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# Gold(I)/Chiral Brønsted Acid Catalyzed Enantioselective Hydroamination–Hydroarylation of Alkynes: The Effect of a Remote Hydroxyl Group on the Reactivity and Enantioselectivity

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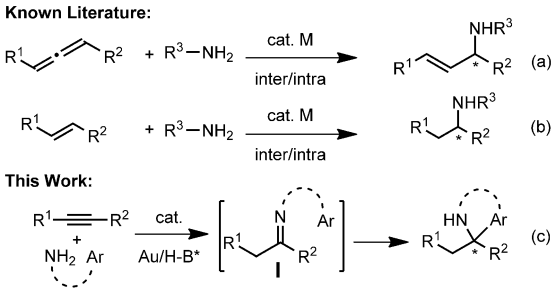
**Abstract:** The catalytic enantioselective hydroamination–hydroarylation of alkynes under the catalysis of ($R_3$P)AuMe/(*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate ((*S*)-TRIP) is reported. The alkyne was reacted with a range of pyrrole-based aromatic amines to give pyrrole-embedded aza-heterocyclic scaffolds bearing a quaternary carbon center. The presence of a hydroxyl group in the alkyne tether turned out to be very crucial for obtaining products in high yields and enantioselectivities. The mechanism of enantioinduction was established by carefully performing experimental and computational studies.




**Scheme 1.** Enantioselective addition of H–Nu to C–C multiple bonds.

The hydroamination of allenes, olefins, and alkynes catalyzed by transition-metal complexes is a fundamentally important reaction, which has been widely used in organic synthesis.[1] The addition of amines to allenes and/or olefins generates chiral amines, and a large number of reports on catalytic enantioselective variants exist (Scheme 1 a and b).[2] We envisioned a different approach involving the addition of amines and electron rich aromatic compounds to alkynes, leading to chiral secondary amines (Scheme 1 c). The process is a catalytic enantioselective hydroamination–hydroarylation, which could be of great importance since chiral aza-heterocycles bearing a quaternary carbon center can be generated. To our surprise, there have been no reports on catalytic enantioselective versions of such processes to date.[3]

The reason for the slow progress in developing a catalytic enantioselective hydroamination–hydroarylation might be the requirement of a catalyst that can perform a hydroamination as well as an enantioselective addition of H–Nu to transient imines. We envisaged that the hydroamination of alkynes with aromatic amines would occur in the presence of a chiral Au catalyst[4] to form imines, which would then undergo an intramolecular attack with the tethered aromatic compound to produce an enantioenriched double-addition product (Scheme 1 c). A crucial aspect for the success of the proposed reaction would be the formation of a tight ion pair[5] between the imine nitrogen atom and the chiral Au catalyst. Based on the available knowledge on enantioselective gold catalysis,[6] two strategies could be easily envisaged. The first strategy involves the use of L*AuX complexes.[5] However, the enantioselective addition of nucleophiles to imines under the catalysis of L*AuX complexes has rarely been reported.[7] We assumed that the shortage of such reports might be due to the inability of Au complexes to coordinate strongly with imines[8]—the phenomenon can be well understood with the HSAB principle and relativistic effects.[4k,9] The alternate strategy involves the use of LAuX* complexes, generated in situ from LAuMe and H–X* (X* = chiral phosphate anion).[10] This strategy is supported by two facts: 1) a chiral phosphate counter ion acts as a ligand bonded to the gold species, thus facilitating the hydroamination reaction[10n,11] and 2) the residual X*H generated in situ can act as a catalyst for the addition of H–Nu to imines.[12] This hypothesis was supported by the pioneering work of Gong and co-workers who reported a consecutive $Au^I$-catalyzed intramolecular hydroamination of alkynes and chiral Brønsted acid catalyzed enantioselective transfer hydrogenation.[10q] Herein, for the first time, we report the catalytic enantioselective hydroamination–hydroarylation of alkynes under the catalysis of a $Au^I$/B*–H binary system to generate optically active pyrrole-containing aza-heterocyclic scaffolds bearing a quaternary carbon center.

