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Catalytic asymmetric synthesis of chromenes and tetrahydroquinolines *via* sequential allylic alkylation and intramolecular Heck coupling†

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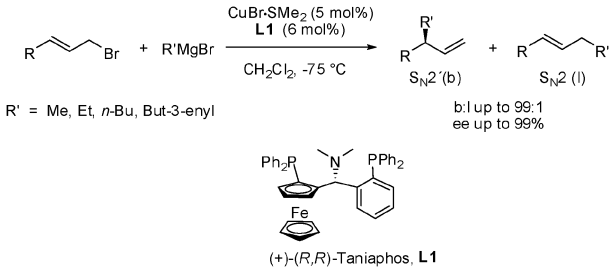
Highly enantioselective synthesis of chiral chromenes and tetrahydroquinolines is achieved by combining asymmetric copper-catalyzed allylic substitution with Grignard reagents and an efficient intramolecular Heck reaction. Moreover, the exocyclic double bond formed in the cyclisation was subjected to RCM, hydroboration and hydrogenation illuminating the synthetic versatility of these heterocycles.

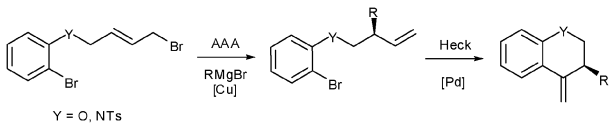
Heterocyclic compounds are indispensable structural units that are crucial in medicinal chemistry and valuable as synthetic organic building blocks. Among the various classes of heterocyclic compounds, chromenes and tetrahydroquinolines are present in a vast number of natural products and bioactive range of substances, with wide applications.[1,2] In view of their importance in various therapeutic areas, the development of the catalytic enantioselective synthesis of these compounds is a major goal. Catalytic methods to prepare chiral chromenes include asymmetric epoxidation, hydrogenation, Pd-catalyzed allylic alkylation or chiral Brønsted acid-mediated cyclization.[1] For tetrahydroquinolines, the Povarov reaction and various hydrogenations of quinolines have mainly been used.[2] Nonetheless, several of these approaches show low selectivities or involve long synthetic routes.

Consequently, there is a major incentive to develop efficient and highly enantioselective catalytic protocols toward these important compounds.

Our group recently reported that copper-catalyzed asymmetric allylic alkylation (AAA) with Grignard reagents can be achieved with excellent regio- and enantioselectivities employing Taniaphos as a chiral ligand (Scheme 1).[3,4] From a synthetic perspective, this catalytic process is especially suited for the introduction of a methyl group using methylmagnesium bromide, one of the most frequently encountered motifs in natural products. Moreover, a major advantage of this methodology is that it furnishes products, which have a terminal olefin adjacent to the stereogenic center formed that can be readily transformed into various other functional groups.[5] This double bond can also be an ideal handle in cyclization reactions. This concept has been successfully applied by combination of AAA followed by olefin ring-closing



Scheme 1 Cu-catalyzed AAA of allyl bromide.



Scheme 2 Chiral chromenes and tetrahydroquinolines *via* sequential AAA and intramolecular Heck reaction.

metathesis to prepare chiral carbo-[6a] and nitrogen heterocycles[6b] of various ring sizes and by a *hetero*-AAA-RCM protocol to prepare naturally occurring butenolides.[7]

As shown in Scheme 2 we anticipated that combining the Cu-catalyzed AAA with an intramolecular Heck reaction[8] would be a very efficient method to prepare nitrogen or oxygen-containing heterocycles. To the best of our knowledge the combination of these two catalytic processes to prepare heterocycles is unprecedented.

Here we present a new and highly versatile catalytic enantioselective synthesis of chromenes and tetrahydroquinolines *via* sequential Cu-catalyzed AAA/Heck reaction with excellent enantiomeric excess (95–99% ee). The required substrates allyl bromides **1** and **2** are readily accessible by reacting *o*-bromophenol or tosyl protected *o*-bromoaniline, respectively, with 1,4-dibromo-2-butene in the presence of base (see ESI† for details).

Compounds **1** and **2**, subjected to methylmagnesium bromide in CH_2Cl_2 in the presence of catalytic amounts of CuBr·SMe_2 and (*R,R*)-(+)-Taniaphos **L1** at −80 °C, undergo substitution to provide the products **3** and **4** in high yields, excellent enantioselectivity (99% ee) and with almost no linear products (branched *vs.* linear ratios >20 : 1) (Table 1, entries 1 and 6). Substrates **1** and **2** can also be ethylated with high regioselectivity and excellent enantioselectivity (Table 1, entries 2 and 7). The use of functionalized alkene Grignard reagents gave

