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Copper-Free Asymmetric Allylic Alkylation of Trisubstituted Cyclic Allyl Bromides Using Grignard Reagents**

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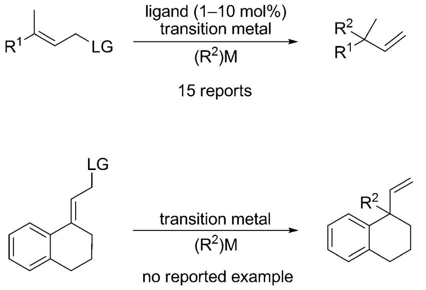
The formation of all-carbon quaternary centers is of considerable importance in modern organic chemistry and has drawn the attention of numerous research groups. Several new catalytic procedures with non-related mechanisms were developed for the formation of all-carbon quaternary centers.[1] The Cu-catalyzed asymmetric allylic alkylation (AAA) emerged as a powerful and versatile method to form C–C bonds in a highly regioselective and enantioselective fashion.[2] Different groups, such as alkyl, vinyl, allyl, alkenyl, aryl, and heteroaryl, could be introduced using a wide variety of hard or soft organometallic reagents and an appropriate transition metal (Cu, Pd, ect.; Scheme 1). Many research groups have reported the use of several chiral ligands for the catalytic enantioselective formation of quaternary centers in acyclic substrates using AAA, which proceeded with relatively high efficiency.[3]



Scheme 1. Formation of quaternary centers in acyclic and cyclic substrates using transition-metal catalysis. M = metal, LG = leaving group.

Noteworthy, there are no examples of the catalytic enantioselective formation of quaternary centers in cyclic substrates. The two existing reports deal with chirality transfer using enantioenriched substrates and a stoichiometric amount of copper.[4] In 2006, Breit and co-workers reported the formation of quaternary centers in a six-membered-ring system with full chirality transfer and excellent regioselectivity.[4a] Unfortunately, the substrate scope was very limited (two substrates). In 2007, Soorukram and Knochel reported a single example for the formation of a quaternary center in a cyclic adduct with full chirality transfer, employing a five-membered-ring starting material and an enantiopure allylic phosphate group.[4b] The asymmetric hydrovinylation developed by Rajanbabu and co-workers could be an interesting alternative for the catalytic formation of the desired quaternary centers in cyclic compounds.[5] They subjected the tetralin substrate to their optimized reaction conditions, but despite a high *ee* value of 95%, the selectivity of the reaction turned out to be modest. Indeed, 30% isomerization of the starting material to the endocyclic olefin was observed by ^{1}H NMR spectroscopy. Moreover, the substrate scope remained limited (2 examples) and the only nucleophile that could be introduced was a methyl moiety.

Our group developed a copper-free AAA catalyzed by a bidendate NHC ligand, affording the desired quaternary centers in the acyclic S_N2' adducts with excellent regioselectivity and high enantioselectivity.[6] Noteworthy, this method is complementary to the transition-metal-catalyzed AAA. Indeed, substrates that did not react efficiently in a conventional transition-metal-catalyzed AAA, reacted well in a copper-free AAA, affording the products with high regioselectivity and enantioselectivity.[7] We thus decided to investigate a model substrate with an exocyclic allyl bromide in the benzylic position of an aryl ring. This substrate class is potentially interesting because the products bearing an exocyclic vinyl chain are precursors for the synthesis of biologically active compounds, such as aphanorphine and eptazocine.[8] Previously, the exocyclic chain was synthesized through an alkylation directed by a stoichiometric amount of oxazoline, through an intramolecular asymmetric Heck reaction, or through an enzyme-catalyzed desymmetrization of a prochiral malonate.[9] Those routes encompass ten steps versus the three potential steps using our method. In our case, the substrate could be easily obtained from commercially available ketone in a two-step procedure (addition of a vinyl Grignard reagent to the ketone, followed by treatment with 48% HBr; Scheme 2).

