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Highly Selective Rhodium Catalyzed Domino C–H Activation/Cyclizations

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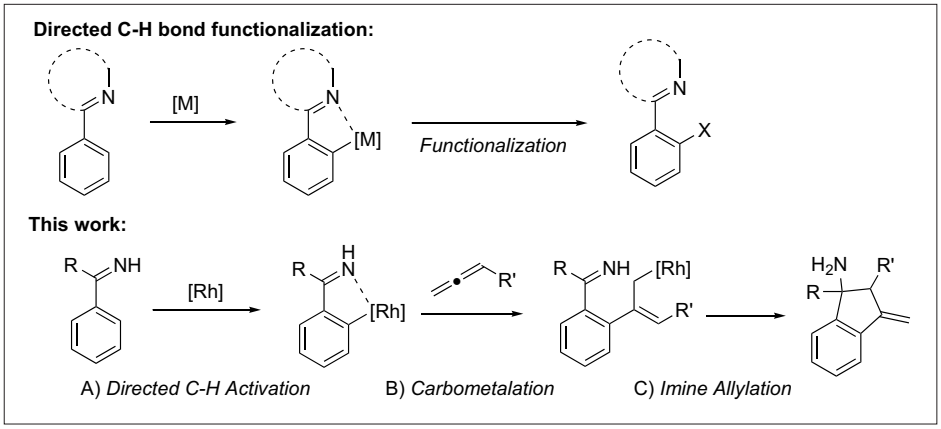
Abstract: The direct functionalization of carbon–hydrogen bonds is an emerging tool to establish more sustainable and efficient synthetic methods. We present its implementation in a cascade reaction that provides a rapid assembly of functionalized indanylamines from simple and readily available starting materials. Careful choice of the ancillary ligand – an electron-rich bidentate phosphine ligand – enables highly diastereoselective rhodium(I)-catalyzed intramolecular allylations of unsubstituted ketimines induced by a directed C–H bond activation and allene carbo-metalation sequence.

Keywords: Allene · Allylation · C–H Activation · Catalysis · Rhodium

Introduction

Over the past decades transition-metal-catalyzed reactions have emerged as indispensable tools enabling numerous powerful transformations that are otherwise impossible. Usually, such processes require predisposed bonds in the form of carbon–halide or carbon–metal bonds. A challenging, but highly attractive alternative comprises the direct and catalytic activation and functionalization of carbon–hydrogen bonds. This approach is more sustainable due to the lack of pre-functionalization, simplicity of starting materials and better atom-economy.[1] Besides their low intrinsic reactivity, the sheer number of very similar C–H bonds in the substrate poses severe selectivity issues. One strategy to address these shortcomings are the use of directing groups, in particular nitrogen-containing groups like 2-pyridyl, oxazolyl or imine that allow for selective *ortho*-metalations of appended arenes. In the last decade, this field has been subject to intensified research efforts by several groups and new transformations that capitalize on directed C–H bond activation processes have been reported.[2] A common theme of these reports is that the directing group remains unchanged and usually stays intact after reaction (Scheme 1). The most popular directing group, 2-pyridyl, is neither a common nor easily interconvertable group in organic synthesis. Thus additional steps for its introduction and removal are required. Therefore, despite the enormous progress in understanding the fundamental reactivity, synthetic applications remain so far scarce.



Scheme 1. Directed C–H bonds activations.

One major research theme of our group involves the design and development of selective activations and functionalizations of C–C[3] and C–H[4] bonds. We seek to identify enabling directing groups for such reactions that are synthetically versatile and/or able to be converted 'on the fly' into another valuable functionality during the reaction. A recent example towards this goal is described herein and outlined in Scheme 1.[4b] As the initial step, unsubstituted ketimines are used to direct *ortho*-aryl C–H bond activation with a rhodium(I) complex. The thereof arising aryl metal species in turn adds across an unsaturation in the form of an allene and provides an allyl rhodium species. In consequence, we anticipated that this species might undergo an intramolecular allylation with the electrophilic center of the imine moiety providing a primary amine as final product.[5] From a purely synthetic point of view, the overall transformation can be seen as a [3+2]-cycloaddition forming potentially valuable methylene indanylamines.

