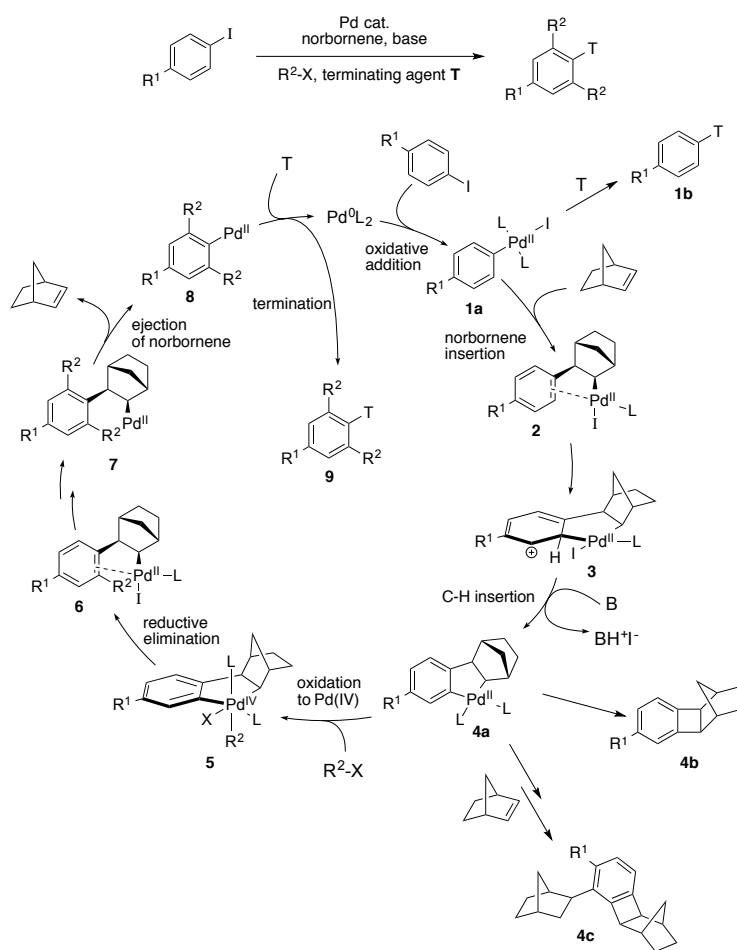
INTRODUCTION

Multicomponent reactions have garnered great interest since the discovery of the Mannich reaction in the early 1900s. Unfortunately, many of these types of reactions generally have a narrow scope and require careful optimization of reaction conditions to accommodate large variation in structure. Additionally, most reactions developed during and after the work of Mannich (*inter alia*, the Hantzsch pyridine synthesis; the Biginelli, Pauson-Khand, Passerini and Ugi reactions) provide a relatively narrow class of products sharing a particular structural feature in common.

In the Catellani reaction (Scheme 1), aryl iodides, alkyl or aryl halides and numerous available terminating agents selectively afford polyfunctionalized aromatic compounds in the presence of a

palladium catalyst, norbornene and an inorganic base in one pot. Over all possible products, the only shared structural feature is an aromatic ring.

Scheme 1. Catalytic cycle for the Catellani reaction



DISCOVERY AND DEVELOPMENT

Initial development of the Catellani reaction arose from studies of the structure and reactivity of palladacycles formed through the action of norbornene on arylpalladium iodide complexes **1a**.¹ Norbornene inserts into the Pd(II)-arene bond, resulting in a *cis-exo* alkylpalladium complex **2**, which is resistant to β -hydride elimination because of the stereoelectronic requirements for *syn*-elimination. The presence of a Pd(II) center in close proximity to an aryl-CH bond results in C-H insertion to form intermediate **4a**. This compound ($R^1 = H$) has been complexed with 1,10-

phenanthroline, isolated and characterized by X-ray crystallography.² This key intermediate eliminates to form **4b** or reacts with additional norbornene to yield **4c** at elevated temperatures. Subjecting **4a** to an

alkyl or aryl halide R^2-X (generally primary alkyl iodides) results in a second oxidative addition to generate the Pd(IV) complex **5**. This complex, particularly when coordinated by phenanthroline, is surprisingly stable. Moderate heating results in reductive elimination into the *ortho*-alkylated product **6**. After a second *ortho*-alkylation, steric effects force decarbopalladation of norbornene, thus reforming an arylpalladium species **8**. The reaction is therefore catalytic in norbornene. It does, however, require a substantial concentration of the strained olefin to form **2** at an acceptable rate and avoid the formation of **1b**. Finally, capture of **8** through a large number of transformations allows for catalytic turnover of Pd(0) and the formation of a diverse group of aromatic products **9**.

APPLICATIONS

The utility of the Catellani reaction has provided the rapid, facile synthesis of myriad substituted aromatic compounds (Scheme 2). *Ortho*-functionalization has been achieved with primary and secondary alkyl halides as well as with aryl halides (**a**),³ furans and pyrroles (**b**),⁴ and amines (**c**).⁵ Termination by Heck olefination (**d**),⁶ Sonogashira coupling (**e**), Suzuki coupling (**f**), Buchwald-Hartwing amination (**g**), arylation with pyrroles, furans and thiophenes (**h**), addition to carbonyls (**i**) and cyanation (**j**) have all been reported.⁷ Medium-sized rings have been prepared using tethered alkylating and terminating agents;⁸ and Heck-terminated products have been subsequently reacted with tethered alcohols and amines in conjugate additions to provide more varied cyclic structures.⁹

SUMMARY

Through application of the Catellani reaction, a great number of diverse scaffolds have been synthesized in one pot from simple starting materials. Over the past decade, this methodology has proven useful for the rapid generation of complexity in organic synthesis.

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Scheme 2. Diversity of Scope for the Catellani reaction.

