Planar Chiral 1,3-Disubstituted Ferrocenyl Phosphine Gold(I) Catalysts

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ABSTRACT: Planar chiral monodentate 1,3-disubstituted ferrocene phosphines inspired on JohnPhos-type ligands have been synthesized and applied to the enantioselective gold(I) catalyzed [4 + 2] cycloaddition of 1,6-arylenynes. Computational studies rationalized the working mode of the catalyst on the folding of the substrate in the chiral environment of the ligand involving attractive noncovalent interactions.

KEYWORDS: gold catalysis, planar chirality, ferrocene phosphines, enantioselective synthesis, enynes, DFT calculations

In the wake of the first introduction of chiral ferrocene-based ligands by Hayashi for the asymmetric rhodium-catalyzed hydrosilylation of ketones,1 ferrocenyl phosphines have become one of the most versatile scaffolds in chiral ligand design. Since the pioneering work of Ugi,2 followed by those of Kagan,3 Richard,4 Uemura,5 and Sammakia,6 C2-functionalization of enantiopure ferrocenes by a chiral directing metalation group allowed the access of a variety of chiral 1,2-disubstituted ferrocene ligands such as PPFA,7 Josiphos,7 Fcphox,4 and Fesulphos,8 among others.9 Ferrocenyl phosphate ligands are mainly bidentate and display central chirality in addition to planar chirality, which plays a crucial role on the enantioinduction.10 The pioneering examples in enantioselective gold(I) catalysis11 referred to the use of a chiral ferrocenyl phosphate-gold(I) catalysts in the asymmetric aldol reaction between aldehydes and isocyanocetates.12 Since then, very few examples have been reported in gold(I) asymmetric catalysis using this type of complex.13 Our group found that digold(I) complexes with 1,2-disubstituted ferrocenyl ligands of the Josiphs family were the most efficient catalysts for the first enantioselective intermolecular gold(I)-catalyzed [2 + 2] cycloaddition of terminal alkynes and alkynes.14

In sharp contrast to the synthesis of 1,2-disubstituted ferrocenes, the enantioselective syntheses of 1,3-disubstituted scaffolds are still scarce,15 even if these structures appear to be promising for different applications.16 Therefore, we focused our efforts on the synthesis of ferrocene phosphine ligands displaying exclusively planar chirality, thus eliminating the possibility of match-mismatch cases and facilitating investigations on the mode of action of the new catalysts. We have recently achieved a high level of enantioselectivity in asymmetric gold(I) catalysis using a chiral JohnPhos-type gold(I) complex 1 with a C2-symmetric pyrrolidine.17 We envisioned that the planar chirality of a 1,3-disubstitued ferrocene could provide a somewhat similar chiral environment to that of the C2-symmetric pyrrolidine, while maintaining the bulky dialkylphosphine that is characteristic of JohnPhos ligands in order to direct the substrate coordinated to gold(I) toward the ferrocene scaffold and the chiral reaction scenario, where the enantiodiscrimination takes place (Scheme 1). Here, we report the synthesis of new 1,3-disubstituted ferrocene ligands and their application to the gold(I)-catalyzed intramolecular formal [4 + 2] cyclization of arylalkynes to alkenes, which takes place with consistently high enantioselectivities.

The readily available enantiopure chiral ferrocenyl sulfoxide 218 was used as the starting material in our synthetic route (Scheme 2). The preparation of the new ligands commenced by diastereoselective lithiation of 2 with LDA, followed by addition of ZnCl2 and Negishi cross-coupling yielding planar chiral ferrocenes 4a–f. For the second directed ortho-lithiation the configuration of the sulfoxide had to be inverted by a reduction–oxidation sequence yielding sulfoxides 5a–f. After...
ortho-lithiation of sulfoxides S with LiTMP and reaction with Bu3SnCl, the sulfoxide group was removed by reaction with tBuLi and protonolysis with iPrOH. The resulting tributylstannyl-ferrocenes underwent Sn−Li exchange with nBuLi, followed by addition of ZnCl2, Negishi coupling with 2-bromo-1-iodoarenes, and palladium-catalyzed coupling reaction with phosphines X2PH giving rise to ligands 6A−I, which afforded the corresponding gold(I)-complexes A−I by addition of Me2S·AuCl. Complexes A and C−F were directly obtained without isolation of the corresponding ligands 6. The structure of complexes A−C, G, and H was confirmed by X-ray diffraction.