Results and Discussion

The anticipated reactivity was initially optimized with di-*p*-tolylmethanimine and octa-1,2-diene as model substrates

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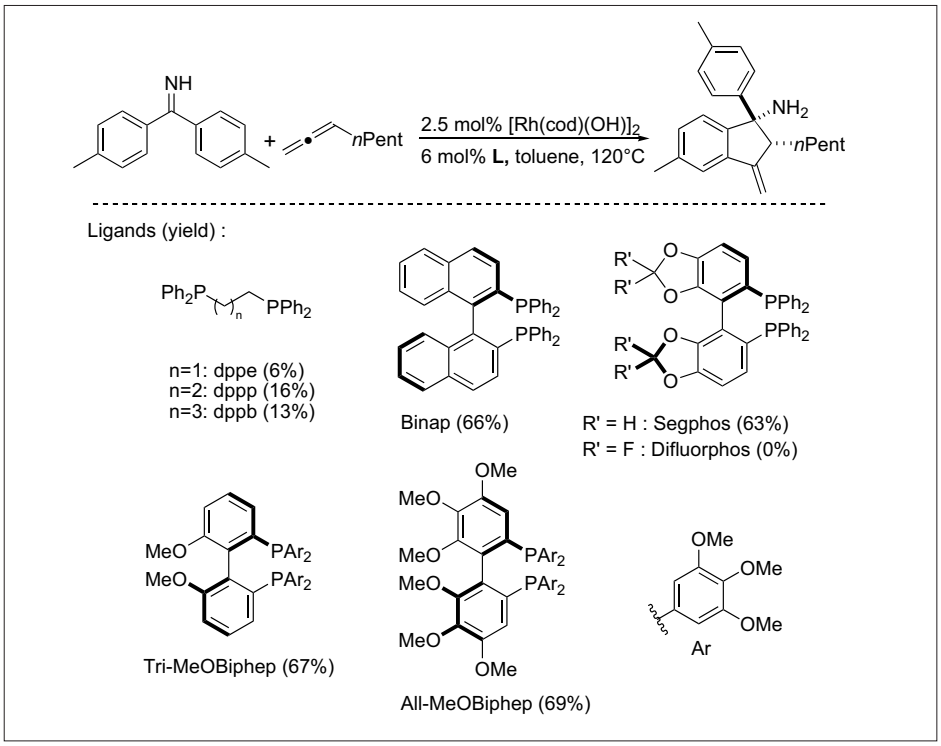
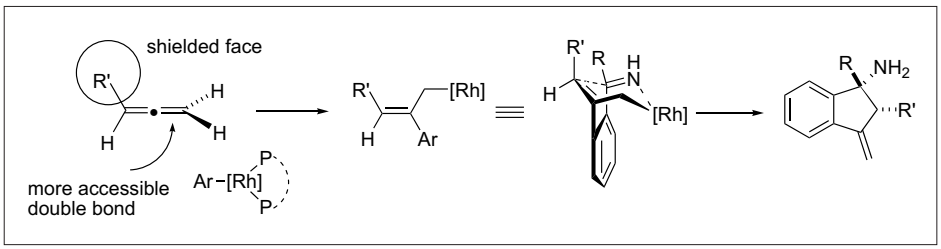


Scheme 2. Screening of ligands.



Scheme 3. Mechanistic model to account for the observed regio- and diastereoselectivity.

