Selective Cross-Coupling Hot Paper

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Palladium-Catalyzed Completely Linear-Selective Negishi Cross-Coupling of Allylzinc Halides with Aryl and Vinyl Electrophiles**

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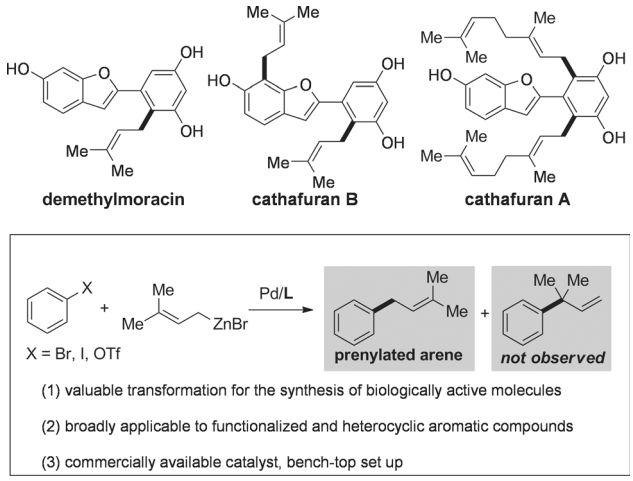
Prenylated arenes are found in a broad spectrum of naturally occurring bioactive compounds (Scheme 1).[1] Studies have revealed that the inclusion of the prenyl side chain could enhance both the bioactivity and bioavailability of natural products, in part due to the increased protein binding affinity and membrane permeability caused by the lipophilicity of the prenyl group.[2] In nature, prenylation processes usually involve enzymatic reactions mediated by a range of substrate-specific prenyltransferases (PTases),[3] giving rise to the corresponding prenylated natural products in a highly selective fashion. However, the ability of synthetic chemists to directly introduce prenyl and related 3,3-disubstituted allyl groups onto functionalized aromatic compounds is generally hampered by poor regioselectivity with respect to the unsymmetrical allyl nucleophile.[4,5] Therefore, a general, reliable, and practical method for regioselective prenylation that emulates the efficiency of nature's biosynthetic machinery is highly desirable.[6]



Scheme 1. Top: Representative biologically active prenylated natural products. Bottom: Regioselective Negishi cross-coupling: rapid access to prenylated compounds.

Recently, Organ et al.[4] and we[5] have developed conditions for the linear-selective Suzuki–Miyaura coupling of 3,3-disubstituted allylboronates using N-heterocyclic carbene (NHC)- and phosphine-based catalysts, respectively. While both methods were highly selective, relatively high temperatures and extended reaction times were required, and the yields of the desired prenylated products were moderate due to the inevitable formation of homocoupling products.[4,5] In an effort to develop milder and more efficient prenylation methods, we sought to utilize alternative prenyl nucleophiles. Prenyl-type organozinc reagents were our first choice, as we had previously demonstrated the high reactivity as well as functional group compatibility of organozinc reagents in a variety of Negishi coupling processes.[7,8] To date, the cross-coupling of 3,3-disubstituted allylzinc reagents with aryl halides remains rare, presumably due to issues of regioselectivity often experienced with this class of nucleophile.[4,5,9] Herein we report the first general and completely linear-selective conditions for the Negishi coupling of 3,3-disubstituted allylzinc reagents with aryl halides and the application of this methodology in the concise and convergent synthesis of anti-HIV natural product siamenol (**1**). Computational studies were also carried out to gain a deeper insight into the high level of selectivity observed with the current catalyst system.[10,11]

