C–C Coupling

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Regiodivergent and Diastereoselective CuH-Catalyzed Allylation of Imines with Terminal Allenes

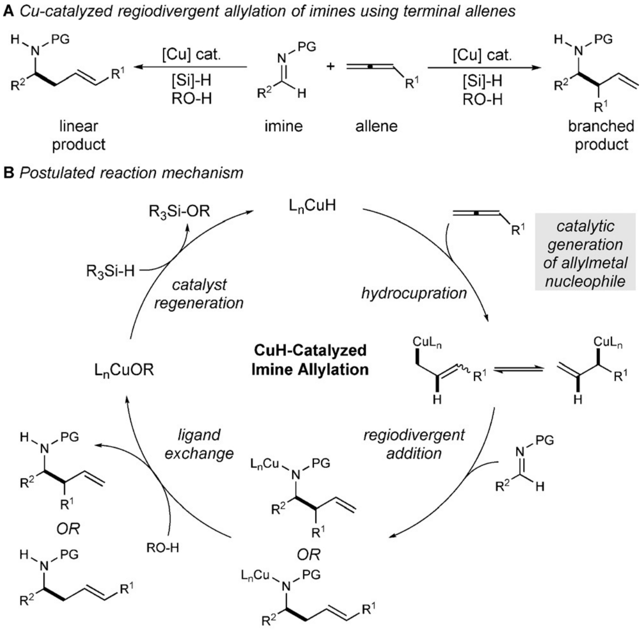
*Richard Y. Liu, Yang Yang, and Stephen L. Buchwald**

***Abstract:** A copper-catalyzed, chemoselective hydrometalation process enables the use of simple allenes as allylmetal nucleophile surrogates in imine allylation reactions. By modulating the nitrogen-protecting group, either highly branched- or linear-selective addition can be achieved from the same allene. Both reactions exhibit excellent diastereoselectivity and broad functional-group tolerance. Preliminary results indicate that good enantioselectivity can also be achieved in the linear-selective reaction. Finally, a mechanistic model for the regiodivergence is proposed on the basis of density functional theory calculations.*

The prevalence of nitrogen-substituted fragments in biologically active molecules has motivated the development of numerous efficient methods for their construction.[1] Among these, the catalytic synthesis of homoallylic amines through the stereoselective addition of an allyl fragment to imines has been the subject of extensive investigation.[2] Typically, these approaches require stoichiometric quantities of an allylmetal reagent as the nucleophilic component.[3–5] Thus, control of the stereoselectivity (*syn*/*anti*, *E*/*Z*) and regioselectivity (linear/branched) of the allylation reaction demands the highly regio- and diastereoselective synthesis of the corresponding precursor. Although elegant solutions exist for simple nucleophiles, the synthesis of more complex reagents, especially those containing base-sensitive functional groups, remains challenging.[6] As an alternative, we considered the possibility of catalytic access to both regioisomers from a common, easily prepared allyl nucleophile surrogate.[7]

Our group and others have investigated the generation of organocopper intermediates through the reaction of catalytic copper hydride with unsaturated substrates.[8,9] When these species are generated in a chemoselective manner in the presence of a suitable electrophile, functional-group-tolerant, stereoselective C–C[8] or C–heteroatom[9] bond formation can be achieved. In particular, we have recently described copper-catalyzed reductive addition reactions of olefin-derived nucleophiles to carbonyl and imine electrophiles.[8a,b,f] Using other metals, several elegant methods for the generation of allylmetal nucleophiles through boro-,[7a,b] carbo-,[7f–h] or hydrometalation[7c–e] of allenes or 1,3-dienes have been the subject of recent publications. We envisioned that a new strategy involving hydrocupration and nucleophilic attack to effect stereo- and regiocontrolled allylation of imines would represent a valuable addition to the existing collection of CuH-catalyzed C–C bond-forming transformations.

Specifically, as shown in Figure 1, we proposed that hydrocupration of readily available[10] terminal allenes might enable the catalytic formation of allylcopper complexes. We reasoned that subsequent addition of the allylcopper intermediate to imines, followed by ligand exchange with an alcohol[8a,e,11] could afford either regioisomer of the homoallylic amine and a copper alkoxide species. Subsequent σ-bond metathesis with a hydrosilane would then regenerate the copper hydride and close the catalytic cycle. Herein, we describe the development of complementary systems for synthesis of the branched and linear regioisomers of homoallylic amines with high diastereoselectivity.



C *Principal challenges*

- **Chemoselectivity:** hydrocupration of C=C bond in the presence of C=N bond
- **Regioselectivity:** access to both branched and linear products
- **Diastereoselectivity:** *syn*/*anti* in branched products; *E*/*Z* in linear products

Figure 1. Overview of the CuH-catalyzed reductive allylation reaction of imines using allenes.

