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Published in:
Journal of the American Chemical Society

DOI:
10.1021/ja312487r

Publication date:
2013

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Copper-Catalyzed Enantioselective Allyl–Allyl Cross-Coupling

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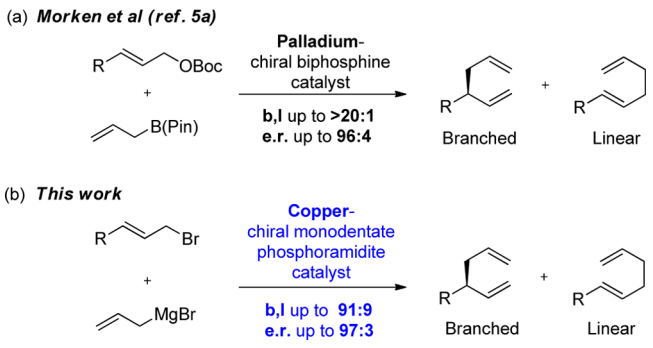
Supporting Information

ABSTRACT: A Cu(I)-phosphoramidite-based catalytic system that allows asymmetric allyl–allyl cross-coupling with high enantioselectivity is reported. This transformation tolerates a large variety of functionalized substrates. The versatility of this new reaction is illustrated in the catalytic asymmetric synthesis of the Martinelline alkaloids chromene derivative core.

Catalytic asymmetric C–C bond formation methodologies with high efficiency and selectivity are among the most important tools in organic synthesis.[1] Of particular importance is the metal-catalyzed allyl–allyl cross-coupling between allylmetal species and allylic electrophiles, which has the capacity to establish a stereogenic center bearing both an allyl and a vinyl group. These chiral 1,5-diene structures are abundant in naturally occurring terpenes and also serve as highly versatile intermediates and building blocks in organic synthesis.[2,3] Several transition-metal catalysts, including Pd, Au, Cu, and Ni, have been employed to enable catalytic allyl–allyl cross-coupling.[4] Nonetheless, high levels of enantioselectivity have only been achieved recently by the use of Pd catalysis.[5] Morken and co-workers[5a] described the Pd-catalyzed regio- and enantioselective cross-coupling of allylic carbonates and allylboronate (Scheme 1a) involving an inner-sphere 3,3′-reductive elimination mechanism. This catalytic allylation represents a highly valuable synthetic tool but leaves ample opportunities to develop non-Pd-based alternatives. To the best of our knowledge, Cu-catalyzed enantioselective allyl–allyl cross-coupling is unprecedented.

Scheme 1. Catalytic Asymmetric Allyl–Allyl Cross-Coupling Methodologies



In recent years, Cu-catalyzed asymmetric allylic alkylation (Cu-AAA) with organometallic reagents has become a very efficient transformation for the enantioselective construction of stereogenic centers.[6] This transformation offers the possibility of using nonstabilized organometallic nucleophiles, allowing the introduction of alkyl,[7] aryl,[8] vinyl,[9] allenyl,[10] or alkynyl[11] fragments. However, the transfer of a simple allyl group (e.g., allylCuX), with control of enantioselectivity, remains a major challenge. Compared with simple alkyl groups, allylcopper species can exist in a delocalized contact η^3 π-allyl ion-pair structure.[4a,12] This structural feature may have hampered the discovery of an effective catalytic system to enable this transformation with high stereoselectivity.

Herein, we report the first Cu-catalyzed enantioselective allyl–allyl cross-coupling of an allyl Grignard reagent and allyl bromides to afford chiral 1,5-dienes in good yields and high enantioselectivity (Scheme 1b).