The allyl bromides **1a** and **1b**, obtained from commercially available, inexpensive α-tetralone and thiochroman-4-one, were selected as model substrates. During our previous study on the copper-free AAA, we found the optimal imidazolium salt (ligand) by screening for both electronic and steric effects on the chelating part (left part of the ligand) and steric effects on the blocking part (right part of the ligand). Gratifyingly, we were able to isolate the desired adduct **2a** with perfect regioselectivity, good yield (63%), and an e.r. of 93:7 e.r. by using ligand **L1** as carbene precursor (Table 1, entry 1). Crucially, when using the same ligand in combination with a catalytic amount of copper thiophene-

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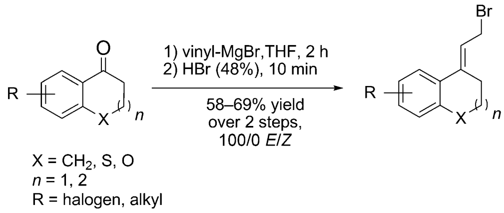
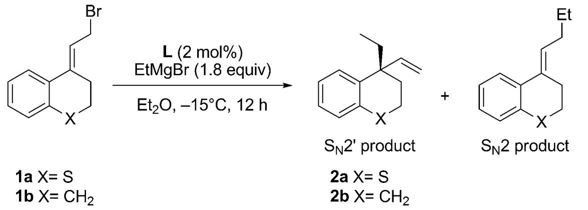


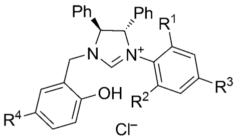
Scheme 2. Synthesis of substrates **1**.

Table 1: Selected optimizations.[a]



Entry	X	L	Yield [%][b]	e.r.[c]
1	S	**L1**	63	93:7
2[d]	S	**L1**	25	90:10
3	S	**L2**	50	91.5:8.5
4	S	**L3**	25	89.5:10:5
5	S	**L4**	30	91:9
6	CH_2	**L1**	66	93:7(S)[e]
7[d]	CH_2	**L1**	20	88:12
8	CH_2	**L2**	50	90:10
9	CH_2	**L5**	20	93:7

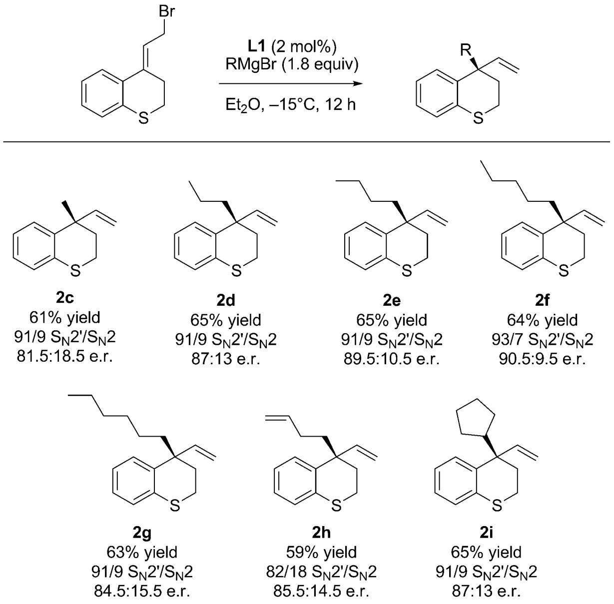
[a] All reactions were carried out on a 0.3 mmol scale, proceeded with full conversion of the starting material, and gave only the S_N2' (vs. S_N2) products, as determined by ^1H NMR spectroscopy. [b] Yields determined after column chromatography on silica gel. [c] Enantiomeric ratios (e.r.) determined by gas (GC) or supercritical-fluid (SCF) chromatography on chiral stationary phases. [d] Reactions were carried out with CuTc (2 mol%). [e] Absolute configuration determined using Ref. [5a].



L1: $R^1 = R^2 = Et, R^3 = R^4 = H$
L2: $R^1 = Et, R^2 = Me, R^3 = R^4 = H$
L3: $R^1 = R^2 = R^3 = Me, R^4 = H$
L4: $R^1 = Et, R^2 = Me, R^3 = H, R^4 = 1\text{-naphthyl}$
L5: $R^1 = Et, R^2 = Me, R^3 = H, R^4 = Ph$

