Gold(I)-Catalysed Hydroarylation of 1,3-Disubstituted Allenes with Efficient Axial-to-Point Chirality Transfer

Gold(I)-Catalysed Hydroarylation of 1,3-Disubstituted Allenes with Efficient Axial-to-Point Chirality Transfer

Daniel R. Sutherland, Luke Kinsman, Stuart M. Angiolini, Georgina M. Rosair and Ai-Lan Lee*[a]

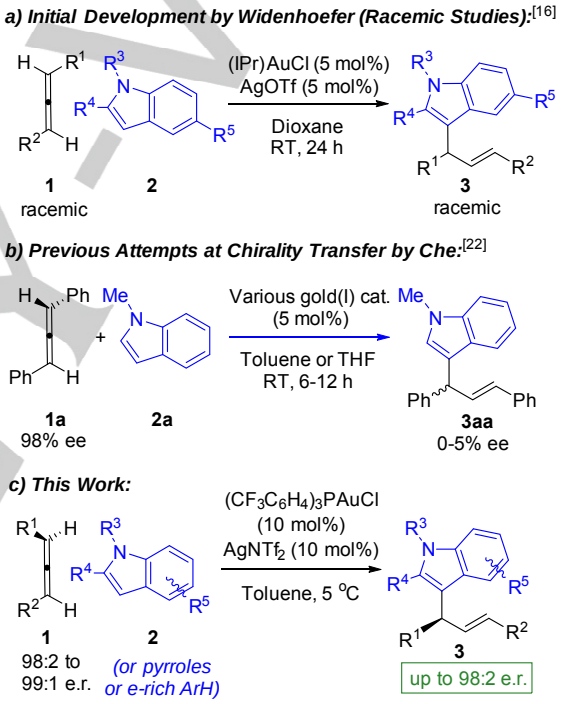
Abstract: Hydroarylation of enantioenriched 1,3-disubstituted allenes has the potential to proceed with axial-to-point chirality transfer to yield enantioenriched allylated (hetero)aryl compounds. However, the gold-catalysed intermolecular reaction was previously reported to occur with no chirality transfer, due to competing allene racemisation. In this full article, we describe the development of the first intermolecular hydroarylations of allenes to proceed with efficient chirality transfer, and summarise some of the key criteria for achieving high regio- and stereoselectivities.

Introduction

The axial chirality present within some 1,3-disubstituted allenes offers a useful opportunity for asymmetric synthesis: *via* axial-to-point chirality transfer upon π-Lewis acid catalysed nucleophilic addition.[1],[2] Within this context, the ability of gold(I) catalysts[3] to activate allenes[4],[1a, 5],[6] towards nucleophilic addition is well documented. The intramolecular gold-catalysed hydroarylation[7] of allenes, for example, has been utilised extensively for the synthesis of cyclic systems,[8],[9] and includes examples of reactions with enantioselectivity[10] as well as excellent diastereoselectivity.[8k] Intramolecular hydroarylation of allenes with chirality transfer have also been reported.[11]

While the *inter*molecular addition of amines (hydroamination) and alcohols (hydroalkoxylation) have been reported to proceed with efficient chirality transfer,[12],[13],[14] efficient intermolecular asymmetric hydroarylation of allenes, however, has proven more elusive. Racemic gold-catalysed hydroarylation of allenes was first reported independently by Li (with aryls)[15] in 2008, Widenhoefer (with indoles, Scheme 1a)[16] and Gagné (with MeO-substituted aryls)[17] in 2009.[18],[19],[20],[21] Two years later, Che and co-workers reported their attempts at hydroarylations with chirality transfer, which resulted in racemic products (Scheme 1b).[22] They attributed the lack of chirality transfer to the competitive gold(I)-catalysed allene racemisation reaction.[23] As a result, Che and co-workers ingeniously utilised the aforementioned racemisation to develop a catalytic enantioselective dynamic resolution method[24] using chiral dinuclear gold(I) phosphine complexes instead.[22] While these efforts let to good yields of desired product, only moderate enantioselectivities were obtained (~35-63% e.e.). The limitations on enantioinduction often posed by the linear geometry of Au(I) catalysts is well documented.[25]

The lack of efficient asymmetric methods is therefore a clear limitation in the field. We herein report the first successful development of intermolecular hydroarylations of allenes with efficient chirality transfer (Scheme 1c). A substrate scope is presented, along with suggested prerequisites for achieving high enantiomeric ratios.



Scheme 1. a) Initial racemic studies by Widenhoefer. b) Previous attempts at chirality transfer by Che. c) This work.

Results and Discussion

We commenced our investigations with a few initial theories and design criteria, based on our previous studies on chirality transfer,[13a, 26] as to the type of allenes and nucleophiles required to achieve efficient chirality transfer. Firstly, if preventing gold-catalysed allene racemization is the key to success, then any substituents (such as aryls used by Che in **1a**), which can stabilize the key planar gold cation intermediate **I** (Scheme 2a),[23] should initially be avoided (see later: Table 2, Entry 13, which supports this criteria). Based on previous related work,[13a],[27] we also predicted that regioselectivity on the allene will be influenced by electronic rather than steric factors (see later: Table 2, Entry 14, which supports this criteria).We therefore intentionally