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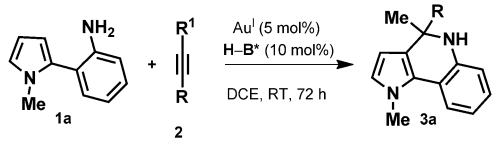
**Table 1.** Optimization of the reaction conditions.[a]




| Entry | 2 | $Au^I$ | BH (5) | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **2a** R = H, $R^1$ = *n*Hex | $Ph_3PAuMe$ | **5a** | 22 | 4.7 |
| 2 | **2a** | **4a**-AuMe | **5a** | 27 | 5.3 |
| 3 | **2a** | **4b**-AuMe | **5a** | 31 | 4.4 |
| 4 | **2a** | **4a**-AuMe | **5b** | 48 | 3.2 |
| 5 | **2a** | **4a**-AuMe | **5c** | 56 | 3.0 |
| 6 | **2a** | **4a**-AuMe | **5d** | 57 | 6.2 |
| 7 | **2b** R = H, $R^1 = (CH_2)_3OH$ | $Ph_3PAuMe$ | **5a** | 76 | 91 |
| 8 | **2b** | $Ph_3PAuMe$ | **5b** | 84 | 78 |
| 9 | **2b** | **4a**-AuMe | **5a** | 80 | 98 |
| 10 | **2b** | **4b**-AuMe | **5a** | 81 | 95 |
| 11 | **2b** | **4a**-AuMe | **5b** | 76 | 39 |
| 12 | **2b** | **4a**-AuMe | **5c** | 69 | 57 |
| 13 | **2b** | **4a**-AuMe | **5d** | 57 | 41 |
| 14 | **2b** | **4a**-AuMe | **5e** | 83 | 63 |
| 15 | **2b** | **4a**-AuMe | **5f** | 83 | 29 |

[a] Reaction conditions: **1a** (0.15 mmol), **2** (0.15 mmol), $Au^I$ (5 mol%), H–B*(10 mol%), DCE (2.0 mL), RT, 24 h. [b] Isolated yields. [c] The *ee* was determined by HPLC analysis on a chiral stationary phase.

Since chiral pyrroles are prevalent building blocks in a variety of natural products and pharmaceuticals, we started our investigation by using 2-(2-aminophenyl)pyrrole (**1a**) as a bis-nucleophile (Table 1). Initially, the reaction was performed by using octyne **2a** and 2-(1-methyl-1H-pyrrol-2-yl) aniline (**1a**) in the presence of 5 mol% [$PPh_3AuMe$] and 10 mol% **5a** (Figure 1).

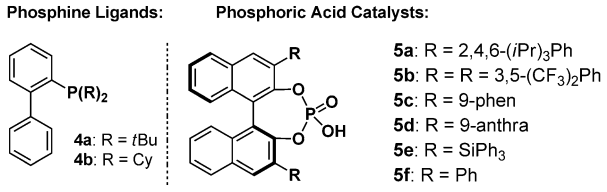
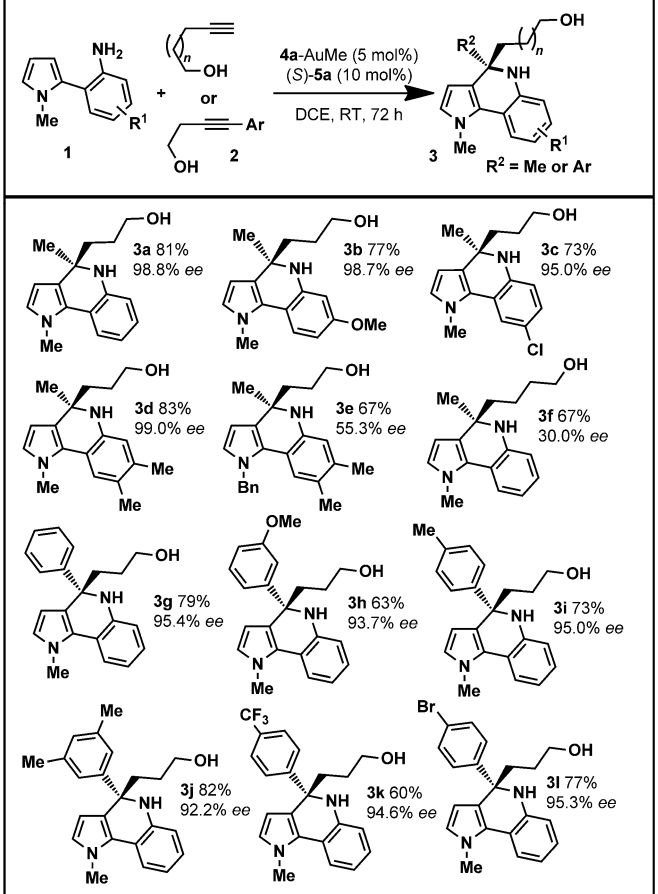