The crystallographic Au−P distance 2.293 Å found for (Sp)-G is essentially identical to that determined for the chiral JohnPhos-type gold(I) complex 1.17 The buried volume for (Sp)-G was calculated using SambVca 2.1 (Figure 1).20 As revealed by the steric profile, the aromatic biphenyl substituents on the ferrocenyl moiety provide rather significant hindrance to the complex with a buried volume of 57.6%. As a comparison, buried volumes of [(PR3)AuCl] complexes with R = tBu, oTol, and Mes are 38.1, 39.4, and 45.0%, respectively (2.28 Å, Au−P length).21 Buried volumes of 45−53% have been reported for other gold(I) complexes bearing bulky alkoxydiaminophosphine22 or acyclic diaminocarbene ligands.23

To compare the reactivity of the new ferrocenyl phosphine gold(I) complexes with that of 1,17 we studied the [4 + 2] cycloaddition of 1,6-arylenynes 7 (Scheme 3). First, we studied the reaction of substrate 7n with A−I complexes (Table 1). Among the tested silver(I) salts, the best results were obtained with AgBF4. The highest enantioselectivity was obtained with complexes A, B, and H with two adamanthyl groups at the phosphine, which yielded cycloadduct 8n in 87−89:13−11 er (Table 1, entries 1−2 and 15). Complexes C−E and G led to lower enantioselectivities (Table 1, entries 10−12 and 14), whereas nearly racemic mixtures were obtained with F and I with two aryl groups at the phosphine (Table 1, entries 13 and 16). Although complex B provided 8n with higher enantioselectivity in toluene than in (CH2Cl)2 at 24 °C (88:12 vs 83:17 er) (Table 1, entries 3 and 7), at −25 °C no conversion of 7n was observed in toluene (Table 1, entries 4 and 8). In general, less clean conversions were observed in toluene or other aromatic solvents (Table 1, entries 5−6 and 9). A related complex with a 1-naphthyl group at C-3 of the ferrocene was also prepared, although product 8a was obtained in poor enantiomeric ratios (75%, 57:43 er).

Complex B, conveniently prepared from ferrocenyl sulfoxide 2 in 48% overall yield in a 0.8 mmol scale, was selected for practical purposes (Scheme 3). 1,6-Enynes 7a−b yielded cycloadducts 8a−b in moderate enantioselectivities, while enyne 7c with a tether with two methoxymethyl groups

Scheme 1. Design of Chiral Monodentate Ferrocene-Based Ligands

Scheme 2. Synthesis of Gold(I) Complexes A−I from Ferrocenyl Sulfoxide (S\texttextsubscript{p})-2

Figure 1. CYLview depiction of the X-ray crystal structure of ferrocenyl gold(I) complex (Sp)-G and steric maps by SamVca 2.1. Hydrogen atoms are omitted for clarity.
Scheme 3. Enantioselective Gold(I)-Catalyzed [4 + 2] Cycloaddition of 1,6-Arylenynes 7a–x with Catalyst B

Table 1. Optimization of the Enantioselective Gold(I)-Catalyzed [4 + 2] Cycloaddition of 1,6-Arylenyne 7n