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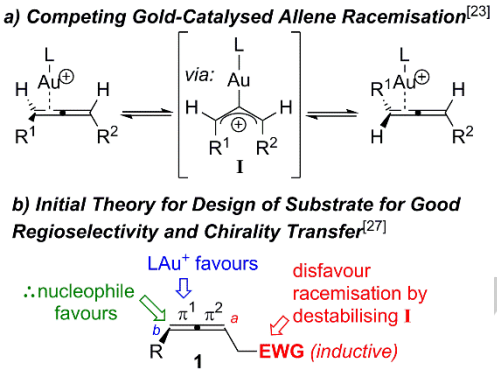
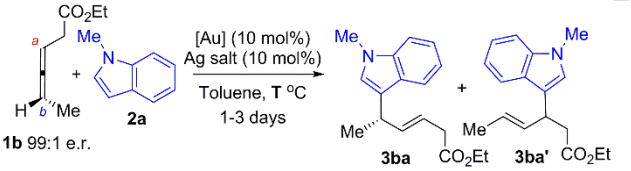
planned to investigate 1,3-disubstituted allenes **1** with one inductively withdrawing substituent (Scheme 2b). Such an approach was designed with the dual aim of destabilizing intermediate **I** and hence disfavouring the competitive racemization reaction, as well as electronically differentiating the two π-bonds on the allene **1** for favourable regioselectivity.[13a] The latter ensures that the gold(I) catalyst will activate the more electron rich π^1-bond, thus favouring (hetero)aryl attack at position *b* rather than *a* (Scheme 2b). Finally, if nucleophilic attack vs. racemization is in competition, then the more electron-rich and subsequently more nucleophilic (hetero)aryls should stand a better chance of out-competing the racemization reaction. Lower temperatures should also help with this competition to ensure higher enantiomeric ratios. It is worth noting that the requirement for an inductively withdrawing group in **1** is not necessarily a limitation, as it allows for the inclusion of a variety of functional groups (see Table 2) which are useful for further synthetic elaboration.



Scheme 2. a) Competing allene racemization reaction. b) Initial Theory for Design of Substrate.

With these initial design criteria in mind, our investigation commenced with optimization studies on allene **1b** and *N*-methylindole **2a**,[28] a selection of which is represented in Table 1. Initial conditions using Gagosz catalyst[29] PPh_3AuNTf_2 at 10 °C provided good regioselectivity for reaction at position *b* vs. *a*, producing **3ba**:**3ba'** in 10:1 ratio, but in a poor 27% yield. A screen of alternative counterions failed to improve the reaction yield, however, higher concentrations successfully increases the yield (Entries 1-3). A reduction in temperature from 10 °C to 5 °C was deemed necessary to improve the enantiomeric ratios (87:13 vs. 90:10 e.r., Entries 3-4). Reducing the equivalents of indole nucleophile **5a** from 4 to 2 equivalents was slightly detrimental to the yield (41% vs. 37%, Entries 4-5). Next, the ligand on the catalyst was varied in an attempt to improve yields and e.r. (Entries 5-7). While changing from PPh_3 to the NHC ligand IMes (1,3-dimesityl-1,3-dihydro-2H-imidazol-2-ylidene)[30] provided an improved yield of 55%, regioselectivity and e.r. decreased to 5:1 and 77:23 respectively (Entry 6). Pleasingly, the use of $(CF_3C_6H_4)_3P$ instead of PPh_3 successfully increases the yield,[31] regioselectivity as well as e.r. to 60%, 11:1 and 93:7 respectively (Entry 7). Extending the reaction time to 3 days increases the yield to 67% (Entry 8). Lower equivalents of nucleophile **5a** (2 equiv., Entry 9) and lower concentration (0.4 M, Entry 10) was confirmed to be detrimental to the reaction yields (58% and 55% respectively).

Table 1. Selected optimisation studies.



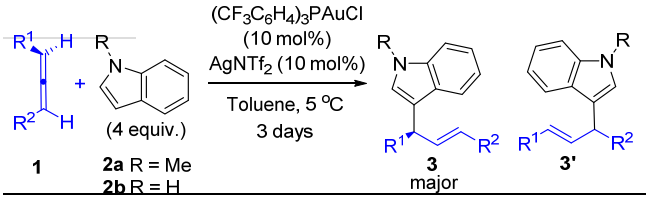
Entry	Conc (M)	T (°C)	Catalyst	**3ba**:**3ba'**[a]	**3ba** e.r.[b]	Yield (%)[c]
1[d][e]	0.15	10	PPh_3AuNTf_2	10:1	N.D.	27
2[d][e]	0.40	10	PPh_3AuNTf_2	8:1	N.D.	39
3[d][e]	0.75	10	PPh_3AuNTf_2	7:1	87:13	50
4[d][e]	1.50	5	PPh_3AuNTf_2	7:1	90:10	41
5[e][f]	1.50	5	PPh_3AuNTf_2	7:1	91:9	37
6[d][e]	1.50	5	(IMes)AuCl/ $AgNTf_2$	5:1	77:23	55
7[d][e]	1.50	5	$(CF_3C_6H_4)_3PAuCl$/ $AgNTf_2$	11:1	93:7	60
8[d][g]	**1.50**	**5**	**$(CF_3C_6H_4)_3PAuCl$ /$AgNTf_2$**	**11:1**	**93:7**	**67**
9[f][g]	1.50	5	$(CF_3C_6H_4)_3PAuCl$/ $AgNTf_2$	10:1	94:6	59
10[d][g]	0.40	5	$(CF_3C_6H_4)_3PAuCl$/ $AgNTf_2$	12:1	90:10	55

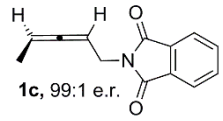
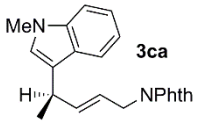
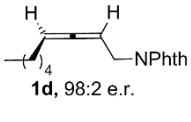
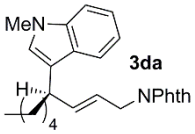
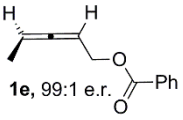
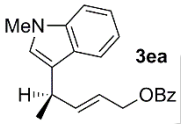
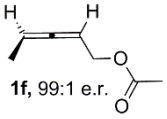
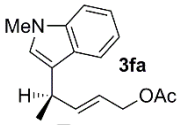
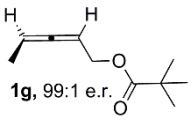
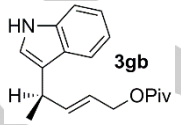
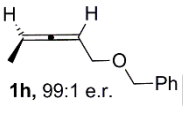
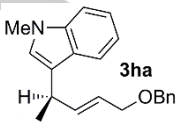
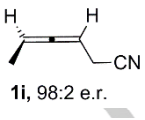
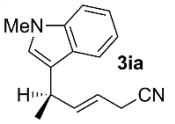
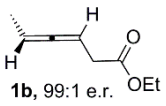
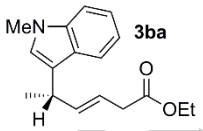
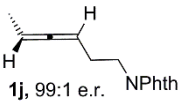
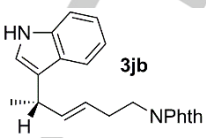
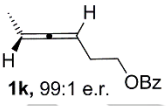
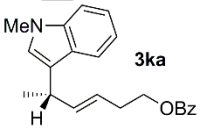
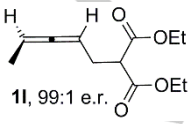
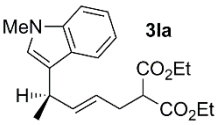
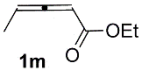
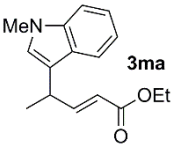
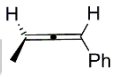
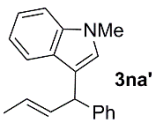
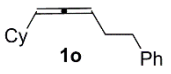
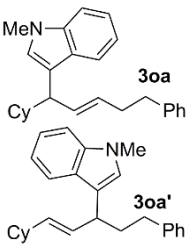
[b] Determined by ^{1}H NMR analysis. >20:1 *E:Z* by ^{1}H NMR analysis. [b] Determined by CSP-HPLC. [c] Isolated yields. [d] 4 Equiv. **2a**. [e] 1 Day. [f] 2 Equiv. **2a**. [g] 3 Days. N.D. = not determined.