We initiated our development of these reactions by examining the reaction of cyclohexylallene with a number of simple N-protected imine electrophiles under copper hydride catalysis conditions. With 1,2-bis(dicyclohexylphosphino)ethane (DCyPE) as the supporting ligand, allylation of N-benzyl imines was observed with high yield, generating

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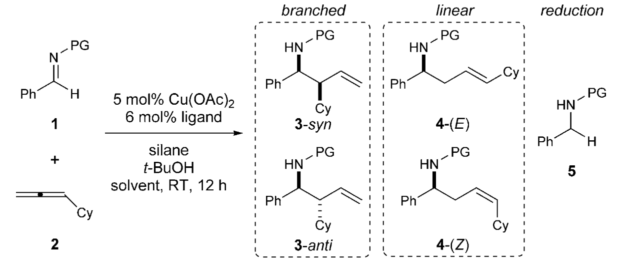
branched product with excellent regioselectivity. The diastereoselectivity was sensitive to solvent, with MTBE providing the highest *syn*/*anti* ratio (Table 1, entries 1–4). Replacement of the benzyl group with 2,4-dimethoxybenzyl (DMB) led to further improvement in the diastereoselectivity (entry 6).

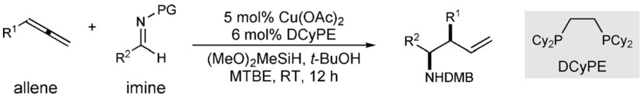
Table 1: Evaluation of the reaction conditions.

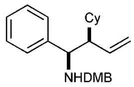


Entry	PG	Silane[b]	Solvent	% yield **3**[c] (*syn*/*anti*)[d]	% yield **4**[c] (*E*/*Z*)[d]
1	Bn	**A**	THF	99 (10:1)	<2
2	Bn	**A**	CyH	84 (5:1)	<2
3	Bn	**A**	toluene	92 (6:1)	<2
4	Bn	**A**	MTBE	88 (13:1)	<2
5	4-CF$_3$-Bn	**A**	MTBE	98 (7:1)	<2
6	2,4-DMB	**A**	MTBE	96 (16:1)	<2
7	Ph	**A**	THF	66 (3:1)	5 (n.d.)
8	S(O)*t*-Bu	**A**	THF	<2	8 (n.d.)
9	Boc	**A**	THF	4 (n.d.)	25 (4:1)
10	P(O)Ph$_2$	**A**	THF	<2	65 ($>$20:1)
11	P(O)Ph$_2$	**B**	THF[e]	<2	85 ($>$20:1)

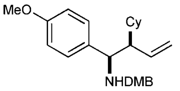
[a] Conditions: 0.1 mmol imine (1.0 equiv), allene (2.0 equiv), copper(II) acetate (0.05 equiv), DCyPE (0.06 equiv), silane (5.0 equiv), *tert*-butanol (2.0 equiv) in solvent (0.2 mL); see the Supporting Information for details. [b] **A** = (MeO)$_2$MeSiH; **B** = PhSiH$_3$. [c] Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [d] Diastereomeric ratio measured by ^{1}H NMR of the crude reaction mixture. [e] Reaction performed using 0.4 mL solvent.

Table 2: Scope of the branched-selective allylation reaction.[a]

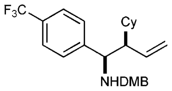




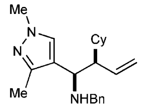
6a
95% yield
>20:1 *branched*/*linear*
16:1 *syn*/*anti*



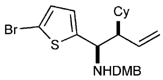
6b
97% yield
>20:1 *branched*/*linear*
>20:1 *syn*/*anti*



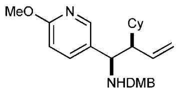
6c
98% yield
>20:1 *branched*/*linear*
9:1 *syn*/*anti*



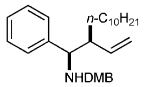
6d
79% yield
>20:1 *branched*/*linear*
10:1 *syn*/*anti*



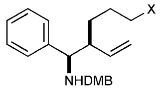
6e
65% yield
>20:1 *branched*/*linear*
15:1 *syn*/*anti*



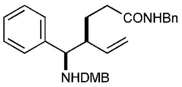
6f
77% yield
>20:1 *branched*/*linear*
14:1 *syn*/*anti*



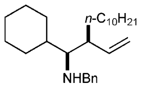
6g
89% yield
>20:1 *branched*/*linear*
19:1 *syn*/*anti*



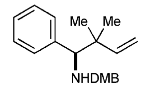
6h (X=OPiv)
72% yield
>20:1 *branched*/*linear*
9:1 *syn*/*anti*
6i (X=NMeTs)
69% yield
>20:1 *branched*/*linear*
8:1 *syn*/*anti*