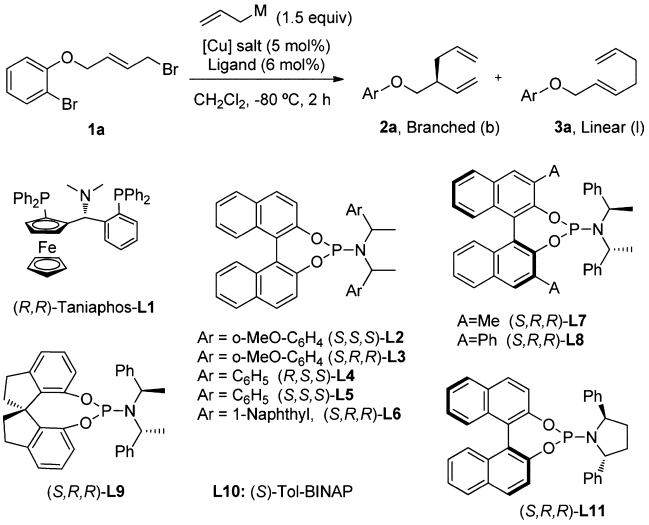
We started our study with a ferrocenyl-type chiral diphosphine **L1** and CuBr·SMe_2 (Table 1), which has been shown previously to be effective for the AAA of allyl bromides with simple alkyl Grignard reagents.[7b] Allyl bromide **1a** was used for the reaction optimization. Unfortunately, reaction between **1a** and allylmagnesium bromide in CH_2Cl_2 at −80 °C, with this catalytic system, led to less than 10% conversion and predominantly linear product (b:l = 15:85) (Table 1, entry 1). Other biphosphine ligands showed similar results, and so monodentate phosphoramidite ligands[13] were tested. We examined the Cu-phosphoramidite ligand **L2** using chloride as a leaving group, which has been also shown previously to be effective for Cu-AAA with alkyl Grignard reagents.[7a] Although in this case the reaction led to full conversion, again very low regioselectivity with negligible enantioselectivity (59:41, e.r.) for the branched product was obtained (Table 1, entry 2). An improved regioselectivity and promising enantioselectivity (87:13 e.r.) were achieved by using the same catalytic system but bromide as a leaving group (entry 3). The nature of the allyl organometallic reagent proved also to be critical to obtain good conversion and selectivity. Thus, the use of allylmagnesium chloride gave only 20% conversion with poor regio- (41:59) and enantioselectivity (58:42 e.r., entry 4). We also used allyllithium, encouraged by our recent discovery of an enantioselective Cu-catalyzed method for the allylic alkylation with organolithium reagents.[7c] Nonetheless, although the conversion was complete, the regioselectivity was very low, albeit high enantioselectivity was found (b:l = 22:78, 91:9 e.r., entry 5).

Encouraged by the results obtained with **L2**, we studied variations in ligand structure (see **L2**–**L11**, entries 6–14) using CuBr·SMe_2. It was found that ligand (*R*,*S*,*S*)-**L4**[13a] led to a major increase in regioselectivity toward the branched product

Received: December 21, 2012
Published: January 27, 2013

   dx.doi.org/10.1021/ja312487r | J. Am. Chem. Soc. 2013, 135, 2140–2143

Table 1. Screening of Different Conditions and Representative Ligands



entry[a,b]	L	M	[Cu]	2a:3a[c]	e.r.,[d] 2a
1[e,f]	**L1**	MgBr	$CuBr{\cdot}SMe_2$	15:85	n.d.
2[g]	**L2**	MgBr	$CuBr{\cdot}SMe_2$	37:63	59:41
3	**L2**	MgBr	$CuBr{\cdot}SMe_2$	47:53	87:13
4[h]	**L2**	MgCl	$CuBr{\cdot}SMe_2$	41:59	58:42
5	**L2**	Li[i]	$CuBr{\cdot}SMe_2$	22:78	91:9
6	**L3**	MgBr	$CuBr{\cdot}SMe_2$	51:49	85:15
7	**L4**	MgBr	$CuBr{\cdot}SMe_2$	65:35	94:6
8	**L5**	MgBr	$CuBr{\cdot}SMe_2$	45:55	61:39
9	**L6**	MgBr	$CuBr{\cdot}SMe_2$	59:41	79:21
10	**L7**	MgBr	$CuBr{\cdot}SMe_2$	65:35	92:8
11	**L8**	MgBr	$CuBr{\cdot}SMe_2$	56:44	86:14
12	**L9**	MgBr	$CuBr{\cdot}SMe_2$	50:50	94:6
13	**L10**	MgBr	$CuBr{\cdot}SMe_2$	60:40	80:20
14	**L11**	MgBr	$CuBr{\cdot}SMe_2$	17:83	72:28
15[j]	**L4**	MgBr	$CuBr{\cdot}SMe_2$	68:32	97:3
16[j]	**L4**	MgBr	CuTC	70:30	97:3
17[j]	**L4**	MgBr	CuCN	82:18	56:44
18[j]	**L4**	MgBr	$(CuOTf)_2{\cdot}C_6H_6$	77:23	97:3

[a]Conditions: 0.2 mmol of allyl bromide, 1.5 equiv of allylmagnesium bromide diluted in CH_2Cl_2, 0.05 M. AllylMgBr was added over 2 h unless otherwise noted. [b]Conversion by GC-MS. All reactions gave full conversion unless noted. [c]**2a**/**3a** ratios determined by GC-MS or ^1H NMR spectroscopy. [d]Determined by chiral HPLC analysis. [e]Normal addition. [f]<10% conversion. [g]Leaving group = Cl. [h]20% conversion. [i]AllylLi was added as a solution in *tert*-butyl methyl ether. [j]AllylMgBr was added over 5 h.