With optimised conditions in hand, we proceeded to investigate the allene substrate scope (Table 2).[32] To our delight, the next two allenes that were subjected to our optimised conditions (**1c** and **1e**) proceeded with excellent yield and chirality transfer (94%, 97:3 e.r. **3ca** and 95%, 97:3 e.r. **3ea**, Entries 1 and 3). Pleasingly, replacing the Me in **1c** with *n*-pentyl in **1d** is not detrimental to the reaction, with desired product **3da** formed in high regioselectivity (>20:1), good yield (81%) and excellent chirality transfer (98:2 e.r., Entry 2). Given the excellent chirality transfer obtained for the OBz containing allene **1e** (Entry 3) a range of protected allenols was investigated next (Entries 4-6). Replacing Ph in **1e** with alkyls (**1f**, **1g**, Entries 4-5) does not seem to significantly affect enantiomeric ratios of the products (97:3 **3fa**, 94:6 **3gb**). However, the regioselectivity of the reaction drops off slightly with the pivaloyl protected allenol **1g** (8:1 **3:3'** vs. 15:1 **3:3'** with **1e** and **1f**). Removing the carbonyl (**1h**) gives a similar drop in regioselectivity (6:1 **3:3'**) but a decrease in chirality transfer is also observed (85:15 e.r.), presumably due to the lower inductive withdrawing ability of OBn (**1h**) *vs.* OBz (**1e**). Moving away from protected allenols, the cyano-substituted allene **1i** (Entry 7)

performs very well under our conditions, giving perfect chirality transfer (98:2 e.r. **1i** →98:2 e.r. **3ia**), yield (77%) and regioselectivity (>20:1). Inserting an extra CH_2 to place the NPhth (**1j**, Entry 9) or OBz group (**1k**, Entry 10) further from the allene moiety causes a noticeable drop in chirality transfer for allene **1j** (76:24 e.r. *vs.* 97:3 e.r. with **1c**) and an expected drop in regioselectivity in both (11:1 **1j** *vs.* >20:1 **1c** and 7:1 **1k** *vs.* 15:1 **1e**), although **3** is still the major product in all cases.

Table 2. Allene Scope



Entry	Allene	Major product	Result[a]
1	 **1c,** 99:1 e.r.	 **3ca**	94% >20:1 **3:3'** 97:3 e.r.[b]
2	 **1d,** 98:2 e.r.	 **3da**	81% >20:1 **3:3'** 98:2 e.r.[b]
3	 **1e,** 99:1 e.r.	 **3ea**	95% 15:1 **3:3'** 97:3 e.r.[b]
4	 **1f,** 99:1 e.r.	 **3fa**	74% 15:1 **3:3'** 97:3 e.r.[b]
5	 **1g,** 99:1 e.r.	 **3gb**	58% 8:1 **3:3'** 94:6 e.r.[b]
6	 **1h,** 99:1 e.r.	 **3ha**	74% 6:1 **3:3'** 85:15 e.r.[b]
7	 **1i,** 98:2 e.r.	 **3ia**	77% >20:1 **3:3'** 98:2 e.r.[b]
8	 **1b,** 99:1 e.r.	 **3ba**	67% 11:1 **3:3'** 92:8 e.r.[b]
9	 **1j,** 99:1 e.r.	 **3jb**	97% 11:1 **3:3'**[b] 76:24 e.r.[b]
10	 **1k,** 99:1 e.r.	 **3ka**	82% 7:1 **3:3'** 92:8 e.r.[b]
11	 **1l,** 99:1 e.r.	 **3la**	96% 18:1 **3:3'** 87:13 e.r.[b]
12[c]	 **1m**	 **3ma**	23% (RT) >20:1 **3:3'**
13	 **1n,** 99:1 e.r.	 **3na'**	86% 1:3 **3:3'** **3'** 79:21 e.r. **3** 53:47 e.r.[b]
14	 **1o**	 **3oa** **3oa'**	28% 1.4:1 **3:3'**

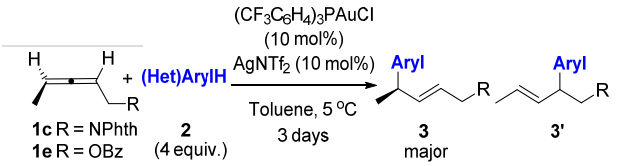
[a] Isolated yields, all >20:1 *E:Z* and reported regioselectivity determined by ^{1}H NMR analysis**. 2b** was used when the product using **2a** could not be separated by CSP-HPLC. [b] E.r. of major product determined by CSP-HPLC [c] Reaction carried out at room temperature (trace product observed at 5 °C).