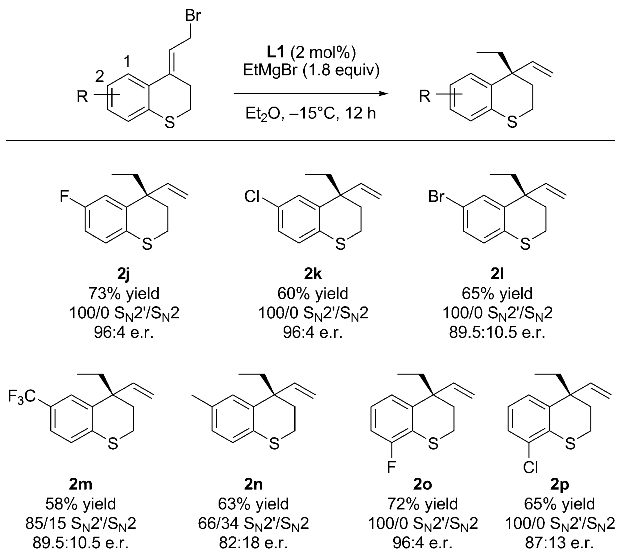
carboxylate (CuTC), we observed a significant decrease of the yield of isolated product (Table 1, entry 1 vs. entry 2), and a slight erosion of the enantioselectivity. A messy ^1H NMR spectrum of the crude led us to presume that the steric environment of the substrate resulted in side reactions when a transition metal was employed. Secondly, the sulfur atom may poison the catalyst. We further investigated the importance of the steric hindrance on the blocking part of the ligand. When we reduced the steric hindrance by switching from two ethyl groups to a methyl/ethyl substitution pattern on the blocking part (**L2**), we noticed a slight decrease in enantioselectivity and yield (Table 1, entry 1 vs. entry 3). By further reducing the steric bulk of the blocking part (**L3**), the trend became more apparent: the desired adduct was isolated with a low yield of 25% and an e.r. of 89.5:10.5 (Table 1, entry 4). The introduction of a bulky 1-naphthyl group in *para* position to the hydroxy group (**L4**) turned out to be detrimental for the yield of the reaction (Table 1, entry 5). The trends described above were also observed when an allyl bromide derived from an α-tetralone was used. Again, the employment of a catalytic amount of CuTC afforded the desired adduct **2b** in a low yield of 20% (Table 1, entry 6 vs. entry 7). Ligand **L1** with its two ethyl groups on the blocking part and an aryl ring on the chelating part turned out to be the ligand of choice (Table 1, entry 6 vs. entries 8 and 9).

Next, the scope of the nucleophile was studied by with a variety of Grignard reagents with different steric hindrance and reactivities. The methyl Grignard reagent could be introduced, giving product **2c** with good regioselectivity and promising enantioselectivity (e.r. = 81.5:19.5) in good yield (Scheme 3). A representative range of linear nucleophiles could be introduced to obtain products **2d–h** with generally good regioselectivity and slightly higher enantioselectivity and yield using Grignard reagents such as *n*BuMgBr or butenyl-MgBr (Scheme 3). Interestingly, secondary bulky Grignard reagents, such as cyclopentyl-MgBr, could also be used, giving product **2i** in encouraging enantioselectivity and regioselectivity, and good yield (Scheme 3). Crucially, even in the less-challenging formation of quaternary centers in acyclic substrates, the use of alkyl Grignard reagents is mainly limited to ethyl Grignard reagents, thus showing the generality and the efficiency of the developed method for the formation of quaternary centers in cyclic substrates with versatile substitution patterns.

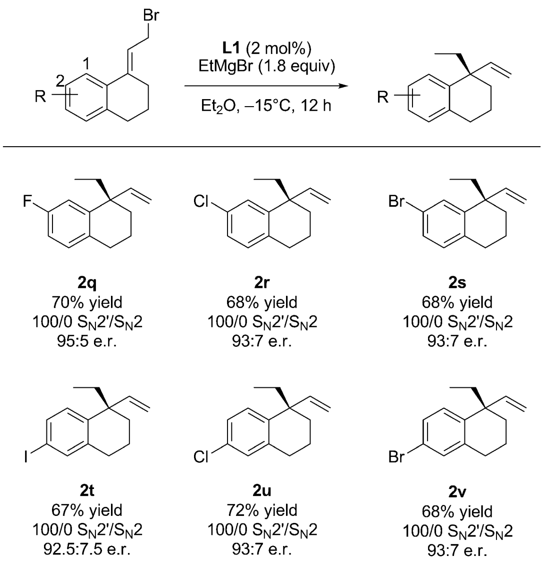


Scheme 3. Scope of nucleophiles. All reactions were carried out on a 0.3 mmol scale and proceeded with full conversion of the starting material. Yields determined after column chromatography on silica gel, S_N2':S_N2 product ratios determined by ^1H NMR spectroscopy, enantiomeric ratios determined by GC or SFC on a chiral stationary phase.

