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Anti-Markovnikov Hydroalkylation of Allylic Amine Derivatives via a Palladium–Catalyzed Reductive Cross-Coupling Reaction

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Abstract

A palladium-catalyzed hydroalkylation reaction of allylic amine derivatives by alkylzinc reagents is reported. This reductive cross-coupling yields anti-Markovnikov products using a variety of allylic amine protecting groups. Preliminary mechanistic studies suggest that a reversible β -hydride elimination/hydride insertion process furnishes the primary Pd-alkyl intermediate, which then undergoes transmetalation followed by reductive elimination to form a new sp^3 - sp^3 carbon-carbon bond.

The functionalization of Pd-alkyl intermediates has classically been difficult due to their propensity to undergo β -hydride elimination. Advances in this field have focused primarily on three general approaches to functionalize the Pd-alkyl: 1) rapid oxidation of the intermediate to allow for either substitution or reductive elimination of the resultant high oxidation state Pd complex,¹ 2) ligand control to slow β -hydride elimination² and/or 3) substrate control through the use of stabilizing interactions such as the formation of π -allyl³ or π -benzyl intermediates.^{1c,4} Using the latter approach, our lab has reported a series of cross-coupling reactions of π -allyl⁵ (**A**, Scheme 1) or π -benzyl (**B**) intermediates⁶ that are formed by in situ generation of a Pd-hydride (through either alcohol oxidation or decomposition of a Pd-alkyl) and subsequent insertion into a conjugated alkene.

One advantage of such a tactic to prepare Pd-alkyl intermediates is the utilization of an alkene as a surrogate for an alkyl electrophile.^{2a} Also, by using a conjugated alkene, a stabilized Pd-alkyl is ultimately formed as the thermodynamic product through reversible β -hydride elimination/hydride insertion processes,^{6a} enabling cross-coupling as well as the formation of a single constitutional isomer. Unfortunately, this approach is limited to alkene coupling partners, which provide formal stabilization. Specifically, without stabilization, reversible β -hydride elimination/hydride insertion processes lead to complex mixtures of alkene isomers and coupled products.⁶ Therefore, to overcome this limitation, we envisioned applying alternative stabilizing motifs that could enable the selective reductive cross-coupling of a non-conjugated alkene and an organometallic, thereby significantly expanding the scope of alkene substrates.

To this effect, a functional group that can act as a versatile synthetic handle and can be easily incorporated into the alkene substrate would be most attractive. A recent report by Feringa and coworkers⁷ demonstrated the use of phthalimide-protected allylic amines to achieve aldehyde-selective anti-Markovnikov Wacker oxidations (Scheme 2). It should be noted that the phthalimide group is uniquely suited in directing the Wacker oxidation to the

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Supporting Information **Available:** Optimization data, experimental procedures, and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

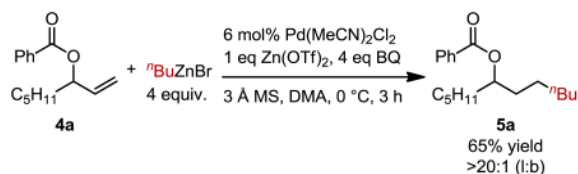
anti-Markovnikov position, as other allylic amine derivatives lead to mixtures of products.⁷ The authors suggest the high selectivity may be attributed to chelation of the phthalimide group to the palladium catalyst prior to oxypalladation. Encouraged by Feringa's results, the evaluation of allylic phthalimides was pursued in order to hypothetically direct the formation of and stabilize the resultant Pd-alkyl complex for subsequent cross-coupling. Herein, we report the development and preliminary mechanistic investigation of a highly selective anti-Markovnikov hydroalkylation reaction of allylic amine derivatives, wherein, a broad range of functional groups at the allylic position are permitted.