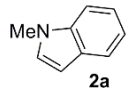
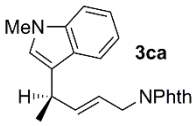
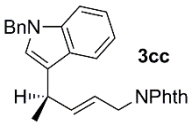
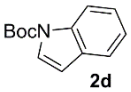
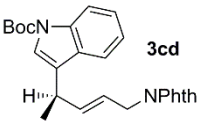
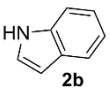
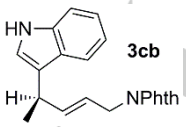
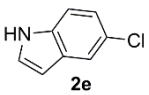
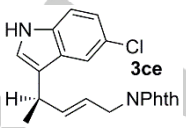
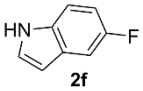
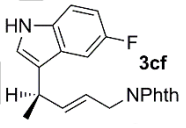
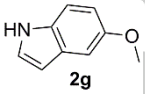
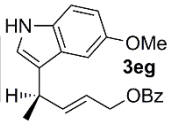
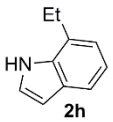
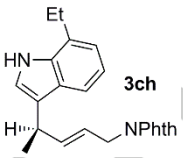
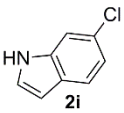
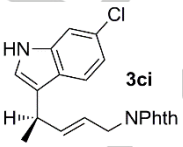
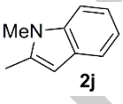
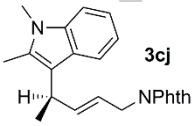
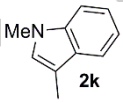
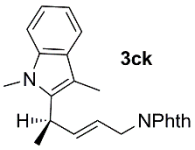
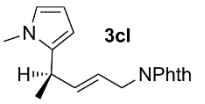
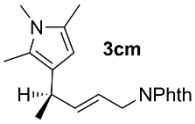
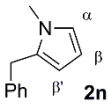
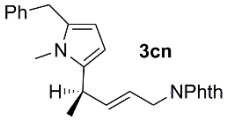
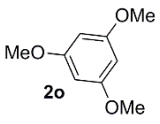
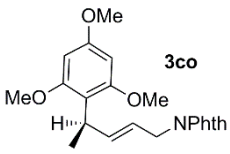
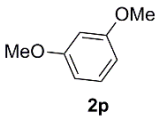
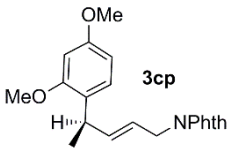
Pleasingly, the diester containing allene **1l** (Entry 11) shows good regioselectivity (18:1) and chirality transfer (87:13 e.r.) despite the electron withdrawing esters being fairly distant from the allene moeity. In contrast to moving the functionality further away from the allene (**1l** *vs.* **1b**), having the ester directly conjugated to the allene (**1m** *vs.* **1b**) is detrimental to the reaction. The more electron poor allene **1m** appears very unreactive compared to allenes **1a**-**1l**: the reaction proceeds very sluggishly, resulting in poor yield (trace product at 5 °C), even when carried out at room temperature (23% yield **3ma**, Entry 12).

To our surprise, the aryl-substituted allene **1n**, which was expected to fully racemise under these conditions (via Ph stabilising intermediate **I**, see Scheme 2a),[33] proceeded with

moderate chirality transfer for the major regioisomer (Entry 13). The regioselectivity is also reversed (1:3 ratio of **3:3′**, 53:47 e.r. for **3** and 79:21 e.r. for **3′**). Therefore, although it does prove that substituents capable of stabilising the cationic intermediate **I** is detrimental to efficient chirality transfer, the effect is not quite as drastic as originally predicted. The 1:3 regioselectivity under these conditions, albeit modest, was also a surprise as hydroarylation with allene **1n** was previously reported to be non-regioselective (1:1.2) under racemic conditions.[16] Finally, and as predicted, the sterically differentiated dialkyl substituted allene **1o** provided very poor regioselectivity (1.4:1 **3:3′**). This result seems to support our initial theory described in Scheme 2b, that it is electronic rather than steric factors that influence the regioselectivity of the gold-catalysed hydroarylation reaction.

Table 3. (Hetero)aryl Nucleophile Scope



Entry	(Het)ArylH	Major product	Result[a]
1	 **2a**	 **3ca**	94% >20:1 **3:3′** 97:3 e.r.[b]
2	 **2c**	 **3cc**	99% >20:1 **3:3′** 95:5 e.r.[b]
3	 **2d**	 **3cd**	32% 18:1 **3:3′** 55:45 e.r.[b]
4	 **2b**	 **3cb**	89% >20:1 **3:3′** 95:5 e.r.[b]
5	 **2e**	 **3ce**	96% 15:1 **3:3′**[b] 85:15 e.r.[b]
6	 **2f**	 **3cf**	90% >20:1 **3:3′** 89:11 e.r.[b]
7	 **2g**	 **3eg**	67% 11:1 **3:3′** 97:3 e.r.[b]
8	 **2h**	 **3ch**	84% >20:1 **3:3′** 96:4 e.r.[b]
9	 **2i**	 **3ci**	98% 15:1 **3:3′**[b] 82:18 e.r.[b]
10	 **2j**	 **3cj**	92% >20:1 **3:3′** 98:2 e.r. [b]
11	 **2k**	 **3ck**	48% >20:1 **3:3′** 82:18 e.r.[b]
12[c]	 **2l**	 **3cl**  **3cl''**	58% 1:1 α/β selectivity[d] >20:1 **3:3′**
13	 **2m**	 **3cm**	41% or 48%[c] >20:1 **3:3′** 98:2 e.r.[b]
14	 **2n**	 **3cn**	40% major[e] 5:1:1 α/β/β′ selectivity[d] 5:1 **3:3′**
15[f]	 **2o**	 **3co**	98% >20:1 **3:3′** 90:10 e.r.[b]
16	 **2p**	 **3cp**	97% 10:1 **3:3′** 57:43 e.r.[b]