**Figure 1.** Catalyst employed for the optimization.

Pleasingly, product **3a** was obtained in 22% yield; however, the *ee* was found to be only 4.7% (entry 1). To investigate the effect of the phosphine ligand, Au complexes **4a** and **4b** were tested regarding their catalytic efficiency; however, none of them was found to be beneficial (entries 2 and 3). When chiral Brønsted acids **5b**, **5c**, and **5d** were used in the presence of **4a**-AuMe, a slight increase in yield was observed; however, the *ee* still remained low (entries 4–6). Based on our previous report,[13] we decided to use an alkyne that bears an –OH group in the tether. When 4-pentyn-1-ol (**2b**) was reacted with **1a** in the presence of 5 mol% [$PPh_3AuMe$] and 10 mol% **5a**, the reaction proceeded smoothly to afford **3a** in 76% yield with 91% *ee* (entry 7). The *ee* dropped to 78% when **5b** was used instead of **5a** (entry 8). The use of the bulky gold catalyst **4a**-AuMe or **4b**-AuMe in combination with **5a** gave **3a** in 80 and 81% yield with 98 and 95% *ee*, respectively (entries 9 and 10). Next, we screened chiral phosphoric acid catalysts **5** bearing various types of substituents at the 3,3′ position on the binaphthyl backbone (Figure 1). As shown in entries 11–15, all of the chiral catalysts **5** performed satisfactory in terms of the yield (except entry 13); however, the *ee* values were found to be strongly dependent on the C-3 substituent. We further extensively studied the effect of the solvent, catalyst loading, and temperature on the reaction outcome.[14] The study revealed that the best conditions are treating **1b** and **2a** in presence of 5 mol% **4a**-AuMe and 10 mol% **5a** in DCE at room temperature (entry 9).

With the optimized conditions in hand, we explored the generality of the catalytic enantioselective hydroamination–hydroarylation reaction by using various 2-(2-aminoaryl)pyrroles and alkynes (Table 2). 4-Pentyn-1-ol reacted smoothly with various 2-(2-aminophenyl)pyrroles (bearing OMe, Cl, and Me substituents) under the established conditions to obtain the desired products **3a–d** in yields ranging from 73–83% and *ee* values ranging from 95–99% (C2–C3 cyclization). When the

**Table 2.** Reaction of 2-(2-aminophenyl)pyrroles and alkynols.[a]



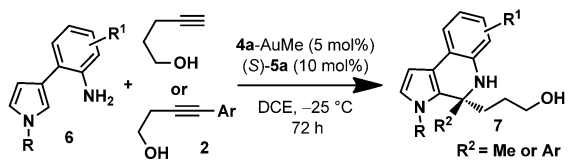

[a] Reaction conditions: **1** (0.15 mmol), **2** (0.15 mmol), **4a**-AuMe (5 mol%), (*S*)-**5a** (10 mol%), DCE (2.0 mL), RT, 72 h. All yields are isolated yields; the *ee* values were determined by HPLC analysis on a chiral stationary phase.