Using prenylZnBr·LiCl prepared by Knochel's protocol[12,13] and 1-bromo-4-butylbenzene as model substrates, we commenced our study by examining our recently developed easily activated palladacycle precatalysts derived from biarylphosphine ligands (Table 1).[14] While SPhos (**L1**) and RuPhos (**L2**)-based catalysts were effective for the linear-selective prenylation, only moderate conversion was observed (Table 1, entries 1 and 2). Both the XPhos (**L3**)- and the CPhos (**L5**)-based catalyst furnished full conversion of the aryl halide component, affording the α-isomer (**4**) in good yield with minimal amounts of the γ-isomer or other side products (entries 3 and 5). Ultimately, the catalyst generated from CPhos[15] was identified as the optimal choice for this coupling reaction, affording the α-coupling product in a highly selective manner.[16] Under the optimized reaction conditions, treatment of the aryl bromide with prenylzinc bromide in the presence of 2 mol% CPhos-based catalyst afforded the prenylated product in 94% yield in 30 min at

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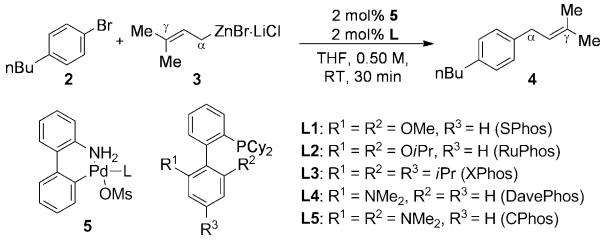
Table 1: Ligand effect on the palladium-catalyzed Negishi cross-coupling of prenylzinc bromide and 1-bromo-4-butylbenzene.



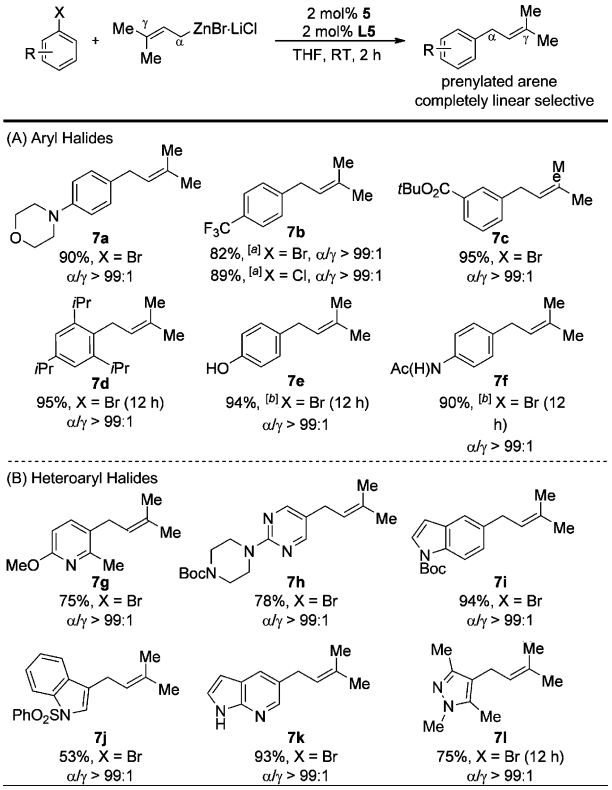
Entry	Ligand	Conversion[a]	Yield[a]	α/γ ratio[a]
1	**L1**	54%	47%	>99:1
2	**L2**	52%	41%	>99:1
3	**L3**	100%	92%	>99:1
4	**L4**	84%	74%	>99:1
5	**L5**	98%	94%	>99:1
6[b]	**L5**	100%	92%	>99:1
7[c]	**L5**	100%	94%	>99:1
8[d]	**L5**	100%	94%	>99:1

[a] Conversions and yields were determined by GC analysis of the crude reaction mixture using dodecane as an internal standard. [b] 70 °C for only 3 min. [c] 1-Butyl-4-iodobenzene was used in lieu of **2**. [d] 4-Butylphenyl triflate was used in lieu of **2**.

room temperature (entry 5). Complete conversion could also be achieved in ≤ 3 min at 70 °C, further demonstrating the excellent activity of this catalyst system (entry 6). Aryl triflates (entry 7) and iodides (entry 8) were also suitable coupling partners using this protocol. Interestingly, the well-tailored NHC-supported PEPPSI precatalyst[4] (PEPPSI-IPent, **6**) proved to be less effective for this transformation (see the Supporting Information). Other commercially available and frequently used catalysts or ligands such as [Pd-(PPh_3)$_4$], dppm, dppp, and dppb were ineffective for this prenylation reaction (see the Supporting Information for details).