Next, the substrate scope of allyl bromides derived from substituted thiochroman-4-ones was investigated (Scheme 4). The introduction of various halogen atoms at the 2 position of



Scheme 4. Scope of substituted allyl bromides derived from thiochroman-4-one. All reactions were carried out on a 0.3 mmol scale and proceeded with full conversion of the starting material. Yields determined after column chromatography on silica gel, S_N2':S_N2 product ratios determined by ^{1}H NMR spectroscopy, enantiomeric ratios determined by GC or SFC on a chiral stationary phase.

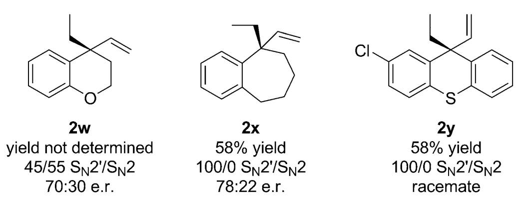


Scheme 5. Scope of substituted allyl bromides derived from α-tetralone. All reactions were carried out on a 0.3 mmol scale and proceeded with full conversion of the starting material. Yields determined after column chromatography on silica gel, S_N2':S_N2 product ratios determined by ^{1}H NMR spectroscopy, enantiomeric ratios determined by GC or SFC on a chiral stationary phase.

the aryl ring afforded the desired adducts (**2j–l**) with perfect regioselectivity, satisfactory yields, and enantiomeric ratios ranging from 89.5:10.5 to 97:3 (Scheme 4). The observed enantioselectivities with different halogen atoms in the 2 position of the aryl ring clearly demonstrated a complex trend as a result of electronic and steric effects. The introduction of a strongly electron-withdrawing group or a moderately electron-donating group resulted in the erosion of both enantioselectivity and regioselectivity (products **2m**,**n**; Scheme 4). The scope of the reaction with regard to electronic density seems to be rather narrow, but the good results obtained for bromide- and chloride-substituted products **2k** and **2l**, respectively, allows the introduction of either various electron-donating groups or a CF_3 group by well-established methods, such as Suzuki coupling or trifluoromethylation of aromatic halides.[10] The influence of a substituent in the 4 position of the aryl ring was probed next (Scheme 4). The synthesis of products **2o**,**p** clearly demonstrated that our method tolerates substituents in both the 2 and 4 position, though a decreased enantioselectivity was noticed in the case of the chlorine-substituted derivative **2k** verus **2p** (Scheme 4).

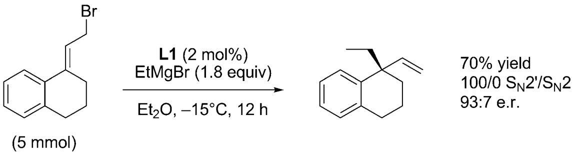
The scope of allyl bromides derived from α-tetralone was examined next (Scheme 5). The presence of various halogen atoms in the 2 position of the aryl ring resulted in the formation of the desired adducts **2q–s** with perfect regioselectivity, satisfactory yield, and excellent enantioselectivity (Scheme 5). The fluoride-substituted substrate again afforded the highest enantioselectivity, as already described for the thiochroman-4-one derivatives (Scheme 4). Additionally, the 3 position of the aryl ring could also be substituted with different halogen atoms, resulting in the corresponding products **2t–v** with perfect regioselectivity, good enantioselectivity, and satisfactory yield (Scheme 5).

The limitation of the method was probed by testing the catalysis on a seven-membered-ring system, which resulted in the erosion of the e:r to 78:22, giving product **2x** with perfect regioselectivity and in 58% yield (Scheme 6). The presence of an oxygen atom instead of a sulfur atom or a CH_2 group resulted in a significant loss of enantioselectivity and regioselectivity (**2w**). This observation is not surprising, as electron-rich starting materials also afforded poor results in the previous study.[11] To investigate the limitation of our catalyst, we subjected the allyl bromide of thioxanthone to our optimized reaction conditions. The desired adduct **2y** was obtained with perfect regioselectivity and good yield, albeit as a racemic mixture (Scheme 6). The synthesis of a five-membered-ring system or the incorporation of a protected amine failed using our method (Scheme 2).