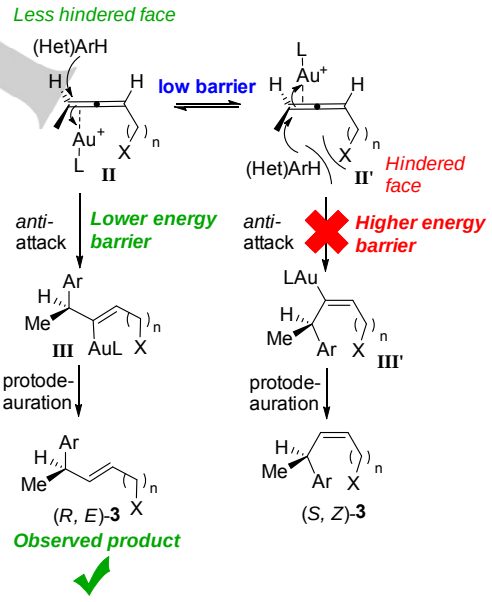
[a] Isolated yields, all >20:1 *E*:*Z* and reported regioselectivity determined by ^{1}H NMR analysis unless otherwise stated. **1e** was used when the product using **1c** could not be separated by CSP-HPLC. [b] E.r. of major product determined by CSP-HPLC. [c] 15 mol% catalyst used. [d] Ratio determined by ^{1}H NMR. E.r. not determined due to inseparable mixtures. [e] Yield calculated by ^{1}H NMR. [f] 6 equivalents of nucleophile used.

The nucleophile scope was investigated next, commencing with different groups on the nitrogen of the indole (Table 3). Both *N*-methylindole as well as *N*-benzylindole (**2a** and **2c**) reacted smoothly in the reaction (Entries 1-2) as did unsubstituted indole **2b** (Entry 4), to give excellent yields (94%, 99%, 89% respectively), regioselectivities (all >20:1) and e.r. (97:3, 95:5, 95:5 respectively). Boc protected indole (**2d**, Entry 3), however, reacted sluggishly due to the electron withdrawing nature of the Boc group and thus less nucleophilic nature of the indole. It is thought that the lower nucleophilicity of the *N*-Boc-indole allows the competing allene racemisation to occur, resulting in a poor enantiomeric ratio (55:45) of product **3cd**. The same pattern is observed with 5-substituted indoles (Entries 5-7), with more electron rich methoxy[34] substituted **2g** outpreforming the less electron rich chloro- and fluoro-substituted indoles (**2e** and **2f**) in terms of chirality transfer efficiency (97:3 e.r. for **3eg** vs. 85:15 and 89:11 e.r. for **3ce** and **3cf**). 7-Ethyl (**2h**, Entry 8) and 6-Cl (**2i**, Entry 9) are also tolerated well in the reaction, again with the more electron rich ethyl substituted indole (**2h**) providing better enantiomeric ratios in the product (96:4 e.r. **3ch** vs. 82:18 e.r. **3ci)**. 1,2-Methyl indole (**2j**, Entry 10) reacts smoothly with excellent yield (92%), regioselectivity (>20:1) and chirality transfer (98:2 e.r.). However, when the most reactive 3-position of the indole is blocked (**2k**, Entry 11), a drop in yield is observed (48% **3ck**). As before, this is accompanied by a drop in chirality transfer (82:18 e.r.), presumably due to the less reactive nucleophile.

Next, pyrrole nucleophiles were investigated (Entries 12-14). Although *N*-methylpyrrole **2l** was reported to be unreactive under Gagné's original conditions,[17] the reaction proceeded with a reasonable yield (58%), good allene regioselectivity (>20:1, Entry 12) and excellent chemoselectivity under the conditions shown in Table 3. It should be noted that chemoselectivity is a well known problem in gold-catalysed reactions with pyrroles, as the mono-alkylated product is more nucleophilic than the starting pyrrole, leading to multiple alkylations.[35] Remarkably, this chemoselectivity issue is not observed under our conditions. To our surprise, however, no regioselectivity was observed between reaction at the α and β position of the pyrrole (**3cl**:**3cl''** 1:1, Entry 12). As a result, an *N*-methylpyrrole, with the α-positions blocked, was investigated next (**2m**, Entry 13). To our delight, **2m** reacted smoothly give **3cm** with excellent regioselectivity (>20:1) and chirality transfer (98:2 e.r.), albeit with a moderate yield (41%). The yield could be improved slightly to 48% upon increasing the catalyst loading to 15 mol% (Entry 13) but increasing the equivalents of pyrrole has no effect on the yield. Encouraged by the success of **2m** a monosubstituted *N*-methylpyrrole **2n** was investigated next. As hoped, the reaction occurred preferentially at the 4-position of the pyrrole albeit with only moderate selectivity over the other two positions (5:1:1, Entry 14).

Finally, electron-rich aryls were investigated as nucleophiles (Entries 15-16). To our delight, **2o** reacted smoothly to give **3co** in excellent yield (98%), regioselectivity (>20:1) and good chirality transfer (90:10 e.r., Entry 15). As predicted, removing one methoxy group (**2p**, Entry 16), substantially reduced the efficiency of chirality transfer (57:43 e.r. **3cp**) even though the yield is still excellent at 97%. This reduction in e.r. is once again thought to be due to the reduced nucleophilicity of **2p** vs. **2o**, which allows the competing allene racemization to occur. Based on the results in Table 3, it is therefore of no surprise that less nucleophilic (hetero)aryls such as benzofurans, 2-methylfuran, 2-methoxythiophene, methoxybenzene and hexamethylbenzene do not react under these conditions.

It is worth noting that the gold-catalysed hydroarylation reaction is highly stereoselective both in terms of chirality transfer (providing the (hetero)aryl is sufficiently nucleophilic, *vide supra*), as well as *E* selectivity (all >20:1 *E:Z* by ^{1}H NMR analysis). A plausible[36] mechanism to describe the observed selectivity is provided in Scheme 3. As described in Scheme 2b, the regioselectivity is thought to originate from the electronic differentiation of the π-bonds on the allene **1**, with the LAu$^+$ catalyst preferring to coordinate to the more electron-rich π. Within this context, the cationic gold catalyst can still coordinate to either face of the allene (**II** and **II'**), and a low barrier of interconversion exists between **II** and **II'**.[37] Nucleophiles tend to approach *anti*- to the gold(I),[1] so the arylation of **II** is expected to be sterically and kinetically favoured over that of **II'**.[38] The resulting intermediate **III** leads to the observed (*R,E*)-**3** product upon protodeauration. On the other hand, arylation onto **II'** should be kinetically unfavourable, which explains why (*S,Z*)-**3** is never observed experimentally.[39]

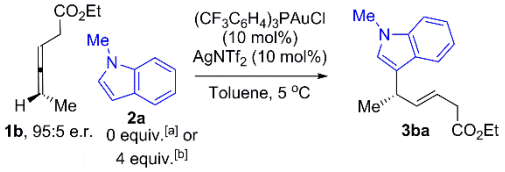


Scheme 3. Postulated origin of stereoselectivity.