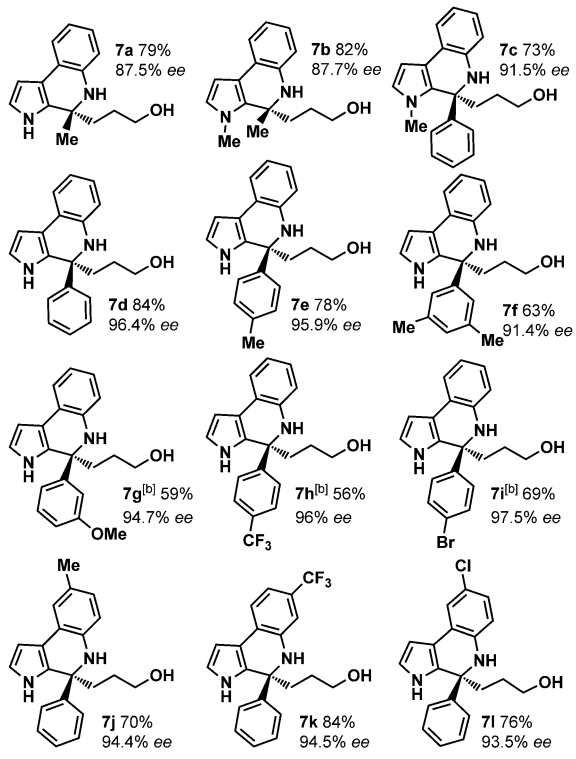
methyl group on the pyrrole nitrogen atom was replaced by a benzyl group, the *ee* dropped down to 55% (**3d** vs. **3e**). It is worth noting that the carbon-chain length between the OH group and the alkyne moiety has a major effect because the use of 5-hexyn-1-ol provided **3f** with only 30% *ee*. Internal aromatic alkynols bearing a halogen, methoxy, trifluoromethyl, or methyl group at the meta and para positions were well tolerated to afford the corresponding dihydropyrolo[3,2-*c*]quinolines in yields ranging from 60 to 82% and *ee* values higher than 90% in all cases.

Next, we turned our attention to 3-(2-aminophenyl)pyrroles (Table 3). Lowering the reaction temperature turned out to be beneficial to obtain dihydropyrolo[2,3-*c*]quinolines in good yields and high enantiomeric purities (C3–C2 cyclization).[14] A variety of substrates were examined to understand the scope and limitations of the reaction. Notably, 4-pentyn-1-ol and internal alkynols bearing an aromatic ring with various steric and electronic modifications were well tolerated. As can be judged from **7a**/**7b** and **7c**/**7d**, the free NH group of the pyrrole is not necessary and even protected pyrrole derivatives work equally well to give the corresponding products in good yields and enantioselectivities.

Next, we endeavored to study the applicability of the 2-amino phenyl pyrroles for the catalytic enantioselective hyroamination–hydroarylation reaction (Table 4). In all cases examined, pyrrolo[1,2-*a*]quinoxalines (N–C2 cyclization) were obtained in good yields with excellent *ee* values (>90%).

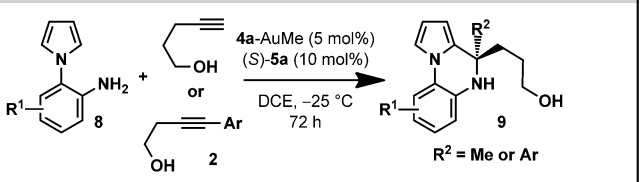
**Table 3.** Reaction of 3-(2-aminophenyl)pyrroles and alkynols.[a]

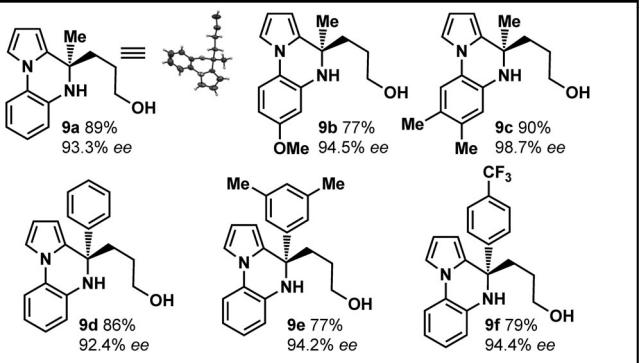



[a] Reaction conditions: **6** (0.15 mmol), **2** (0.15 mmol), **4a**-AuMe (5 mol%), (*S*)-**5a** (10 mol%), DCE (2.0 mL), −25 °C, 72 h. All yields are isolated yields; the *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] Reaction performed at −15 °C.

**Table 4.** Reaction of *N*-(2-aminophenylpyrroles) and alkynols.[a]



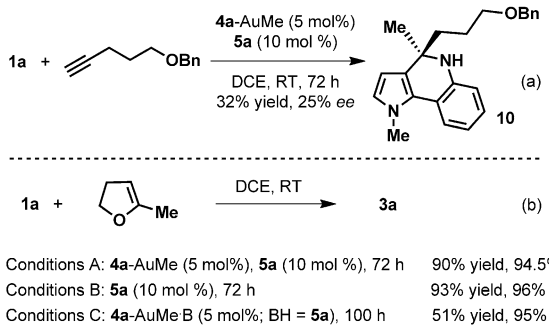




[a] Reaction conditions: **8** (0.15 mmol), **2** (0.15 mmol), **4a**-AuMe (5 mol%), (*S*)-**5a** (10 mol%), DCE (2.0 mL), −25 °C, 72 h. All yields are isolated yields; the *ee* values were determined by HPLC analysis on a chiral stationary phase.