We next investigated the substrate scope of the method (Scheme 2). It was found that with the CPhos-based catalyst, both electron-donating (**7a**) and electron-withdrawing (**7b**, **7c**) substituents were tolerated with no decrease in the observed regioselectivity. An extremely sterically hindered substrate (**7d**) could also be successfully transformed. Substrates containing acidic functional groups, such as an acetamide (**7e**) and a phenol (**7f**), were also transformed to the desired products. Given the importance of heterocycles in medicinal chemistry,[17] we examined a variety of sterically and electronically diverse heteroaryl halides (Scheme 2B). We found that pyridine (**7g**), pyrimidine (**7h**), indoles (**7i**, **7j**), azaindole (**7k**), and pyrazole (**7l**) all underwent smooth transformation using this protocol.

One limitation of our previously developed Suzuki–Miyaura coupling was its ability to effectively engage vinyl electrophiles. Lower levels of regioselectivity were often observed with regard to vinyl bromides,[18] and in the case of vinyl triflates, competitive hydrolysis resulted in low yields of the desired coupling products. The current Negishi coupling protocol successfully addressed these problems. Vinyl bromides and triflates were converted to the corresponding "skipped dienes", which represent key structural motifs in

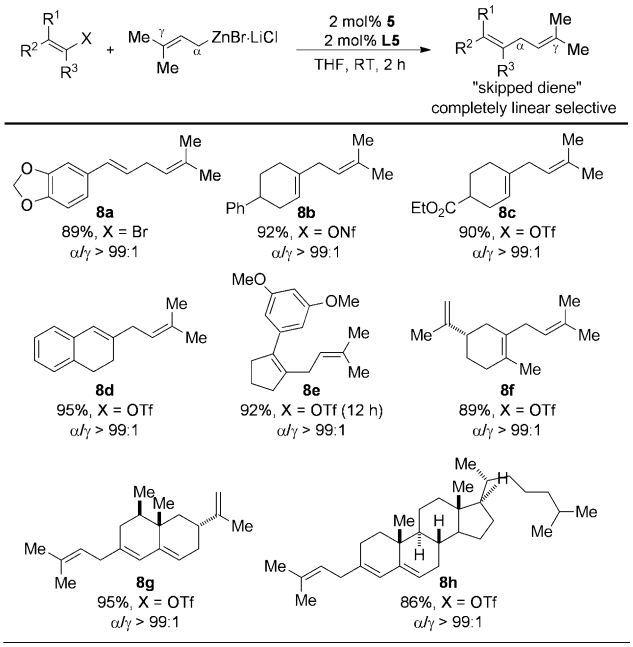


Scheme 2. Substrate scope of aryl and heteroaryl halides. Reaction conditions: Ar-X (1.0 mmol), prenylZnBr·LiCl (1.3 mmol), **3** (0.02 mmol), **L5** (0.02 mmol), RT, THF, 2 h. Yields are of isolated product as an average from two runs. [a] Determined by ^{1}H NMR spectroscopy due to the volatility of coupling product. [b] 2.3 equiv prenylzinc was used.