Preliminary investigations utilized the optimal conditions for the previously reported Pd(*i*Pr)(OTs)₂-catalyzed hydroalkylation of styrene derivatives^{6c} with organozinc reagents. Using allylic phthalimide **1a**, an 80% GC yield of **2a** was delivered in high selectivity for the linear product (entry 3, Table 1). Control studies of the reaction conditions involving the removal of the NHC ligand (entry 4) and the use of Pd(MeCN)₂Cl₂ as the catalyst (entry 5) resulted in similar yields and selectivity, prompting the use of these simplified conditions in further optimization. Lowering the temperature and the utilization of molecular sieves resulted in excellent yield and 17:1 selectivity favoring the linear over the branched product (entry 7).

Evaluation of the scope initially focused on the use of various organozinc reagents with **1a**. Simple alkyl organozinc reagents perform well, giving linear products **2a** and **2b** in high selectivity. Functionalized organozinc reagents were then examined, which led to products containing a TBDPS-protected alcohol (**2c**), an alkyl chloride (**2d**), and an ester (**2e**). Methylcyclohexyl zinc bromide, which contains substitution at the β-position, gave product **2f** in 46% yield with excellent selectivity. We next examined the effect of varying groups on the allylic phthalimide substrate. Lower selectivity for the linear product (2:1) was observed when the substrate lacks additional substitution at the carbon bearing the phthalimide group (**2g**). Introduction of a benzyl group (**2h**) resulted in a 91% yield with modestly diminished selectivity for the linear product. Substrates containing a benzyl ether (**2i**) and a heteroaromatic (**2g**) both gave moderate yields with >20:1 selectivity. Although these substrates could potentially competitively coordinate to palladium, they produce the anti-Markovnikov product selectively. Substrates containing larger groups adjacent to the phthalimide (**2k**, **2l**) also gave good yields with high selectivity for the linear product.

It was initially believed, based on Feringa's report, that allylic phthalimides were uniquely suited to stabilize the resultant Pd-alkyl intermediates, potentially through chelation,^{7,8} and selectively deliver the linear product. Therefore, it was surprising that under our optimized conditions, a variety of electronically disparate amine protecting groups also gave the linear hydroalkylation product (Table 3). Several attractive and commonly employed amine protecting groups were evaluated including doubly protected *N*-Cbz-*N*-Boc allylic amines (**3a**, **3b**) suggesting that this strategy may be more general than anticipated. Additionally, a variety of singly protected amines were tolerated under the reaction conditions, including a Cbz protected amine, which gave the coupled product in 82% yield with >20:1 selectivity (**3c**) for the linear product. Electron poor protecting groups such as trichloroacetamide (TAc, **3d**) and sulfonamide protected amines gave the cross-coupled products in excellent selectivity (**3e**, **3f**). These cases are especially interesting in that the Lewis basicity of the carbonyl or sulfonyl groups should be significantly reduced, raising questions about our previous hypothesis involving chelation to the catalyst. Finally, the use of *N*-tosyl allyl amine, which also lacks additional substitution at the amine-bearing carbon, gave the anti-Markovnikov product in >20:1 selectivity (**3f**) in contrast to the related phthalimide protected product **2g**.

Encouraged by the successful coupling of various protected allylic amines, we subjected a protected allylic alcohol, a ubiquitous intermediate in organic synthesis, to our reductive cross-coupling reaction conditions. To our delight, a benzoyl-protected allylic alcohol (**4a**) gave the corresponding product **5a** in 65% yield and >20:1 selectivity (eq. 1). Submission of dodecene to the reaction conditions resulted in alkene isomerization and trace amounts of product isomers, suggesting that allylic substitution is required to achieve selectivity for the anti-Markovnikov product.⁹



(1)