1b (b:l = 65:35) with high enantioselectivity (94:6 e.r., entry 7). The use of other phosphoramidite or BINAP-derived ligands (Table 1, entries 6, 8−14, and Supporting Information, Table S1) did not improve these results. In all cases, full conversion was obtained overnight at −80 °C. It is remarkable that introduction of methyl groups at the 3,3′ positions in the binaphthol moiety (entry 10) or use of a spiro-biphenol structure in the ligands (entry 12) led to similar e.r. values. However, variations of the amine moiety caused a drastic decrease of e.r. (entry 14 and Table S1). It should also be noted that this reaction does not proceed in the absence of the Cu catalyst, leading to complete recovery of the substrate.

The effects of different conditions, solvents, and temperatures were also studied. Slow addition (5 h) of the allyl Grignard reagent to the reaction mixture increased both regio- and enantioselectivity (entry 15), but longer addition times did not lead to further improvement. Variations in solvents and temperatures did not improve the selectivity of the reaction. (See Table S2 for details.)

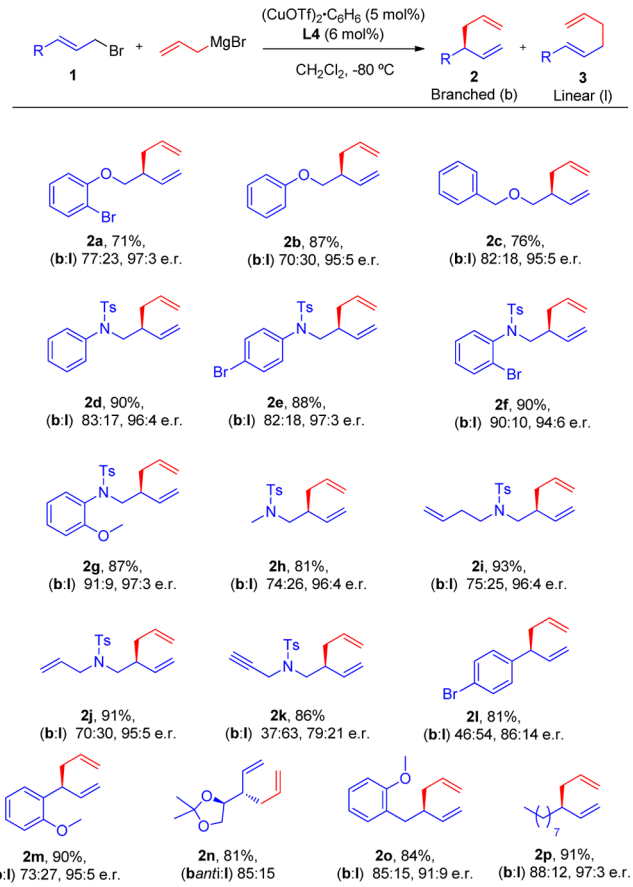
We next investigated the role of the Cu salt. It has been shown that the use of Cu(I) cyanide as catalyst provides high S_N2' selectivity in the reaction between allylic substrates and Grignard reagents.[4b,14] Indeed, the highest regioselectivity for the reaction between allyl bromide **1a** and allylmagnesium bromide was obtained for CuCN; however, it gave a negligible enantiomeric excess (entry 17). All the other Cu(I) salts tested provided similar high enantioselectivity in C−C bond formation as observed for $CuBr{\cdot}SMe_2$ in the allylation of allyl bromide **1** (Tables 1 and S2). In general, the use of Cu salts with noncoordinating counteranions favors the branched allyl−allyl cross-coupling product, and $(CuOTf)_2{\cdot}C_6H_6$[15] was found to be the most suitable Cu source for this reaction (b:l = 77:23, 97:3 e.r., entry 18). A more electron-deficient Cu species presumably accelerates the reductive elimination step, preventing the formation of a linear allyl−allyl cross-coupling product.[14a]