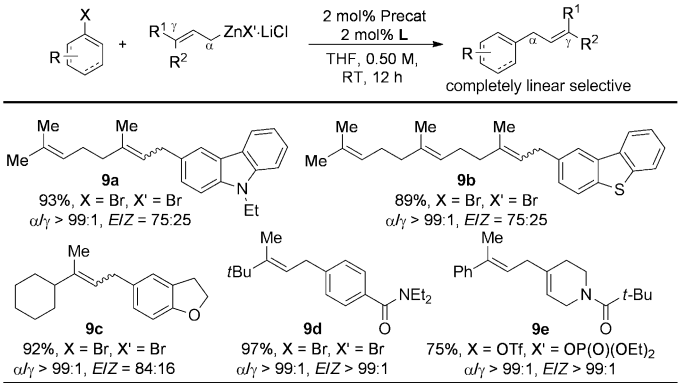
a number of biologically active natural products,[19] in a completely regioselective manner (Scheme 3). Notably, mono- (**8a**), di- (**8b–8d**), and trisubstituted (**8e**, **8f**) vinyl electrophiles could all be applied in this reaction without noticeable erosion of regioselectivity. Five- (**8e**) and six-membered (**8b–8d**) cyclic vinyl triflates represented compatible coupling partners as well.

In an effort to expand the utility of this method, we examined the coupling of various 3,3-unsymmetrically disubstituted allylzinc halides (Scheme 4). In all cases examined, the allylation proceeded smoothly furnishing the linear-coupling product exclusively in excellent yields. While both geranyl- (**9a**) and farnesylzinc bromides (**9b**) afforded 75:25 mixtures of olefin stereoisomers, allylzinc halides bearing two substituents of greater steric difference reacted with improved stereoselectivity with respect to the trisubstituted olefin moiety (**9c–9e**). For example, while the use of 3-methyl-3-cyclohexylallylzinc bromide (**9c**) furnished coupling product as stereoisomeric mixtures (E/Z ratio = 85:15), the coupling of 3-methyl-3-*tert*-butylallylzinc bromide provided the trisubstituted olefin exclusively with E geometry (**9d**).

To further showcase the utility of this prenylation methodology in a complex setting, we performed a concise synthesis of siamenol (**1**), a prenylated natural product isolated from *Murraya siamensis* and exhibiting anti-HIV activity.[20] Beginning with 4-bromotoluene (**10**), palladium-



Scheme 3. Substrate scope of vinyl halides and pseudohalides. Reaction conditions: vinyl halide (0.5 mmol), prenylZnBr·LiCl (0.65 mmol), **3** (0.01 mmol), **L5** (0.01 mmol), RT, THF, 2 h. Yields are of isolated product as an average from two runs.

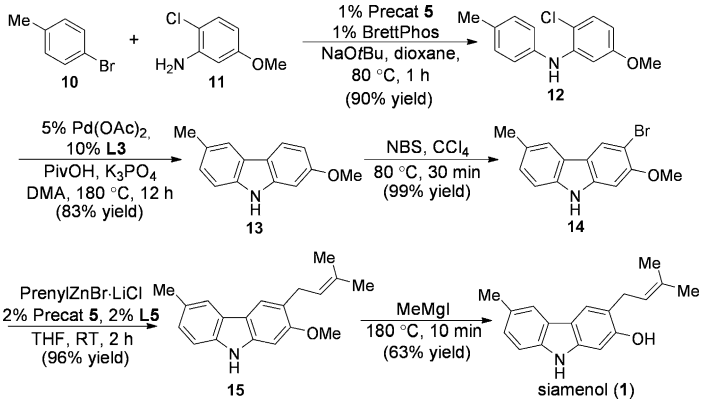


Scheme 4. Substrate scope of 3,3-disubstituted allylzinc reagents. Reaction conditions: Ar-X (0.50 mmol), allylZnX′·LiCl (0.65 mmol), **3** (0.01 mmol), **L5** (0.01 mmol), RT, THF, 2 h. Yields are of isolated product as an average from two runs.

catalyzed amination proceeded smoothly to deliver the unsymmetrical diarylamine **12** (Scheme 5). Subsequently, palladium-catalyzed intramolecular C–H activation and bromination at C3 furnished the carbazole **14**, which in turn, underwent the completely linear-selective Negishi cross-coupling to afford the prenylated carbazole **15**. In the final step, demethylation employing methylmagnesium iodide furnished the natural product, siamenol (**1**). Overall, the strategic applications of a series of palladium-catalyzed cross-coupling reactions facilitated by the use of dialkylbiarylphosphine ligands developed in our laboratory have enabled the rapid assembly of a prenylated carbazole natural product.