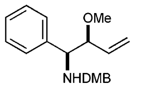
6j
71% yield
>20:1 *branched*/*linear*
12:1 *syn*/*anti*



6m
48% yield
>20:1 *branched*/*linear*
2:1 *syn*/*anti*



6k
99% yield
>20:1 *branched*/*linear*



6l
95% yield
>20:1 *branched*/*linear*
>20:1 *syn*/*anti*

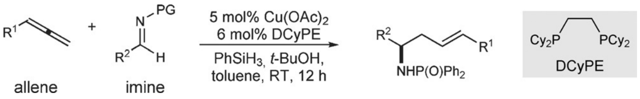
[a] Conditions: 1.0 or 0.5 mmol imine (1.0 equiv), allene (1.2 equiv), copper(II) acetate (0.05 equiv), DCyPE (0.06 equiv), (MeO)$_2$MeSiH (5.0 equiv), *tert*-butanol (2.0 equiv) in MTBE (1.0 or 2.0 mL); see the Supporting Information for details. MTBE = methyl *tert*-butyl ether. Average yield of isolated product from two experiments. Diastereomeric ratio measured by ^{1}H NMR of the crude reaction mixture.

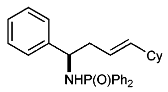
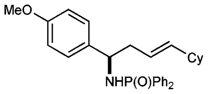
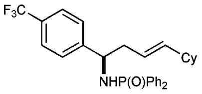
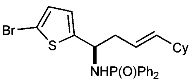
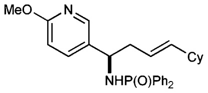
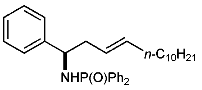
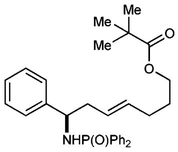
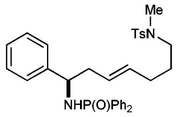
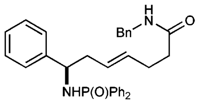
At this point, we considered whether other N-protecting groups, especially those potentially favoring different coordination modes, could alter the regiochemical outcome of this reaction (Table 1, entries 7–10). The effect of these modifications was most profound in the case of the diphenylphosphinoyl (DPP) group, which overturned the observed regioisomer preference to exclusively linear with excellent selectivity for the *E* olefin (Table 1, entry 10). Importantly, the amine-protecting groups identified for both regioselective methods (DMB and DPP) can be cleaved under mildly acidic conditions.[12]

The two sets of conditions established above were next evaluated for their scope in terms of compatible reaction partners. For the branched-selective reaction (Table 2), imines spanning a range of electronic properties could be transformed with high *syn* selectivity (**6a**–**6c**). Heterocyclic imines were also suitable reactants (**6d**–**6f**), with the heteroaryl bromide group remaining intact under the reaction conditions. An aliphatic imine was successfully allylated as well, although selectivity for the *syn* diastereomer was modest in this instance (**6k**). For this imine, use of the parent benzyl protecting group resulted in better reactivity than the DMB group. This strategy was also employed for other less-reactive imines, including *ortho*-substituted pyrazole **6d**. Terminal allene substrates bearing various functional groups were also suitable, including those containing an ester (**6h**), a sulfonamide (**6i**), and a secondary amide (**6j**). Finally, the branched-selective allylation conditions can also provide near-quantitative yields of reverse prenylation (**6l**) and protected *syn*-1,2-aminoalcohol (**6m**) products.

Using the second set of conditions, the linear homoallylic amines were obtained with excellent regioselectivity and high selectivity for the *E* alkene geometry (Table 3). Again, aldimines bearing both electron-rich and electron-poor (hetero)aryl groups (**7a**–**7f**) could be utilized. Unbranched allenes were also suitable substrates for this reaction (**7g**), and polar functional groups such as an ester (**7h**), a sulfonamide (**7i**), and an amide (**7j**) could also be employed without any detrimental effect on the regioselectivity or geometric purity. In all of these linear-selective reactions, no undesired branched regioisomer was observed, and only trace amounts of the *Z*-alkene product was produced in a few instances.