Having established the optimal copper−ligand combination (Table 1, entry 18), we next explored the scope and limitation of this new reaction. A variety of synthetically useful allylic substrates bearing different functionalities, including protected alcohols, amines, alkenes, and acetals, were tolerated, showing excellent enantioselectivities in nearly all cases (Table 2). Allylation of compound **1c**, bearing a benzyloxy group, was accomplished with good regioselectivity and excellent enantioselectivity, providing **2c**, an advanced intermediate in the synthesis of *d*-sabinene,[16] a monoterpene widely distributed in essential oils from plants. Allylic bromides bearing a protected amine were also suitable substrates for this reaction, delivering chiral building blocks for natural product synthesis (**2d**−**2k**). The presence of a methoxy group or bromide substituent (which can be sensitive to oxidative addition in a Pd-based catalytic system) in the aromatic part of the substrate was also well tolerated, providing synthetically useful functionalities for further transformations (**2a**, **2e**−**2g**). An interesting behavior can be observed with amines bearing *ortho*-substituents at the aryl ring. Both *o*-bromo and *o*-methoxy substituents led to an increase in regioselectivity when compared to the unsubstituted analogues (**2d** vs **2f** and **2g**). Amines **2i** and **2j** can be readily transformed to the corresponding unsaturated piperidines, azepanes, or azocanes by using olefin ring-closing metathesis.[17] A decrease in the regio- and enantioselectivity was observed for enyne **2k**, where a possible intramolecular coordination between the Cu catalyst and the triple bond might interfere in the enantiodiscriminating step.

p-Bromocinnamyl bromide **1l** underwent facile reaction to give the coupling product **2l** with good yield albeit moderate regio- and enantioselectivity. A major improvement in the regioselectivity was again observed when a coordinating functionality in the *ortho* position, such as an *o*-methoxy substituent, was introduced at the phenyl ring, providing diene **2m** with high enantioselectivity. This result and those for **2a**, **2f**, and **2g** suggest a possible coordination between the methoxy or bromide substituent and the Cu complex, which could also be a key factor to increase the enantioselectivity in cinnamyl-type substrates. The use of a dioxolane-containing allylic bromide[18] **1n** led to the diastereoselective formation of valuable 1,2-hydroxyallyl moiety **2n** with good stereocontrol of the *anti* isomer. It should be mentioned that simple linear substrate **1p**

dx.doi.org/10.1021/ja312487r | J. Am. Chem. Soc. 2013, 135, 2140−2143

Table 2. Scope of Cu-Catalyzed Enantioselective Allyl–Allyl Cross-Coupling[a]



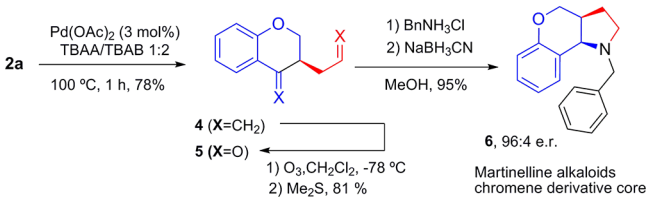
[a]Conditions: 0.2 mmol of allyl bromide (1 equiv), 1.5 equiv of allylmagnesium bromide diluted in CH_2Cl_2, 0.05 M in CH_2Cl_2, 5 h addition time. All reactions gave full conversion (GC-MS). Branched/linear ratios determined by ^1H NMR spectroscopy or GC-MS. Enantiomer ratios determined by chiral HPLC or chiral GC analysis.

provides branched product **2p** with high regio- and enantioselectivity.

To illustrate the synthetic utility of the method, allyl–allyl cross-coupling product **2a** was easily converted into the Martinelline alkaloids chromene derivative core (Scheme 2).[19,20] This class of natural occurring chromene derivatives finds utility in the treatment of impulsive disorders, Parkinson's disease, psychoses, memory disorders, and anxiety.[20]