In order to prove that the chirality transfer in this reaction is a kinetic phenomenon, the rate of allene **1** racemisation *vs.* formation of product **3** was investigated next (Table 4). In the absence of nucleophile **2**, the allene **1b** is fully racemised within 1 h (Entries 1-2). However, the racemisation of allene **1b** is significantly slower under our hydroarylation reaction conditions, when nucleophile **2** is present (Entries 3-8). This could be due to reversible coordination of the nucleophile to the cationic gold catalyst.[40] As predicted, the gold-catalysed hydroarylation

outcompetes the allene racemisation under our reaction conditions, proving that the chirality transfer is indeed a kinetic phenomenon (Table 4, Entries 3-8).

Table 4. Rate of reactions vs. racemisation studies.



Entry	Time (h)	Allene **1b** e.r.[c]	Product **3ba** e.r.[d]	NMR conv.[e]
1[a]	0.25	55:45	-	-
2[a]	1	50:50	-	-
3[b]	0	95:5	-	-
4[b]	0.25	94:6	-	<5%
5[b]	1	93:7	92:8	26%
6[b]	6	90:10	92:8	56%
7[b]	16	87:13	91:9	78%
8[b]	24	83:17	90:10	89%

[a] In absence of nucleophile **2a**. [b] 4 Equiv. nucleophile **2a**. [c] Determined by CSP-GC. [d] Determined by CSP-HLPC. [e] Determined by ^{1}H NMR analysis.

Conclusions

We have developed the first intermolecular hydroarylation of 1,3-disubstituted allenes to proceed with efficient chirality transfer, thereby providing access to functionalized, allylated indoles, pyrroles and aryls (**3**) in up to 99% yields, >20:1 regioselectivity and 98:2 e.r. This development is of significance as such reactions were previously reported to occur with no chirality transfer under gold-catalysis, due to competing gold-catalysed racemization of the allene substrates. In order to overcome this, several criteria have to be adhered to. Firstly, the enantioenriched allenes should not contain substituents such as aryls, which can promote the competing racemization *via* stabilizing the intermediate **I**. Instead, the inclusion of a σ-withdrawing substituent not only disfavours racemization, but also ensures good regioselectivity *via* electronic differentiation of the π-bonds on the allene, as well as providing a handle for further synthetic elaboration. Finally, more nucleophilic (hetero)aryls have a better chance of outcompeting the allene racemization reaction, thereby furnishing products with much higher enantiomeric ratios. For example, more electron-rich (hetero)aryls such as *N*-Me, *N*-Bn and unprotected indoles proceed with excellent chirality transfer, greatly outperforming their less nucleophilic counterparts such as *N*-Boc-indole. Rate of hydroarylation *vs*. racemization studies prove that the chirality transfer is efficient under our reaction conditions as it outcompetes the rate of gold-catalysed allene racemization.

Experimental Section

General Procedure

Allene **1** (0.15 mmol, 1 equiv.), toluene (0.1 mL) and nucleophile **2** (0.6 mmol, 4 equiv.) were added to a 1 dram vial equipped with a small stirrer bar and cooled to 5 °C. (4-$CF_3C_6H_4)_3$PAuCl (0.015 mmol, 10 mol%) followed by $AgNTf_2$ (0.015 mmol, 10 mol%) were added in quick succession and the reaction was allowed to stir at 5 °C for 3 days. The reaction mixture was purified by column chromatography to give product **3**. Full experimental procedures, characterisation for all new compounds and copies of ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information.

Acknowledgements

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Keywords: gold • allene • chirality transfer • hydroarylation • asymmetric

[1] For reviews on chirality transfer with allenes, see: a) J. M. Alonso, M. T. Quiros, M. P. Munoz, *Org. Chem. Front.* **2016**, *3*, 1186-1204; b) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074-3112.

[2] For a review of chirality transfer in gold-catalysed reactions, see: a) N. T. Patil, *Chem. Asian J.* **2012**, *7*, 2186-2194. For selectivity issues in transformations of allenes, see: b) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3590-3593.

[3] For selected reviews on homogenous gold catalysis, see: a) D. Pflasterer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331-1367; b) C. Obradors, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 16-28; c) N. Bongers, N. Krause, *Angew. Chem., Int. Ed.* **2008**, *47*, 2178-2181; d) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378; e) J. Muzart, *Tetrahedron* **2008**, *64*, 5815-5849; f) A. Fürstner, P. W. Davies, *Angew. Chem., Int. Ed.* **2007**, *46*, 3410-3449; g) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403; h) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180-3211; i) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem., Int. Ed.* **2006**, *45*, 7896-7936; j) G. Dyker, *Angew. Chem., Int. Ed.* **2000**, *39*, 4237-4239.

[4] a) N. Krause, A. S. K. Hashmi, *Modern Allene Chemistry*, Wiley-VCH, Weinheim, Germany, **2004**; b) S. Ma, *Chem. Rev.* **2005**, *105*, 2829-2872; c) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed.* **2000**, *39*, 2285-2288; d) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537-2538; e) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553-11554.

[5] For selected reviews on allene synthesis, see: a) S. C. Yu, S. M. Ma, *Chem. Commun.* **2011**, *47*, 5384-5418; b) S. M. Ma, *Aldrichimica Acta* **2007**, *40*, 91-102; c) X. Huang, T. Cao, Y. L. Han, X. G. Jiang, W. L. Lin, J. S. Zhang, S. M. Ma, *Chem. Commun.* **2015**, *51*, 6956-6959; d) R. Gurubrahamam, M. Periasamy, *J. Org. Chem.* **2013**, *78*, 1463-1470. For selected reviews on asymmetric allene synthesis, see: e) W. D. Chu, Y. Zhang, J. B. Wang, *Catal. Sci. Technol.* **2017**, *7*, 4570-4579; f) R. K. Neff, D. E. Frantz, *ACS Catal.* **2014**, *4*, 519-528; g) S. C. Yu, S. M. Ma, *Angew. Chem., Int. Ed.* **2012**, *51*, 3074-3112; h) J. Ye, S. Ma, *Org. Chem. Front.* **2014**, *1*, 1210-1224.