Considering the breadth of protecting groups allowed and the generally high selectivity for the anti-Markovnikov product, an important mechanistic consideration is whether insertion into the Pd-hydride is selectively directed by the allylic amine. To probe this, a perdeuterated alkylzinc reagent was prepared and submitted to the hydroalkylation reaction conditions (Scheme 3). Surprisingly, 91% deuterium incorporation results with a similar amount of deuterium incorporation observed at both alkene carbons. This suggests that, after formation of a Pd-hydride (deuteride, C) via transmetalation with the organozinc reagent and β -hydride elimination,^{6c} coordination and insertion of the allylic amine (**A**) can result in either a 1,2-insertion (**D'**) or a 2,1-insertion (**D**). In the case of a 2,1-insertion, intermediate **D** rearranges to the primary Pd-alkyl complex (**F**) via a β -hydride elimination (**E**) followed by a migratory insertion. Primary Pd-alkyl intermediates **F** and **D'** then undergo transmetalation followed by reductive elimination. It should be noted that no deuterium is incorporated into the allylic position, which is consistent with the observed stereochemical retention when using an enantioenriched substrate (Scheme 3). The combination of this information with the ability to successfully use electron poor allylic amine derivatives suggests that the success of this reaction arises from a slowing of β -hydride elimination at the allylic position in combination with a relatively fast cross-coupling of the primary Pd-alkyl intermediate.

In summary, we have reported a Pd-catalyzed hydroalkylation reaction of various protected allylic amines, which we have also extended to an allylic alcohol derivative. This process features the ability to incorporate a remote stereocenter in regions devoid of other functionality. Initial mechanistic studies suggest a reversible β -hydride elimination/hydride insertion process to arrive at a primary Pd-alkyl intermediate, which predominantly undergoes cross-coupling. While the precise role of the protecting group on the amine remains unclear, it is required to achieve selective anti-Markovnikov addition products. Future work will be focused on exploring the synthetic utility of this method and elucidating the features required to control β -hydride elimination in related processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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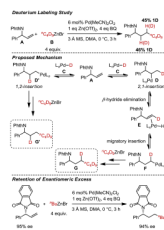
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- Internal alkenes were also submitted to the reaction conditions, which resulted in <10% yield of a mixture of product isomers.



Scheme 1. Pd-Alkyl Stabilization Using Conjugated Alkenes



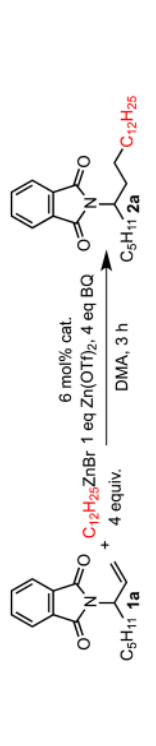
Scheme 2. Feringa and Coworkers' Wacker Oxidation and Our Proposed Hydroalkylation Approach PG = protecting group R' = PG or H



Scheme 3. Deuterium Labeling Study and Evaluation of Retention of Enantiomeric Excess

Table 1

Reaction Optimization



entry	catalyst	temp.	additive	% conv. ^a	% yield ^a	(l:b) ^b
1	no palladium	RT	--	<2	--	--
2 ^c	Pd(^t Pr) ₂ (OTf) ₂	RT	Cu(OTf) ₂ , O ₂	<2	--	--
3	Pd(^t Pr) ₂ (OTf) ₂	RT	--	85	80	15:1
4	Pd(MeCN) ₂ (OTf) ₂	RT	--	86	81	16:1
5	Pd(MeCN) ₂ Cl ₂	RT	--	88	80	17:1
6	Pd(MeCN) ₂ Cl ₂	0 °C	--	95	86	17:1
7	Pd(MeCN) ₂ Cl ₂	0 °C	3 Å MS	99	91	17:1

^a Measured by GC using an internal standard.^b Ratio of linear:branched product isomers determined by GC. Yields are a combination of both linear and branched products.^c Zn(OTf)₂ and BQ were not added.

Table 2

Palladium-Catalyzed Cross-Coupling of Phthalimide Protected Allylic Amines with Alkylzinc Reagents.