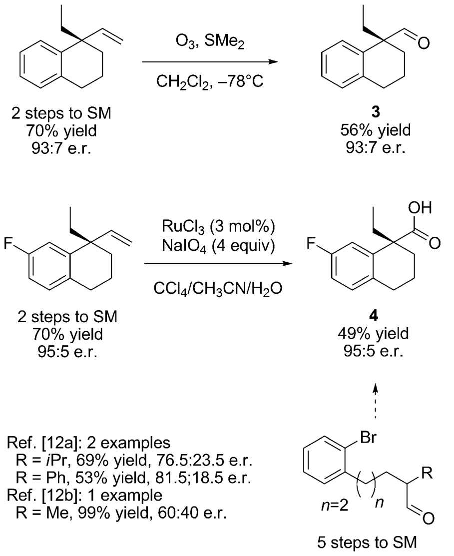


Scheme 6. Scope of miscellaneous substrates. All reactions were carried out on a 0.3 mmol scale and proceeded with full conversion of the starting material. Yields determined after column chromatography on silica gel, S_N2':S_N2 product ratios determined by ^{1}H NMR spectroscopy, enantiomeric ratios determined by GC or SFC on a chiral stationary phase.

The reaction is scalable to 5 mmol with no erosion of the enantioselectivity or regioselectivity (Scheme 7). The terminal double bond of the adduct could be transformed to the corresponding carboxylic acid by employing an oxidative cleavage with a catalytic amount of ruthenium trichloride and four equivalents of sodium metaperiodate, giving **3** in good yield. This compound can also be formed by Pd-catalyzed intramolecular γ arylation of a carbonyl compound. However, this method was reported to be efficient only for the formation of the five-membered ring.[12] Concerning the six-membered ring, only a few examples with low enantiomeric ratios were disclosed (Scheme 8). In addition, the accessibility of the starting materials for our method is better more appealing (two vs. five steps).



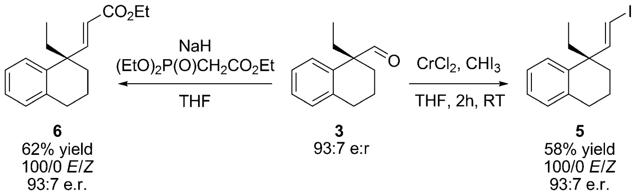
Scheme 7. Scale-up experiment.



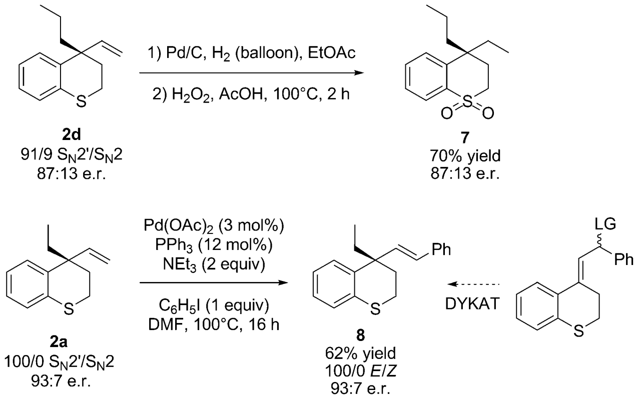
Scheme 8. Oxidative cleavage of the double bond. SM = starting material.

Aldehyde **3**, derived from product **2b**, can be converted to the versatile *E*-vinyl iodide **5** using the Takai reaction (Scheme 9).[13] On the other hand, intermediate **6** is a potential substrate for the formation of two contiguous stereocenters by 1,4-conjugate addition using copper catalysis, as previously reported by Feringa and co-workers (Scheme 9).[14]

Secondly, adducts containing a sulfur atom could be hydrogenated using palladium on charcoal with hydrogen under atmospheric pressure, followed by oxidation to give the enantioenriched sulfone **7** (Scheme 10). These adducts could also be engaged in a Heck reaction to give **8** without erosion of enantioselectivity in an acceptable yield (Scheme 10).



Scheme 9. Use of enantioenriched aldehydes.



Scheme 10. Oxidation of the sulfur atom and Heck coupling. DYKAT = dynamic kinetic asymmetric transformation.

To conclude, the formation of quaternary centers in cyclic substrates through asymmetric allyl alkylations using Grignard reagents was disclosed. The reaction tolerates a large range of nucleophiles and has a wide substrate scope, delivering the desired adducts with high regioselectivity and enantioselectivity, and good overall yield. Simple derivatizations of the double bond were performed to give access to interesting and challenging synthons for the synthesis of drug analogues or the extension of well-established catalytic asymmetric methods. Another clear advantage is the ease of preparation of the starting materials (two steps).

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