(Scheme 2). Different classes of phosphine ligands were screened. Whereas the use of simple monodentate phosphine ligands degrades only the allene slowly, bidentate ligands such as dppe, dppp, dppb provide that desired product, albeit in poor yield. In stark contrast, bidentate ligands based on a biaryl backbone display a much higher reactivity and enhanced yield (66% for Binap). A systematic screening of related phosphines revealed the All-MeOBiphep ligand as the best performer with 69% yield. Both the dihedral angle of the backbone and the electronic properties of the phosphorous atom influence the reactivity. The particular importance of the electronic tuning becomes apparent by comparing the electron-poorer Difluorphos (0% yield) with the electron-richer Segphos (49% yield) ligand. Conveniently, this property of the ligands can be correlated to the carbonyl stretching frequency of their corresponding complex [LRh(Cl)CO], simply measured by FT-IR spectroscopy. For example, the wavenumbers of Difluorophos, Segphos and All-MeOBiphep are 2017, 2004 and 2000 cm^{-1}, respectively. For similar dihedral angles, the ligand with the more basic phosphorous atom provides higher yields. In contrast, however, even more basic alkyl substituents on the phosphorous atom give no product at all. These results underline the crucial importance of the right ligand to enable reactivity. Despite the striking differences in yield, all evaluated ligands provide exclusively the same *syn*-stereochemistry of the newly generated stereogenic centers of the product. Besides the phosphine ligand, the rhodium(I) source and its counterion itself play an important role for the desired reactivity. Screening different rhodium(I) sources revealed that oxygen-based counterions such as hydroxide, acetate or methanolate are essential. For example, no reaction occurs with the common complex $[Rh(cod)Cl]_2$ or the cationic $[Rh(cod)_2]BF_4$. For performance and convenience, we choose the combination of $[Rh(cod)OH]_2$ and All-MeOBiphep for the further studies.

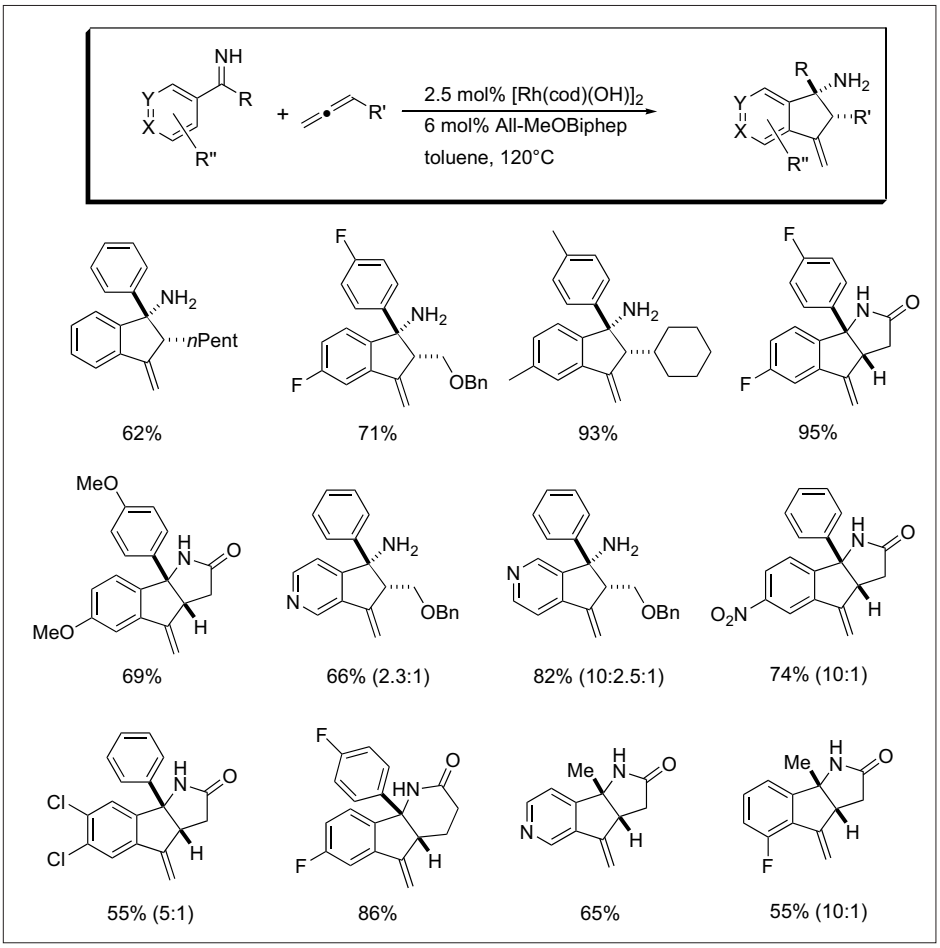
Mechanistic Rationale for the Regio- and Diastereoselectivity