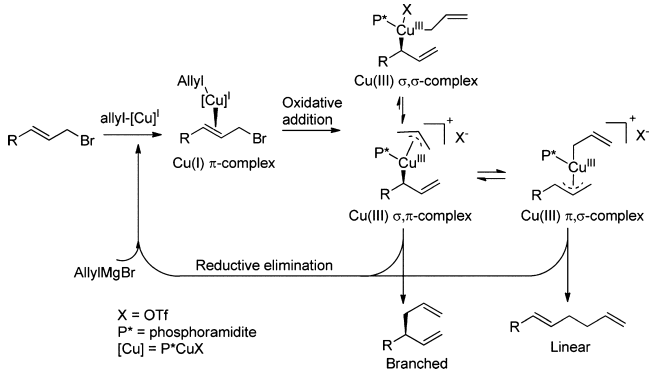
Synthesis of **2a** was executed on a larger scale (5 mmol, 1.5 g) and still furnished the product with high enantioselectivity (96:4 e.r.) without erosion of yield. The use of catalytic amounts of $Pd(OAc)_2$ under ligand-free conditions[21] resulted in selective transformation of this bromide into the six-membered-ring Heck product **4** with no isomerization to the endocyclic double bond. Ozonolysis of both double bonds followed by reductive amination gave compound **6** in good overall yield without lowering the e.r.

Scheme 2. Transformation of Product 2a into the Martinelline Alkaloids Chromene Derivative Core



Although detailed mechanistic studies are currently being pursued, a catalytic cycle can be proposed for this novel Cu-catalyzed allyl–allyl cross-coupling. In accordance with the proposed mechanism for the Cu-catalyzed AAA,[14] the allylcopper species generated by transmetalation between the Cu(I) salt and allylmagnesium bromide would undergo oxidative addition with the allylic substrate. Taking into account the behavior of allylcopper complexes,[4a,12] the resulting Cu^{III} σ–σ complex could probably equilibrate to a 16-electron penta-coordinated-Cu^{III} σ–π intermediate,[22] where the allyl group is coordinated to Cu via an η^3 coordinative mode (Scheme 3). This Cu^{III} σ–π intermediate would lead directly to

Scheme 3. Proposed Mechanism for the Cu-Catalyzed Allyl–Allyl Cross-Coupling



the branched product via reductive elimination. Nonetheless, in this case, the extra stabilization caused by the η^3 bonding mode of the allyl group would retard the reductive elimination and could slightly favor the isomerization from the σ–π complex to the π–σ complex (it also maintains the penta-coordination), which gives rise to the linear product. This behavior would explain the variation in S_N2' selectivity. Similarly, the aryl ring (especially with electron-withdrawing groups present) of a cinnamyl-type substrate further might reduce the rate of reductive elimination, favoring the formation of the π–σ complex, since the transition state for the reductive elimination involves a decrease of electron density at the benzylic carbon.[14a] The results obtained with **2l** and **2m** (Table 2) support this explanation.[23]

In summary, the first Cu-catalyzed asymmetric allyl–allyl cross-coupling has been described. The use of commercially available allylmagnesium bromide and easily accessible allylic bromides with cheap Cu-phosphoramidite catalyst is key for the success of this reaction. The only waste produced in this novel transformation is $MgBr_2$. The use of Cu complexes with noncoordinating counteranions as present in $(CuOTf)_2{\cdot}C_6H_6$ was found beneficial to increase the regioselectivity of the reaction. The potential applications in total synthesis were demonstrated in a three-step synthesis of the biologically active Martinelline alkaloid chromene derivative core structure.

dx.doi.org/10.1021/ja312487r | J. Am. Chem. Soc. 2013, 135, 2140–2143

■ ASSOCIATED CONTENT

Supporting Information

Optimization tables, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Netherlands Organization for Scientific Research (NWO-CW) and the National Research School Catalysis (NRSC-C) are acknowledged for financial support. V.H. thanks the Spanish Ministry of Science and Innovation (MICINN) for a postdoctoral fellowship. M.P. thanks the Xunta de Galicia for an Angeles Alvariño contract.

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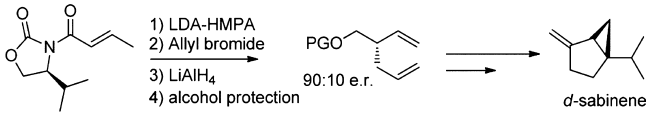

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(22) The fact that the reaction between **1a** and crotylmagnesium bromide resulted in a nonselective mode of substitution at the two different allylic termini supports the formation of this intermediate (see Scheme S1).

(23) For a similar behavior in the Cu-catalyzed allylic alkylation with allenyl boron reagents, see ref 10.