To gain further understanding into the regiocontrol of this reaction, we analyzed the reaction coordinate by computation of intermediates and transition state structures (Figure 1).[21,22] The catalytic cycle begins with the initial complexation of the Pd^0 catalyst with the aryl bromide (**I**). Oxidative addition into the C–Br bond (**TS-II**) affords the resting state intermediate **III**. The two possible transmetalation processes involving α-prenylzinc were next investigated, namely a four-membered transition state (**TS-IV-α-4-mem**) and a six-membered transition state (**TS-IV-γ-6-mem)** leading to α- and γ-prenyl palladium intermediates **V**, respectively. Given that the prenylzinc species undergoes rapid 1,3-shift at room temperature,[23] we also evaluated two additional mechanisms utilizing γ-prenylzinc bromide as the transmetalating agent (Figure 1, **TS-IV-γ-4-mem** and **TS-IV-α-6-mem**, respectively). We found that there is an energetic preference for the α-4-membered transition state over the α-6, but this was reversed in the γ case presumably due to the steric bulk around the forming Pd–C bond in **TS-IV-γ-4-mem**. The minimum-energy pathway involves the **TS-IV-α-4-mem**, generating the α-prenyl palladium intermediate **V**, which then undergoes product-determining η^1-α reductive elimination (**TS-VI**) to afford the product–catalyst complex **VII**. We also investigated γ reductive elimination leading to the γ-isomer and found that the η^3-γ elimination was preferred over the η^1-γ. The η^3-γ process was found to be disfavored by 12.2 kcal mol^{-1}. In a model system in which the prenyl substrate is replaced with an allyl, the η^1 reductive elimination is preferred over η^3 by 2.2 kcal mol^{-1}.[24] In the prenyl case, the steric bulk around the forming C–C bond precludes the γ reductive elimination from achieving the more stable η^1 geometry. The α isomer is favored universally for all steps, including the α-4-mem transmetalation. The high level of linear-selectivity observed with the current catalyst system is controlled by the preference for the α-isomer-forming reductive elimination via **TS-VI-η^1-α**.

In summary, we have developed the first general, practical, and completely linear-selective Negishi coupling of 3,3-disubstituted allyl organozinc reagents with aryl, heteroaryl, and vinyl halides. This reaction features exceptionally mild reaction conditions and is broad in scope with respect to both aryl/vinyl halide and allylzinc coupling partners. This linear-selective allylation methodology provides an effective means for accessing highly functionalized aromatic and heteroaromatic compounds bearing



Scheme 5. Concise synthesis of siamenol (**1**).