[6] For recent reviews on gold-catalysed reactions with allenes, see: a) W. Yang, A. S. K. Hashmi, *Chem. Soc. Rev.* **2014**, *43*, 2941-2955; b) C. Winter, N. Krause, Wiley-VCH Verlag GmbH & Co. KGaA, **2012**, pp. 363-

389; c) M. P. Munoz, *Org. Biomol. Chem.* **2012**, *10*, 3584-3594; d) A. S. K. Hashmi, M. Buehrle, *Aldrichimica Acta* **2010**, *43*, 27-33. See also: e) N. Morita, N. Krause, *Angew. Chem., Int. Ed.* **2006**, *45*, 1897-1899.

[7] For selected reviews, see: a) N. Ahlsten, X. C. Cambeiro, G. J. P. Perry, I. Larrosa, in *Au-Catalyzed Synthesis and Functionalization of Heterocycles* (Ed.: M. Bandini), Springer International Publishing, Cham, **2016**, pp. 175-226; b) M. Bandini, *Chem. Soc. Rev.* **2011**, *40*, 1358-1367; c) P. de Mendoza, M. Echavarren Antonio, in *Pure Appl. Chem., Vol. 82*, **2010**, p. 801; d) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885-3903.

[8] For selected examples, see: a) B. Alcaide, P. Almendros, S. Cembellin, T. M. d. Campo, I. Fernandez, *Chem. Commun.* **2013**, *49*, 1282-1284; b) B. Alcaide, P. Almendros, S. Cembellín, T. Martínez del Campo, *J. Org. Chem.* **2015**, *80*, 4650-4660; c) M. Jia, G. Cera, D. Perrotta, M. Monari, M. Bandini, *Chem. Eur. J.* **2014**, *20*, 9875-9878; d) C.-H. Liu, Z.-X. Yu, *Org. Chem. Front.* **2014**, *1*, 1205-1209; e) T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2007**, *9*, 4821-4824; f) A. Fazeli, D. Pflästerer, M. Rudolph, A. S. K. Hashmi, *J. Organomet. Chem.* **2015**, *795*, 68-70; g) R. M. Zeldin, F. D. Toste, *Chem. Sci.* **2011**, *2*, 1706-1709; h) M. A. Tarselli, M. R. Gagné, *J. Org. Chem.* **2008**, *73*, 2439-2441; i) B. Chen, W. Fan, G. Chai, S. Ma, *Org. Lett.* **2012**, *14*, 3616-3619; j) B. Alcaide, P. Almendros, J. M. Alonso, M. T. Quirós, P. Gadziński, *Adv. Synth. Catal.* **2011**, *353*, 1871-1876; k) Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352-10353; l) L.-Y. Mei, Y. Wei, X.-Y. Tang, M. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 8131-8137; m) W. Kong, C. Fu, S. Ma, *Eur. J. Org. Chem.* **2010**, *2010*, 6545-6555; n) W. Kong, C. Fu, S. Ma, *Chem. Eur. J.* **2011**, *17*, 13134-13137; o) B. Alcaide, P. Almendros, J. M. Alonso, S. Cembellin, I. Fernandez, T. M. del Campo, M. R. Torres, *Chem. Commun.* **2013**, *49*, 7779-7781; p) J. Barluenga, M. Piedrafita, A. Ballesteros, Á. L. Suárez-Sobrino, J. M. González, *Chem. Eur. J.* **2010**, *16*, 11827-11831; q) D. Weber, M. A. Tarselli, M. R. Gagné, *Angew. Chem. Int. Ed.* **2009**, *48*, 5733-5736; r) D. Pflasterer, M. Rudolph, B. F. Yates, A. Ariafard, A. S. K. Hashmia, *Adv. Synth. Catal.* **2017**, *359*, 866-874; s) D. Pflasterer, P. Dolbundalchok, S. Rafique, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2013**, *355*, 1383-1393.

[9] For example of intramolecular Pt-catalysed allene hydroarylations, see: a) J. Mo, P. H. Lee, *Org. Lett.* **2010**, *12*, 2570-2573; b) W. Kong, C. Fu, S. Ma, *Chem. Commun.* **2009**, 4572-4574; c) W. Kong, C. Fu, S. Ma, *Org. Biomol. Chem.* **2012**, *10*, 2164-2173; d) Y.-Y. Zhang, Y. Wei, X.-Y. Tang, M. Shi, *Chem. Commun.* **2017**, *53*, 5966-5969.

[10] C. Liu, R. A. Widenhoefer, *Org. Lett.* **2007**, *9*, 1935-1938;

[11] a) Y. A. Qiu, J. Zhou, J. Z. Li, C. L. Fu, Y. L. Guo, H. Y. Wang, S. M. Ma, *Chem. Eur. J.* **2015**, *21*, 15939-15943; b) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066-9073.

[12] For hydroaminations with chirality transfer, see: a) N. Nishina, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 3314-3317; b) Z. J. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard III, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 13064-13071; c) K. L. Butler, M. Tragni, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2012**, *51*, 5175-5178; d) D. A. Khrakovsky, C. Tao, M. W. Johnson, R. T. Thornbury, S. L. Shevick, F. D. Toste, *Angew. Chem. Int. Ed.* **2016**, *55*, 6079-6083.

[13] For hydroalkoxylations with chirality transfer, see: a) S. Webster, D. R. Sutherland, A.-L. Lee, *Chem. Eur. J.* **2016**, *22*, 18593-18600; see also: b) M. S. Hadfield, A.-L. Lee, *Org. Lett.* **2010**, *12*, 484-487.

