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Enantioselective aryl–aryl coupling facilitated by chiral binuclear gold complexes†

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Herein, we report stoichiometric investigations embodying the first highly enantioselective aryl–aryl coupling facilitated by a gold complex. With up to 91% ee, this is the first demonstration of a transmetalation and C(sp^2)–C(sp^2) reductive elimination sequence with high enantioselectivity using a gold complex. The results offer a basis for development of enantioselective gold-catalyzed aryl–aryl coupling reactions.

Atropisomers can be found in natural products and they play an increasingly important role in medicinal chemistry.[1] In addition, atropisomeric C_2-symmetric ligands, such as the BINOL, BINAP, and SEGPHOS ligand-families, have revolutionized asymmetric metal catalysis.[2] Other applications of atropisomers include BINOL-based Brønsted acid catalysts for enantioselective Brønsted acid catalysis,[3] and atropisomeric phosphines for enantioselective nucleophilic phosphine catalysis.[4] Due to the high importance of atropisomers, their enantioselective synthesis has received considerable attention in recent years.[5,6]

Since the seminal report on gold-catalyzed homocoupling of arenes by C–H functionalization by Tse *et al.* in 2008,[7] the field of gold-catalyzed aryl–aryl coupling reactions has advanced tremendously (Scheme 1). In 2012, Lloyd-Jones and Russell *et al.* reported the selective cross-coupling of arylsilanes with arenes in the presence of an external oxidant.[8] In 2015, Larrosa *et al.* developed a selective cross-coupling reaction taking place through double C–H functionalization.[9] The same year, You *et al.* showed that by using a directing group, cross-coupling between arylboronic acids and arenes is also possible.[10] Based on a seminal publication from Glorius *et al.*,[11] various gold-catalyzed cross-coupling reactions using aryldiazonium salts under external oxidant-free conditions have been developed for aryl–aryl bond formation.[12,13] In 2017, Nevado *et al.* reported cross-coupling between arylboronic esters and electron-rich arenes.[14] The same year, Bourissou *et al.* showed that cross-coupling with aryl iodides is possible by using a P,N-ligand.[15] Finally, Xie *et al.* have reported that cross-coupling of two organometallic nucleophiles can be catalyzed by a binuclear gold complex bearing a PNP-type ligand.[16] The ease of C–H functionalization, mild reaction conditions, and especially the orthogonality to palladium-catalyzed cross-coupling reactions, in terms of functional group tolerance (*e.g.* aryl halides) and regioselectivity, makes gold catalysis an appealing complementary method for aryl–aryl coupling reactions.

In spite of the intensive research efforts in gold-catalyzed aryl–aryl coupling reactions, there are still no examples of enantioselective synthesis of atropisomers using oxidative gold catalysis.[17] In 2018, Hermange and Fouquet *et al.* reported the only example of a stoichiometric study toward this goal.[18] By using stoichiometric amounts of mononuclear gold complexes bearing chiral P,N-ligands, they obtained the atropisomeric product in very modest 26% ee (44% yield).

Herein, we report that by using binuclear gold complexes bearing C_2-symmetric chiral ligands, the atropisomeric biaryl product can be obtained in up to 91% ee (70% yield). These stoichiometric investigations embody the first demonstration of a highly enantioselective transmetalation and aryl–aryl reductive elimination sequence for a gold complex. The realization of high enantioselectivity for these elementary steps offers a basis for successful development of enantioselective gold-catalyzed aryl–aryl cross-coupling reactions and the results can serve as a guide for ligand choice for such reactions.[19]

As part of our interest in asymmetric catalysis and catalysis with group 11 metals, we set out to investigate the possibility for enantioselective aryl–aryl coupling reactions with gold complexes.[20] Inspired by a report from 2014 by Toste and coworkers,[21] we hypothesized that enantioselectivity could be achieved for an aryl–aryl coupling reaction by the introduction of appropriate chiral bisphosphine ligands on gold.[22,23]

We initiated the investigation by subjecting (*S*)-BINAP(AuCl)$_2$ to 2-methoxynaphthaleneboronic acid (**1**) and CsF in CH_2Cl_2 at

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† Electronic supplementary information (ESI) available: Experimental procedures, NMR data and spectra, and HPLC traces. See DOI: 10.1039/c9cc07175j