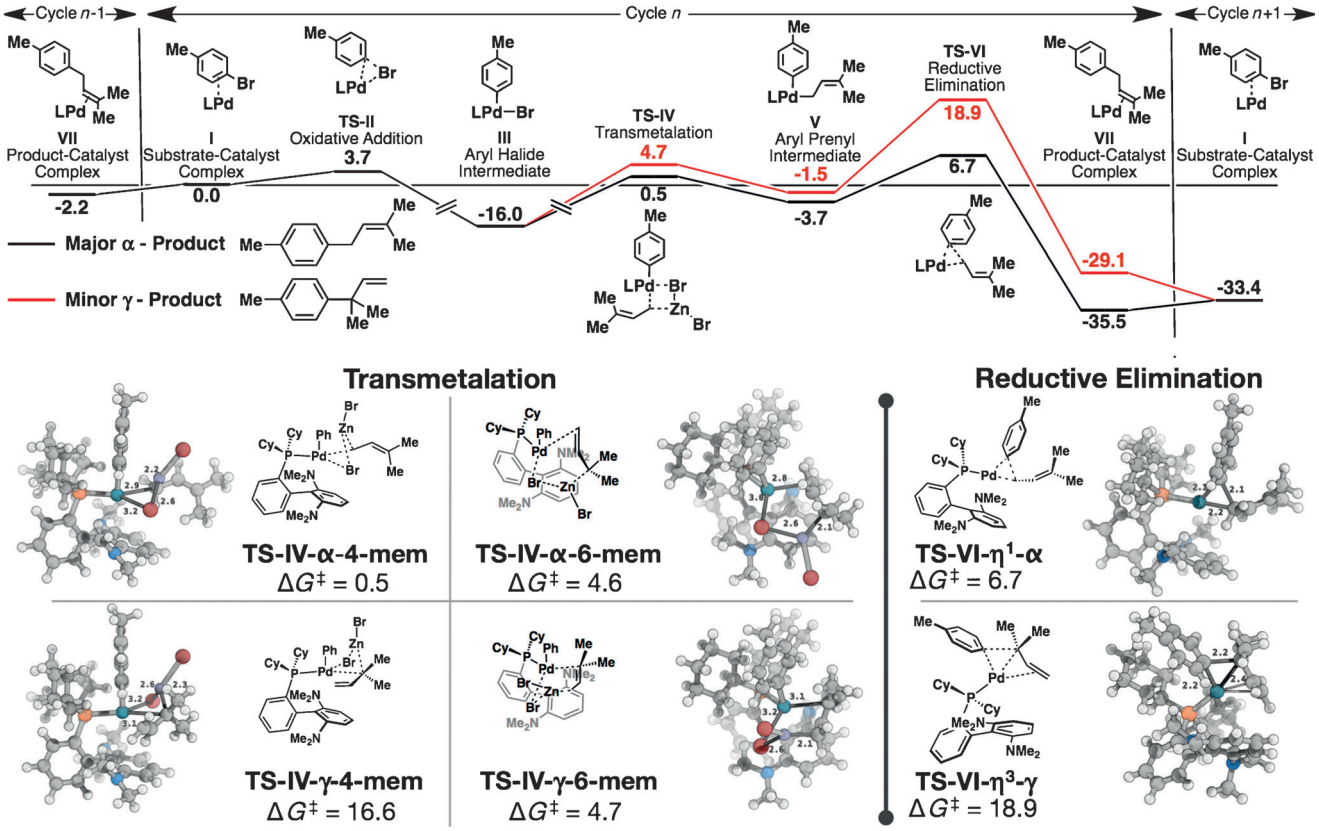


Figure 1. Top: Reaction coordinate of the Pd^0-catalyzed cross-coupling of prenylZnBr (**3**) with *p*-bromotoluene. Bottom: Transition structures for and transmetalation and reductive elimination transition structures.[22] Energies are given in kcal mol^{-1} and distances in Å. Computed structures are rendered in Pymol.[23]

prenyl-type side chains, as illustrated by the concise synthesis of anti-HIV natural product siamenol. Finally, theoretical calculations provided insights into the regiochemical-controlling parameters of these coupling processes, demonstrating the critical choice of the catalyst and the transmetalating reagent in achieving good selectivity for coupling reactions involving 3,3-disubstituted allyl nucleophiles.

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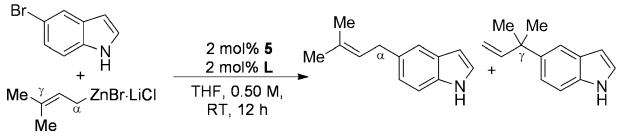

L = XPhos (**L3**)	60%	38%
L = CPhos (**L5**)	95%	<1%

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