| entry | complex | solvent | T (°C) | yield (%) | er  |
|-------|---------|---------|--------|-----------|-----|
| 1     | (S)−A  | (CH2Cl)2 | 0      | 88        | 87:13 |
| 2     | (S)−B  | (CH2Cl)2 | 0      | 95        | 88:12 |
| 3     | (S)−C  | (CH2Cl)2 | 24     | 92        | 83:17 |
| 4     | (S)−D  | (CH2Cl)2 | −25    | 81        | 94:6  |
| 5     | (S)−E  | CH2Cl2   | 24     | 90        | 85:15 |
| 6     | (S)−F  | CH2Cl2   | −25    | 82        | 95:5  |
| 7     | (S)−G  | toluene  | 24     | 75        | 88:12 |
| 8     | (S)−H  | toluene  | −25    | nd h      | -    |
| 9     | (S)−I  | PhCF3    | 24     | 77        | 86:14 |
| 10    | (S)−J  | (CH2Cl)2 | 0      | 95        | 82:18 |
| 11    | (S)−K  | (CH2Cl)2 | 0      | 89        | 74:26 |
| 12    | (S)−L  | (CH2Cl)2 | 0      | 95        | 73:27 |
| 13    | (S)−M  | (CH2Cl)2 | 0      | 89        | 56:44 |
| 14    | (S)−N  | (CH2Cl)2 | 0      | 93        | 85:15 |
| 15    | (S)−O  | (CH2Cl)2 | 0      | 92        | 89:11 |
| 16    | (S)−P  | (CH2Cl)2 | 0      | 89 i      | 49:51 |

aPreviously reported reactions performed using catalyst 1 (4 mol %), AgPF6 (4 mol %), and at 24 °C.17 Reaction performed at −10 °C. Reaction time = 12 days (vs 14 days with 1). **Reaction time = 6 days (vs 7 days with 1).**

afforded product 8c in excellent yield and enantioselectivity. Substrates 7d-o with bulky, electron-donating or electron-withdrawing groups in para- and ortho-positions of the aryl ring underwent [4 + 2] cycloaddition in high to excellent yields and enantioselective ratios. The cyclization of 1,6-ene syn 7g with a free phenol was carried out at −10 °C, as this substrate is insoluble in (CH2Cl)2 at −25 °C, and yielded product 8g with good enantioselectivity. 2,4-Disubstituted arylarylenynes 7p and 7q reacted smoothly delivering respectively products 8p and 8q in good yield and high enantiomeric ratio. Using complex H as the catalyst, substrate 7p led to 8p almost quantitatively in 98:2 er.

Lower enantioselectivity was obtained with 3,5-dibromo-phenyl-substituted 1,6-arylene 7r, which gave product 8r quantitatively but only in 77:23 er, while trimethoxy substituted arylenyne 7s gave 8s in 92:8 er. Phenanthrene-substituted enyne 7v delivered product 8v in excellent yield and enantioselectivity. Sulfur-containing heterocycles 7t and 7u, respectively bearing thiophene and benzenethiophene moieties, also reacted smoothly, affording the corresponding products 8t and 8u in high yields and good enantioselective ratios. In general, the intramolecular [4 + 2] cycloadditions were completed in 18–48 h at −25 °C with ferrocenyl phosphine gold(1) complex (S)−B, whereas reactions with complex I had to be performed at 24 °C. Previous results obtained with catalyst 117 are also included in Scheme 3. Comparison of the rate of formation of 8c from enyne 7c using gold(1) complexes B and I in the presence of AgBF4 or AgPF6 showed B the significantly more reactive.24 On the other hand, reactions leading to 8w and 8x were very slow with both catalysts B and I. Performing reaction of 7w at 25 °C with catalyst B afforded 8w in 65% yield after 84 h but only with 66:34 er. The absolute configuration of products 8 was assigned by comparison with previously reported results.17