Table 3: Scope of the linear-selective allylation reaction.[a]



 **7a** 80% yield >20:1 *linear*/*branched* >20:1 *E*/*Z*	 **7b** 92% yield >20:1 *linear*/*branched* >20:1 *E*/*Z*	 **7c** 69% yield >20:1 *linear*/*branched* >20:1 *E*/*Z*
 **7e** 85% yield >20:1 *linear*/*branched* >20:1 *E*/*Z*	 **7f** 92% yield >20:1 *linear*/*branched* >20:1 *E*/*Z*	 **7g** 95% yield >20:1 *linear*/*branched* >20:1 *E*/*Z*
 **7h** 90% yield >20:1 *linear*/*branched* >20:1 *E*/*Z*	 **7i** 81% yield >20:1 *linear*/*branched* >20:1 *E*:*Z*	 **7j** 55% yield >20:1 *linear*/*branched* >20:1 *E*/*Z*

[a] Conditions: 0.5 mmol imine (1.0 equiv), allene (2.0 equiv), copper(II) acetate (0.05 equiv), DCyPE (0.06 equiv), phenylsilane (5.0 equiv), *tert*-butanol (2.0 equiv) in toluene (4.0 mL); see Supporting Information for details. Average yield of isolated product from two experiments. Diastereomeric ratio measured by ^{1}H NMR of the crude reaction mixture.

During the course of our optimization, we found that the chiral ligand Ph-BPE promoted the linear-selective reaction with high efficiency. When enantiomerically pure ligand was used, promising levels of enantioselectivity were obtained under improved conditions (Figure 2).[13] In this case, the crystallinity of N-DPP amines proved to be advantageous: following linear allylation, a small amount of nearly racemic product could be separated from the crude reaction as a solid following a single crystallization from ethyl acetate/hexanes, leaving behind more enantioenriched material. X-ray diffraction analysis of (−)-**7a** confirmed the connectivity and absolute configuration. With additional optimization, highly enantioselective versions of these allylation conditions might be achieved to further enhance the utility of these already highly diastereo-, regio-, and chemoselective transformations.

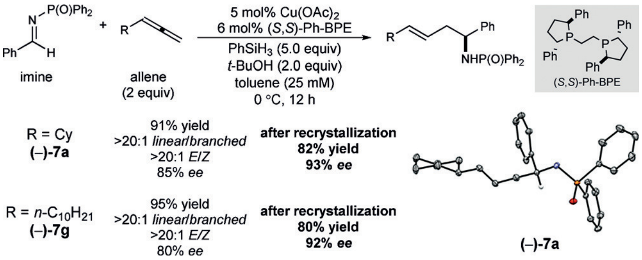


Figure 2. Enantioselective variants of the linear-selective allylation reaction.

Aiming to elucidate the mechanistic basis for the observed regiodivergence, we performed density functional theory (DFT) calculations on the reaction of DCyPE-ligated copper hydride with allenes and imines (Figure 3). Calculations suggest that irreversible hydrocupration of an allene forms a mixture of allylcopper species that quickly equilibrates to form the thermodynamically favored terminal *E*-allyl copper intermediate as the predominant species (see the Supporting Information for details). In the case of N-phosphinoyl imine electrophiles, we found that an allylation transition-state structure involving copper coordination to oxygen is favored over alternative open or N-bound geometries (Figure 3 A). Transfer of the allyl fragment via the copper-bound carbon atom results in the linear product. In contrast, for N-benzyl imines, the only closed transition-state structure involves copper coordination to the imine nitrogen (Figure 3 B). This six-membered, chair-like transition state leads to transfer of the allyl fragment via the internal carbon, leading to the branched product.

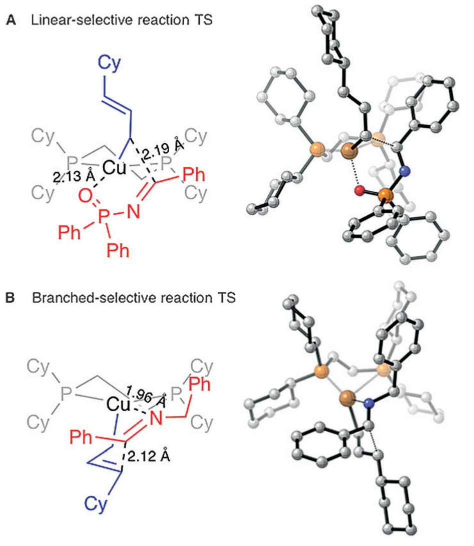


Figure 3. DFT transition-state models of regiodivergence in copper-catalyzed allylation reactions.[14]

In summary, a new copper-catalyzed regiodivergent allylation reaction of imines has been developed. Using simple allenes as allyl nucleophile surrogates, either linear or branched homoallylic amines can be obtained with high stereoselectivity. Further efforts towards the catalytic generation of organometallic nucleophiles from alkenes for selective bond-forming reactions are ongoing.

Acknowledgements

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Keywords: amines · C–C coupling · copper · multicomponent reactions · regioselectivity

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[14] M06/6-311 + G(d,p)-SDD/SMD(THF)//B3LYP/6-31G(d)-SDD plus a harmonic vibrational correction at 298 K. Further details and results can be found in the Supporting Information.

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