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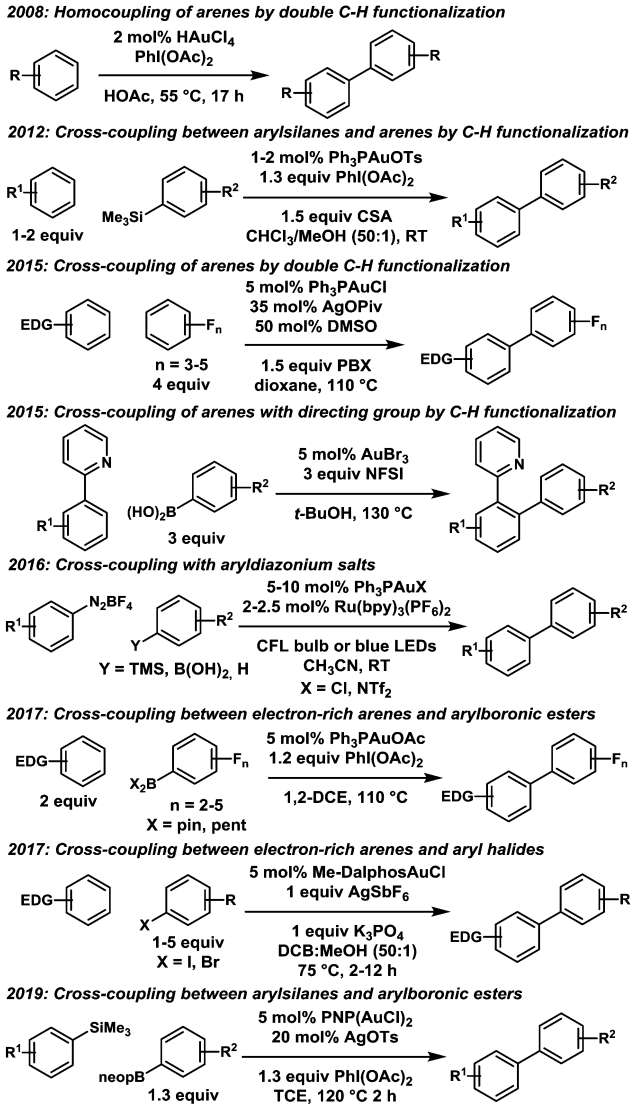
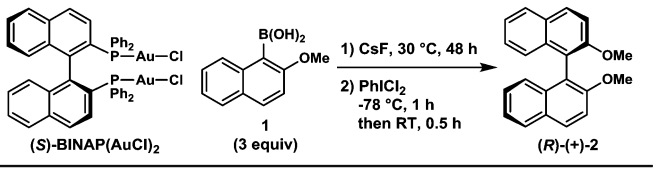


Scheme 1 Milestones in development of gold-catalyzed aryl–aryl coupling.

Table 1 Initial optimization of reaction conditions for enantioselective aryl–aryl coupling mediated by a chiral gold complex



Entry	CsF (equiv.)	$PhICl_2$ (equiv.)	Yield[a] (%)	ee[b] (%)
1	3	3	59	50
2	6	3	71	50
3	6	2	73	50

[a] Based on ^{1}H NMR relative to an internal standard. [b] Determined by chiral HPLC after purification.

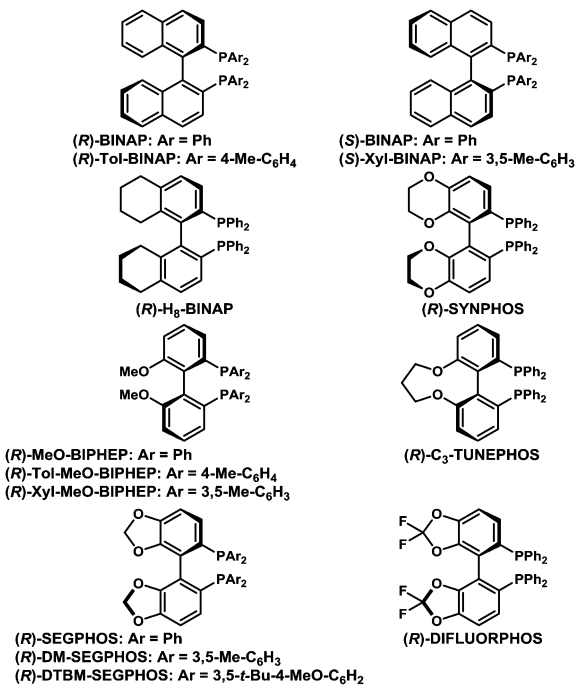


Fig. 1 Ligands utilized for investigation of the aryl–aryl coupling reaction.