To better rationalize the working mode of these novel ferrocenyl-based phosphate gold(1) complexes, we carried out DFT calculations.24 We started our investigations computing the reaction coordinate for the cyclization of enyne 7c (Figure 2a). BP86-D3 has been chosen as a functional due to its efficiency proved in other studies of enantioselective gold(I) catalysts14,17,25 and in our recent benchmark of DFT functionals using similar systems.26 We used (S)−G as gold(I) catalyst (Bu substituted phosphine), which is similar but simpler than (S)−B. Our calculations herein center on the intramolecular electrophilic addition of [LAu(η2-alkyne)]+ complex to the alkene (Int1a−b to Int2a−b), as the enantiodetermining step of the transformation. We calculated two possible minima resulting from the reaction of the two enantiotopic faces of the alkene (R and S pathways) and examining the evolution of the two possible gold(I)-complexes Int1a−b following an exocyclic pathway. The calculated energy difference between the lowest transition states that lead to Int2a and Int2b ΔG‡[S 80–100]kcal/mol are in good agreement with the experimental results (96:4 er). The lowest transition state TSInt1−2a was found to be stabilized by π-π interactions27 and the lack thereof in TSInt1−2b. Therefore, cyclopropyl gold(I) carbene Int2a with the R absolute configuration is preferentially formed. We further examined the attractive interactions between the π-systems of the substrate and the catalyst. Hence, larger green surfaces were observed in the NCI plots28 of the lowest-energy transition state TSInt1−2a in comparison to TSInt1−2b confirming that noncovalent inter-
actions play a fundamental role in the stabilization of the corresponding transition states.

Although this theoretical study provided a model to explain the preferred formation of the R-enantiomer of 8c, we further examined this system by changing the aromatic ring substituents on the substrates (R1−4 in Int1) to better understand the limitations of our catalysts (Figure 2b). Thus, we computationally studied enynes 7j, 7l, 7q, 7r using the same (Sp)-G gold complex. For para-substituted aryl enynes 7j and 7l, the activation energies to reach Int2a was lower by at least 1.1 kcal/mol than the alternative pathway that gives rise to Int2b in both cases, in agreement with the experimental results (95:5 er for product 8j and 96:4 er for 8l). Interestingly, both cyclopropyl gold carbenes Int2a of enynes 7j and 7l were found to be more stable than the other examples due to the conformation adopted in the chiral pocket. Having a methyl group in the ortho- and para-position of the aryl ring of enyne 7q was crucial to achieve higher enantioselectivity (∆∆G‡R,S = 1.4 kcal/mol). However, very similar activation energies were found for the two competing pathways of the 3,5-dibromophenyl-substituted 1,6-arylene 7r. Thus, in this case, formation of Int2a was favored by only 0.3 kcal/mol, in good agreement with the lower enantiomeric ratio obtained experimentally (77:23 er). This drop of enantioselectivity can be rationalized by the lower noncovalent interactions in the transition state as well as the steric repulsion due to the bulkiness of the bromine forcing the substrate away from the chiral environment of the catalyst.

In summary, we have synthesized unprecedented gold(I) complexes with planar chiral monodentate ferrocene-based ligands by iterative ortho-lithiation/transmetalation/Negishi cross-coupling reactions and palladium-catalyzed phosphine cross-coupling. This is the first synthetic route leading to planar chiral analogues of the JohnPhos-type ligands. The new chiral 1-(2′-dialkylarylphosphine)-3-arylferrocene gold(I) complexes allow performing the formal intramolecular [4 + 2] cycloaddition of arylalkynes with alkenes with high enantioselectivities and with higher reactivity than our recently reported JohnPhos-type gold(I) complexes with a C2-symmetric pyrrolidine. Computational studies provide a working model showing a very good agreement with the experimental results, which indicates that noncovalent π−π-interactions between substrates and the ligand are responsible of the selective folding of substrates in the chiral environment of the gold(I) catalyst.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c05827.

Experimental procedures, characterization data, NMR data, UPC2 and HPLC traces, computational details, and X-ray data (PDF)

Accession Codes
CCDC 2129524–2129528 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

Figure 2. (a) Free-energy profile for the gold(I)-catalyzed cyclization of 1,6-enzyme 7c with (Sp)-G. S-pathways are depicted in green and R-pathways in purple (energies in kcal/mol). CYLview representations and NCI plots of the two possible transition states TSInt1–2a and TSInt1–2b. Hydrogens are omitted for clarity. Color-filled RDG isosurface. Blue color: strong attractive interactions (C−C bond formation), green color: attractive noncovalent interactions, red color: areas of repulsion (steric and ring effects). (b) Calculation of difference in activation energies (∆∆G‡R,S) between R and S enantiomers in different substrates.
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Notes
The authors declare no competing financial interest.

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