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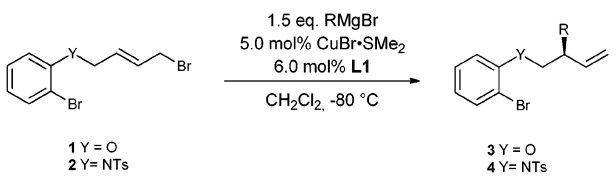
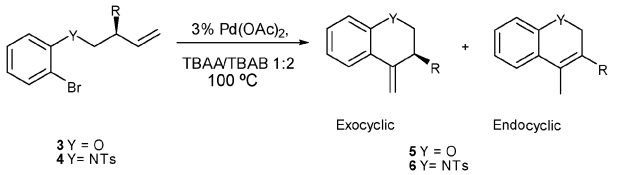
Table 1 Cu-catalysed enantioselective allylic alkylation of **1** and **2** with Cu/Taniaphos ((*R*,*R*)-**L1**) and Grignard reagents[a,b]

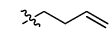
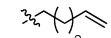
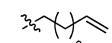
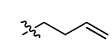
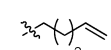
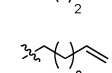


Entry	Y	Product	R	Yield[c] (%)	ee[d] (%)
1	O	**3a**	Me	88	99
2	O	**3b**	Et	97	99
3	O	**3c**		86	96
4	O	**3d**		90	95
5	O	**3e**		94	97
6	NTs	**4a**	Me	72	99
7	NTs	**4b**	Et	99	99
8	NTs	**4c**		87	96
9	NTs	**4d**		86	95
10	NTs	**4e**		68	98

[a] *Reagents and conditions*: RMgBr (1.7 eq.), $CuBr{\cdot}SMe_2$ (5 mol%), **L1** (6 mol%), CH_2Cl_2, −80 °C, 4 h. [b] All conversions >99% (^{1}H-NMR). [c] S_N2' *vs.* S_N2 > 20 : 1 (^{1}H-NMR). [d] Enantiomeric excess determined by chiral GC or HPLC (see ESI for details).

Table 2 Intramolecular Heck reaction on chiral substrates **3** and **4**[a,b]

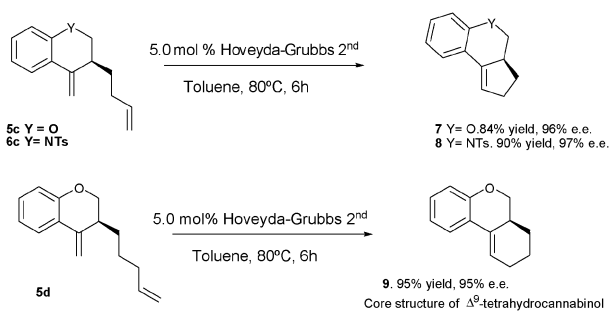


Entry	Y	Product	R	Yield (%)	*Exo*/*Endo*[c]	ee[d] (%)
1	O	**5a**	Me	93	96 : 4	99
2	O	**5b**	Et	96	98 : 2	98
3[e]	O	**5c**		84	99 : 1	96
4[e]	O	**5d**		92	99 : 1	95
5[e]	O	**5e**		89	99 : 1	99
6	NTs	**6a**	Me	92	96 : 4	99
7	NTs	**6b**	Et	93	98 : 2	99
8[f]	NTs	**6c**		87	98 : 2	97
9[f]	NTs	**6d**		86	98 : 2	97
10[f]	NTs	**6e**		77	97 : 3	98

[a] *Reagents and conditions*: $Pd(OAc)_2$ (3 mol%), TBAB (1 g), TBAA (0.45 g, 1.5 mmol), 100 °C, 0.25 h. [b] All conversions >99% (^{1}H-NMR). [c] *Exo*/*Endo* rate determined by ^{1}H-NMR. [d] Enantiomeric excess determined by chiral GC or HPLC (see ESI for details). [e] Reaction time: 1.5 h. [f] Reaction time: 1 h.

products **3c–e** and **4c–e** in high yields allowing for further ring-closing metathesis after the Heck reaction (*Vide infra*, Scheme 3). An important feature is that the reaction is readily scalable to 3 mmol with similar results as observed in the reaction of allyl bromide **1** and MeMgBr (see ESI†, compound **3a** for details).

With the isolated AAA products **3** and **4** in hand, we turned our attention to the study of the intramolecular Heck reaction. When using standard conditions (catalytic amounts of $Pd(OAc)_2$ and PPh_3 and Bu_4NBr as an additive in MeCN or DMF),[8b] moderate yields of the bicyclic compounds **5** and **6** were obtained (37% and 62%, respectively). The product was always an, approximately, 70 : 30 mixture of the expected exocyclic olefin and its isomer with the olefin in the internal position. Since the Heck catalytic cycle can only furnish the cyclized product with an exocyclic double bond, this isomerization

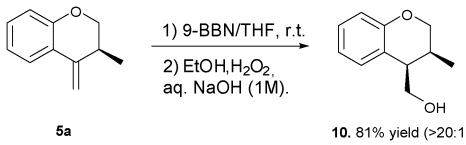


Scheme 3 Ring-closing metathesis of substrates **5c**, **6c**, and **5d**.