[14] For previous work on hydroalkoxylations with chirality transfer, see also: a) Z. B. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 2079-2081; b) N. Nishina, Y. Yamamoto, *Tetrahedron* **2009**, *65*, 1799-1808.

[15] R. Skouta, C.-J. Li, *Can. J. Chem.* **2008**, *86*, 616-620.

[16] K. L. Toups, G. T. Liu, R. A. Widenhoefer, *J. Organomet. Chem.* **2009**, *694*, 571-575.

[17] M. A. Tarselli, A. Liu, M. R. Gagné, *Tetrahedron* **2009**, *65*, 1785-1789.

[18] See also: C. N. Kona, M. H. Shinde, C. V. Ramana, *Org. Biomol. Chem.* **2015**, *13*, 5358-5362.

[19] For Pd-catalysed intermolecular hydroarylation on allenes, see: a) Z. Fang, C. Fu, S. Ma, *Chem. Eur. J.* **2010**, *16*, 3910-3913; b) R. R. Suresh, K. C. K. Swamy, *J. Org. Chem.* **2012**, *77*, 6959-6969.

[20] For Pt-catalysed intermolecular hydroarylation on allenes, see: M. P. Muñoz, M. C. de la Torre, M. A. Sierra, *Chem. Eur. J.* **2012**, *18*, 4499-4504.

[21] For acid-catalysed intermolecular hydroarylation on allenes, see: Z. Fang, C. Fu, S. Ma, *Eur. J. Org. Chem.* **2011**, *2011*, 1227-1231.

[22] M.-Z. Wang, C.-Y. Zhou, Z. Guo, E. L.-M. Wong, M.-K. Wong, C.-M. Che, *Chem. Asian J.* **2011**, *6*, 812-824.

[23] a) V. Gandon, G. Lemière, A. Hours, L. Fensterbank, M. Malacria, *Angew. Chem. Int. Ed.* **2008**, *47*, 7534-7538; b) R. J. Harris, K. Nakafuku, R. A. Widenhoefer, *Chem. Eur. J.* **2014**, *20*, 12245-12254.

[24] a) Z. Zhang, C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2007**, *129*, 14148-14149; b) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291-8327.

[25] a) S. Sengupta, X. Shi, *ChemCatChem* **2010**, *2*, 609-619; b) W. Zi, F. Dean Toste, *Chem. Soc. Rev.* **2016**; c) Y.-M. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2014**, *47*, 889-901; d) N. Huguet, A. M. Echavarren, in *Asymmetric Synthesis II*, Wiley-VCH Verlag GmbH & Co. KGaA, **2012**, pp. 205-211; e) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382-5391; f)A. Pradal, P. Y. Toullec, V. Michelet, *Synthesis* **2011**, *2011*, 1501-1514; g) A. S. K. Hashmi, *Nature* **2007**, *449*, 292-293.

[26] G. Barker, D. G. Johnson, P. C. Young, S. A. Macgregor, A.-L. Lee, *Chem. Eur. J.* **2015**, *21*, 13748-13757.

[27] Eletronic rather than steric factors were found to influence the regioselectivity of the related hydroalkoxylation reaction, see ref. 13a.

[28] For our previous work on gold-catalysed reactions with indoles, see: P. C. Young, M. S. Hadfield, L. Arrowsmith, K. M. Macleod, R. J. Mudd, J. A. Jordan-Hore, A.-L. Lee, *Org. Lett.* **2012**, *14*, 898-901.

[29] N. Mezailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133-4136.

[30] P. de Frémont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 2411-2418.

[31] K. Nunokawa, S. Onaka, T. Tatematsu, M. Ito, J. Sakai, *Inorg. Chim. Acta* **2001**, *322*, 56-64.

[32] The (*R*) absolute stereochemistry of product **3co** was determined by XRD analysis and the absolute stereochemistry of all other products **3** were assigned by analogy. See Supporting Information.

[33] This allene resulted in totally racemic product when subjected to related gold-catalysed hydroalkoxylation reaction, see ref. 12a.

[34] For nucleophilic reactivities of indoles, see: S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, *71*, 9088-9095.

[35] A. S. K. Hashmi, R. Salathe, W. Frey, *Eur. J. Org. Chem.* **2007**, 1648-1652.

[36] A. S. K. Hashmi, *Angew. Chem., Int. Ed.* **2010**, *49*, 5232-5241.

[37] T. J. Brown, A. Sugie, M. G. D. Leed, R. A. Widenhoefer, *Chem. Eur. J.* **2012**, *18*, 6959-6971.

[38] A related sterical repulsion of the substituent on the other end of the allenes has been described: Y. Yu, W. Yang, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, *52*, 7586-7589.

[39] Any observed erosion of e.r. is proposed to occur via competing racemisation of the allene substrate, as described earlier, rather than via this kinetically unfavourable pathway.

[40] For examples of reversible coordination of nucleophiles and solvents with the active cationic gold species, see: a) A. Zhdanko, M. Ströbele, M. E. Maier, *Chem. Eur. J.* **2012**, *18*, 14732-14744; b) P. C. Young, S. L. J. Green, G. M. Rosair, A.-L. Lee, *Dalton Trans.* **2013**, *42*, 9645-9653.

[41] S. J. Coles, P. A. Gale, *Chem. Sci.* **2012**, *3*, 683-689.

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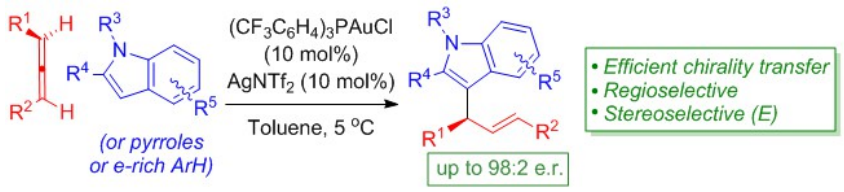

Intermolecular hydroarylation of allenes with efficient axial-to-point chirality transfer has been developed for the first time, using gold(I)-catalysis. A substrate scope is presented, along with suggested prerequisites for achieving excellent regio- and stereoselectivities.

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Gold(I)-Catalysed Hydroarylation of 1,3-Disubstituted Allenes with Efficient Axial-to-Point Chirality Transfer