30 °C in order to facilitate double transmetalation to the gold complex (Table 1). Subsequently, the reaction mixture was cooled to −78 °C and $PhICl_2$ added to oxidize the intermediate complex, (*S*)-BINAP(AuAr)$_2$. Upon heating to room temperature, the biaryl product forms by reductive elimination.[21] By varying the amount of CsF and $PhICl_2$, clean double transmetalation was observed by ^{31}P NMR after 48 hours, and 73% yield obtained of the aryl–aryl coupling product (Table 1, entry 3). Importantly, the biaryl coupling product was formed with 50% ee, which is already the best enantioselectivity reported for aryl–aryl coupling with a gold complex.

In order to further optimize the enantioselectivity, a series of gold complexes bearing chiral bisphosphine ligands were synthesized (Fig. 1) and their potential for enantioselective aryl–aryl coupling evaluated (Table 2). First, it was confirmed that the ligand controls the major enantiomer formed. The use of (*R*)-BINAP(AuCl)$_2$ leads to the opposite enantiomer of the biaryl product **2** compared to (*S*)-BINAP(AuCl)$_2$ (entries 1 and 2).[24]

Introducing tolyl groups on the BINAP scaffold gave a significant increase in enantioselectivity affording the product in 78% ee (entry 3). However, the use of a more sterically hindered BINAP ligand containing xylyl groups led to diminished reactivity and enantioselectivity (entry 4). Other variations to the BINAP motif, (*R*)-H_8-BINAP and (*R*)-SYNPHOS, gave 58 and 63% ee, respectively (entries 5 and 6). Next, the MeO-BIPHEP ligand family was examined. The use of (*R*)-MeO-BIPHEP(AuCl)$_2$ led to a faster transmetalation than for any of the other complexes tested. Furthermore, the biaryl product **2** was obtained in 77% yield and 76% ee (entry 7). Increasing the sterical bulk led to markedly slower transmetalation and poor yields, as observed for (*R*)-Tol-MeO-BIPHEP(AuCl)$_2$ and (*R*)-Xyl-MeO-BIPHEP(AuCl)$_2$ (entries 8 and 9). (*R*)-C_3-TUNEPHOS, which structurally resembles the MeO-BIPHEP ligand family, was also tested and afforded the product with 66% ee (entry 10). Finally, the SEGPHOS ligand class was examined. By using (*R*)-SEGPHOS(AuCl)$_2$ as the gold

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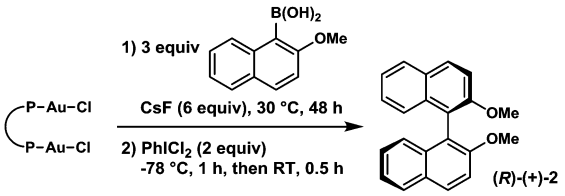
Table 2 Influence on yield and enantioselectivity from different chiral ligands



Entry	Ligand	Yield[a] (%)	ee[b] (%)
1	(*S*)-BINAP	73	50
2	(*R*)-BINAP	64	−51
3	(*R*)-Tol-BINAP	59	−78
4	(*S*)-Xyl-BINAP	40[c]	49
5	(*R*)-H_8-BINAP	59	−58
6	(*R*)-SYNPHOS	44	−63
7	(*R*)-MeO-BIPHEP	77[d]	−76
8	(*R*)-Tol-MeO-BIPHEP	13[c]	ND
9	(*R*)-Xyl-MeO-BIPHEP	15[c]	−51
10	(*R*)-C_3-TUNEPHOS	58[e]	−66
11	(*R*)-SEGPHOS	70	−91
12	(*R*)-DM-SEGPHOS	39[c]	−71
13	(*R*)-DTBM-SEGPHOS	43	−11
14	(*R*)-DIFLUORPHOS	47	−76

[a] Based on ^{1}H NMR relative to an internal standard. [b] Determined by chiral HPLC after purification. [c] Additional $ArB(OH)_2$ (3 equiv.) and CsF (6 equiv.) added after 48 h, and the transmetalation stirred for another 24 h. [d] Transmetalation stirred for 24 h. [e] Additional $ArB(OH)_2$ (1 equiv.) and CsF (2 equiv.) added after 48 h, and the transmetalation stirred for another 24 h. ND = not determined.

complex, the atropisomeric product **2** was formed in 91% ee and 70% yield (entry 11).[25] Similar to the trend observed for the BINAP and MeO-BIPHEP ligand families, the introduction of more sterical bulk on the parent SEGPHOS ligand led to decreased yields and enantioselectivities as observed for both (*R*)-DM-SEGPHOS(AuCl)$_2$ and (*R*)-DTBM-SEGPHOS(AuCl)$_2$ (entries 12 and 13). As the only one of the complexes examined, (*R*)-DTBM-SEGPHOS(AuCl)$_2$ led to a very unclean transmetalation. The use of (*R*)-DIFLUORPHOS(AuCl)$_2$, a fluoride-containing SEGPHOS derivative, led to 76% ee (entry 14). Interestingly, the use of binuclear complexes appears crucial under our reaction conditions as PPh_3AuCl led to clean transmetalation (6 h), but only 5% yield of biaryl **2** after the second step. Beneficial effects of binuclear complexes were also reported by Xie *et al.*[16]