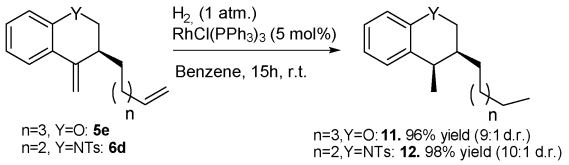
probably takes place by reaction of the chiral product with palladium hydrides formed after β-elimination of the Pd-intermediate.[9] We studied a variety of coupling conditions (palladium sources, phosphines, solvents and additives) but we could not avoid this isomerization and improve the yield. Recently Nacci *et al.*[10] described the use of catalytic amount of $Pd(OAc)_2$ in a molten mixture of tetrabutylammonium bromide (TBAB) and tetrabutylammonium acetate (TBAA) as base under ligand-free conditions for the intermolecular Heck coupling of a variety of chloroarenes, although this method was not applied to chiral compounds. To our delight, by applying these conditions to **3a** and **4a** we obtained the cyclized product **5a** and **6a** with excellent yields (Table 2, entries 1 and 6) while only 4% of isomerization of the double bond to the internal position was observed. The reaction was finished in only 15 min for both substrates. It is worth noting that despite the reaction temperature of 100 °C the ee was not compromised.

It was proposed that bromide ions from TBAB, poorly solvated in this reaction medium, provide adequate electron density to the palladium(0) species instead of the common electron-rich phosphane ligands to facilitate the oxidative-addition step.[10]

High isolated yields were also found for the products with an ethyl group while improving the ratio of isomers (Table 2, entries 2 and 7). Compounds with a longer alkyl chain required a little more time to reach full conversion while insignificant isomerization was found in the preparation of



Scheme 4 Stereoselective hydroboration of substrate **5a**.



Scheme 5 Stereoselective hydrogenation of substrates **5e** and **6d**.

chromenes and tetrahydroquinolines (Table 2, entries 3–5 and 8–10). To ensure that racemization during the cyclisation did not occur, the enantiomeric purity of all Heck reaction products was determined independently by chiral GC or chiral HPLC analysis (see ESI† for details).

The newly formed exocyclic double bond in position 4 of the chromenes and tetrahydroquinolines opens a wide array of possible transformations. To illustrate the synthetic utility of the method, compounds **5c**, **6c** and **5d** with an alkyl chain in position 3 bearing a terminal double bond were subjected to ring closing metathesis[11] since the products obtained provide core structures of natural products (Scheme 3). So **5c** and **6c** were transformed to the corresponding tricyclic compounds **7** and **8** using 5.0 mol% of Hoveyda–Grubbs second-generation catalyst in toluene providing 84% and 90% yield, respectively. The formation of the six member ring annulated to the chromene structure proceeded also in excellent yield from **5d**. Again, no loss of ee was observed in these transformations. It should be noted that tetrahydroquinoline **8** is the nucleus of many neurotransmitters targeted by membrane receptors including calcium-activated potassium channel (BKCa), α_7 nicotinic acetylcholine receptor or estrogen-activated G protein-coupled receptor.[2a] On the other hand, compound **9** represents the core structure of biologically active cannabinols.[12]

Another interesting transformation could be obtained *via* stereoselective hydroboration–oxidation of the exocyclic double bond directed by the stereogenic center in the α position. For instance, compound **5a** was transformed into the corresponding alcohol by reaction with an excess of 9-BBN and subsequent treatment with H_2O_2 in basic medium.[5b,13] Alcohol **10** was obtained as a single diastereoisomer in 81% yield (Scheme 4).

Finally, chromene **5e** and tetrahydroquinoline **6d**, both with a terminal double bond in the alkyl chain in position 3 were subjected to stereoselective hydrogenation of the exocyclic double bonds in the presence of 5 mol% of Wilkinson's catalyst in benzene (Scheme 5).

In this case the alkyl chain in the α position to the exocyclic double bond controls the hydrogenation to reach high selectivity (9 : 1 and 10 : 1 for the chromene and tetrahydroquinoline, respectively) for the *cis*-dialkylated product.[14]

In summary, we have demonstrated that chiral chromenes and tetrahydroquinolines can be obtained in excellent enantiomeric excess and high yields *via* sequential Cu-catalyzed AAA and a very efficient intramolecular Heck reaction. By using a molten mixture of TBAB and TBAA we could obtain the cyclized products with excellent yields and without isomerization of the exocyclic double bond. Taking advantage of this generated olefin, the core structure of natural products and bioactive substances is obtained by RCM. Moreover two stereoselective derivatisation reactions of the exocyclic double bond were applied to further demonstrate the synthetic versatility of these compounds.

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