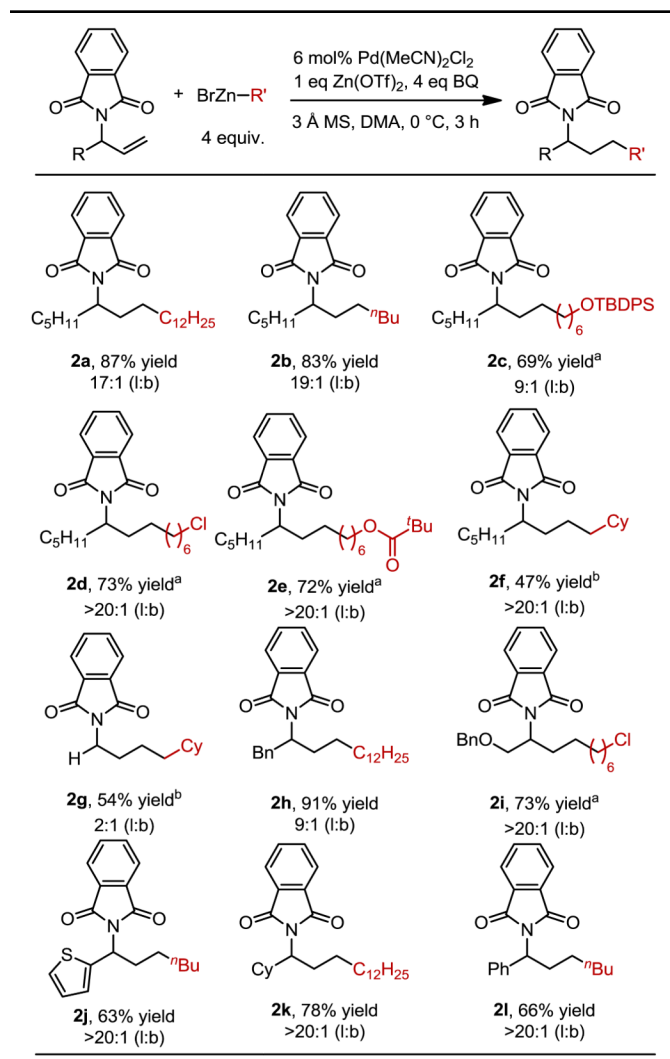
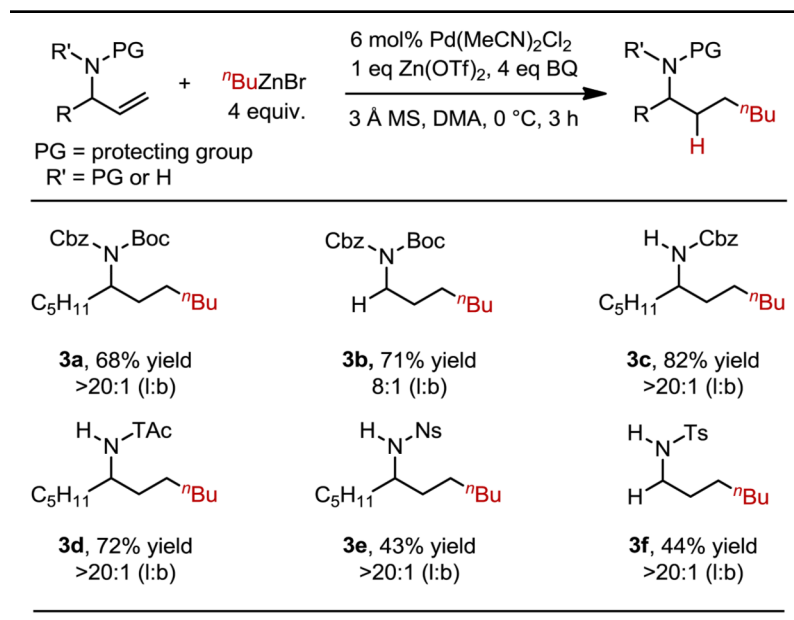
Ratio of linear:branched product isomers determined by GC, ¹H NMR integration, and/or yields of isolated products.^a 8 equiv. of BrZn-R was used.^b The reaction was performed at rt. All yields represent an average of two experiments on at least 0.5 mmol scale.

Table 3
Scope of Protecting Groups



Ratio of linear:branched product isomers determined by GC, ^1H NMR integration, and/or yields of isolated products. All yields represent an average of two experiments on at least 0.5 mmol scale.