The general trends for the 13 examined chiral gold complexes are that a significant increase of the steric bulk within a ligand class leads to slower, and in rare cases unclean, transmetalation. The enantioselectivity does not benefit from the increase in steric bulk. The best enantioselectivity was achieved with the complex bearing the relatively cheap (*R*)-SEGPHOS ligand.[26] The obtained 91% ee is even more notable, when keeping in mind that asymmetric gold catalysis is a very difficult task with enantioselectivities reported for gold(III) catalysis in the range of 41–90% ee[23,27] and for gold(I) catalysis, in many cases, around 80–95% ee.[22,28]

When monitoring the reaction with (*R*)-SEGPHOS(AuCl)$_2$ by ^{31}P NMR, one major peak is observed at the end of the transmetalation (Fig. 2). This observation indicates that transmetalation with the arylboronic acid **1** proceeds with high diastereoselectivity.[29] After the reductive elimination of **2**, the

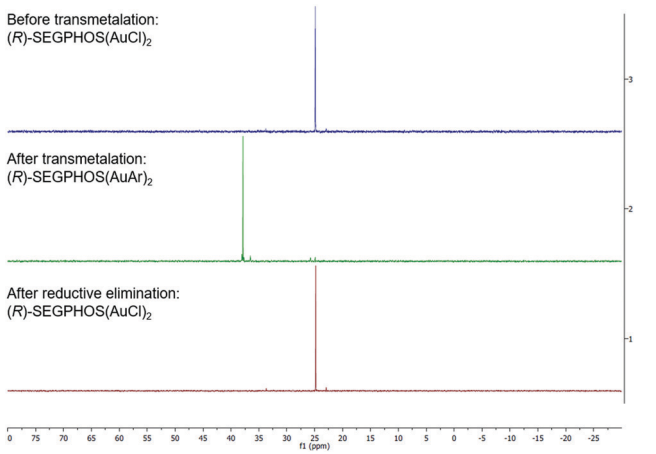


Fig. 2 ^{31}P NMR of the starting complex (top), the reaction mixture after transmetalation (middle), and the reaction mixture after reductive elimination (bottom).

starting complex is cleanly reformed suggesting the potential for development of a catalytic cycle (Fig. 2).

After the oxidation at −78 °C, the reductive elimination is facilitated by removing the dry ice-bath and allowing the reaction to quickly heat to room temperature. The same yield and ee was obtained for (*R*)-SEGPHOS(AuCl)$_2$ when letting the reaction mixture heat to room temperature very slowly (over 7 h). This result suggests that there is little influence of the heating profile on the enantiodetermining step. In contrast, the enantioselectivity is sensitive to the solvent used as a reaction in a toluene : CH_2Cl_2 (7 : 3) solvent mixture afforded the product with 76% ee, and a reaction in DCE (−30 °C to RT) led to 74% ee.

We hypothesize that the reactions follow the mechanism elucidated by Toste *et al.* for the achiral dppp(AuCl)$_2$ complex.[21] After transmetalation with the arylboronic acid, the gold complex is oxidized by $PhICl_2$ to a mixed-valence Au(I)–Au(III) complex,[30] which can undergo fast intramolecular transmetalation placing both aryl moieties on one gold atom. Finally, reductive elimination forms the enantioenriched biaryl product and regenerates (*R*)-SEGPHOS(AuCl)$_2$. Currently, it is unclear whether the intramolecular transmetalation or aryl–aryl reductive elimination is enantiodetermining; however, none of these elementary steps have been reported as enantiodetermining before with a gold complex.[31]

In summary, we have demonstrated the first highly enantioselective aryl–aryl coupling mediated by a gold complex. By synthesizing and evaluating 13 binuclear gold complexes bearing different C_2-symmetric chiral ligands, we found that the atropisomeric biaryl product (**2**) can be obtained in 91% ee and 70% yield by using the (*R*)-SEGPHOS(AuCl)$_2$ complex. At the end of the reaction, (*R*)-SEGPHOS(AuCl)$_2$ is reformed. The results reported here indicate the potential for development of highly enantioselective aryl–aryl coupling reactions catalyzed by chiral gold complexes.

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Conflicts of interest

There are no conflicts to declare.

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