Addition of organometallic species to allenes usually places the metal portion at the distal position of the allene giving rise to a reactive allyl metal compound. For example, allene hydro-metalations have been recently exploited for highly efficient and atom-economic carbonyl allylation reactions.[6] Relating to that, we anticipated that the aryl-rhodium species we obtained through the imine-directed C–H activation would be competent partners for allene carbo-metalations. Indeed, carbo-metalation occurs on the less encumbered terminal double bond of the allene forming an allyl-rhodium species (Scheme 3).

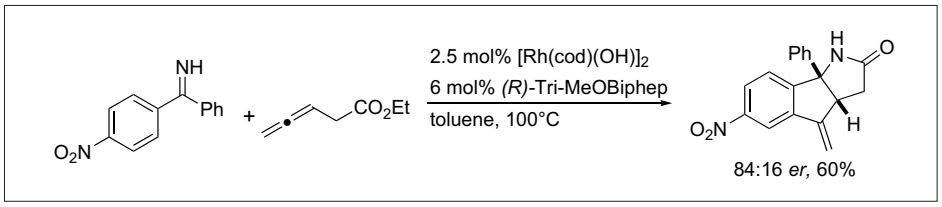
Moreover, as one face of allene is shielded by substituent R', a *trans*-relationship of the aryl group and R' is largely favoured. In the regime of a slow σ–π–σ isomerization of the allyl species, an allylation *via* a closed chair-like transition state accounts for the exclusive *syn*-stereochemistry of the indanyl amine product. Remarkably, even at the elevated reaction temperatures of 120 °C, this regio- and diastereoselectivity of the addition is completely maintained.

Scope of the Reaction

The scope of the reaction is illustrated in Scheme 4. Diverse functional groups and substituents of the imine as well as the allene are well tolerated and provide the desired products in good yields. In all cases, the reaction yields terminal methylene substituents and *syn*-adducts. Electronically modulated symmetrical diaryl ketimines reveal that the electron-poorer substrates react faster. Thus, this distinction allows differentiation of the two aryl groups in unsymmetrical diaryl ketimines, preferentially activating the electron-poorer one with selectivities ranging from 2.3:1 to 10:1. This finding indicates that the mechanism for the initial C–H activation operates through an oxidative addition or a concerted deprotonation metalation pathway rather than through electrophilic addition pathways. Alkyl aryl ketimines participate as well in this reaction, although they have an attenuated reactivity which again can be enhanced by an electron-poor aryl group. With 3-fluorophenylimine, a pronounced *ortho*-fluorine effect[7] is operative forming mainly the product arising from an activation *ortho* to the fluorine atom instead of the usually preferred, less hindered position *para* to the substituent R'. Allenes with terminal ester moieties cyclize *in situ* with the formed primary amine giving 5- or 6-membered lactams.



Scheme 4. Scope of C–H activation/allene addition sequence.



Scheme 5. Lead result for an asymmetric version.

Development of an Enantioselective Version

We have also briefly investigated an enantioselective version of the addition sequence to underscore the high potential of this transformation. Using (*R*)-Tri-MeO-Biphep, the desired indanyl-amine was obtained in 60% yield and a promising selectivity of 84:16 *er* (Scheme 5). Further studies to generalize and optimize this lead are currently on-going efforts in our laboratory.

Conclusion

In summary, we have presented a novel rhodium(I)-catalyzed cascade reaction initiated by imine directed C–H activation and a subsequent addition across an allene which in turn converts the initial directing group into a primary amine. The transformation provides new opportunities for a rapid increase in molecular complexity from two simple starting materials. This prototype reactivity and ligand dependencies can be seen as a blue print for the development of related reactivities allowing access to synthetically valuable structures and building blocks.

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