The scalability and practicality of the developed method is demonstrated by the gram-scale asymmetric synthesis of **3g** (82% yield, 94.5% *ee*) from **1a** and **2g**. Because of the importance of pyrrole-containing heterocycles in pharmaceutical chemistry, the present reaction can provide an efficient access to such molecules in enantiomerically pure form. Moreover, the hydroxyl group in the product provides a versatile handle for further transformations to access additional molecular complexity.

The absolute configuration of products **9a** (Table 4) and **3g** (after dehydrative cyclization) was determined by single-crystal X-ray analysis[14] and that of the other products was assigned by analogy. It is worth noting that the absolute configuration in the products varies depending on the type of alkyne used (4-pentyn-1-ol vs. 4-arylbut-3-yn-1-ols); however, the mode of enantioinduction remains the same.[15]

Control experiments have been performed carefully, which led us to conclude that the OH group in the alkyne is essential to provide the products in good yields and enantioselectivities (Scheme 2). The reaction of benzyl-protected 4-pentyn-1-ol with **1a** under the optimized reaction conditions gave **10** only with 25% *ee* (Scheme 2a). In this case, the product might have been formed through a direct hydroamination–hydroarylation




**Scheme 2.** Control experiments.

reaction, as previously reported by our research group.[3a] When commercially available 2-methylenetetrahydrofuran was treated with **1a** under conditions A and B, **3a** was obtained in almost identical yield and *ee* (Scheme 2b, conditions A and B). The use of preformed gold phosphate, generated in situ from **4a**-AuMe and (*S*)-**5a**, delivered **3a** only in 51% yield, although the reaction time was prolonged to 100 h. However, the *ee* of the product remained almost identical (95% *ee*; Scheme 2b, conditions C). All these observations clearly indicate the importance of the tethered hydroxyl group in the alkyne. It can also be concluded that the hydroalkoxylation is catalyzed by the in situ generated gold phosphate, while the condensation is promoted only by (*S*)-**5a**. The formation of the product in low yield (Scheme 2b, conditions C) can be attributed to of a small amount of phosphoric acid (*S*)-**5a**, which is generated by degradation of gold phosphate in the presence of substrates bearing OH and $NH_2$ groups. The involvement of a gold phosphate in the condensation reaction can be ruled out based on computational studies.[14]

To clearly understand the role of the tethered OH group and the mode of enantioinduction, DFT calculations were performed by using the Turbomole 6.4 suite of programs and the TZVP/PBE/B3LYP approach. The studies indicate that the "*Re*-face" attack of the nucleophile is kinetically preferred over the "*Si*-face" attack by 5.8 ($\Delta G$) and 3.6 kcal mol$^{-1}$ ($\Delta E$; Figure 2). Clearly, the highest level of enantioinduction can be accounted by the transition state involving the H-bonding interaction between the transient imino alcohol and B*–H. The bifunctional nature of the chiral phosphoric acid[12] is responsible for the concurrent activation of both the imine nitrogen atom and the tethered hydroxyl group through hydrogen-bonding interactions, which creates a chiral environment and exhibits products with very high enatioselectivities.

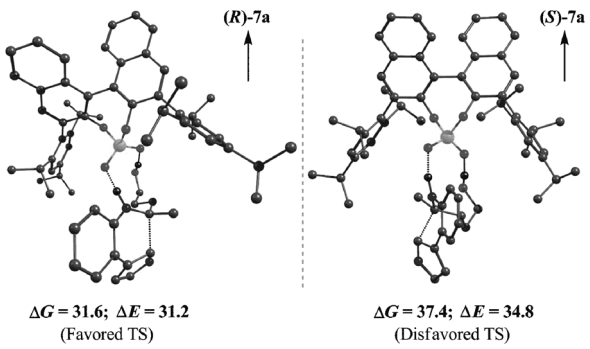



**Figure 2.** "*Si*-face" attack versus "*Re*-face" attack.

A literature analysis revealed that the organocatalytic enantioselective condensation reaction between aromatic amines with carbonyl compounds (or equivalent) is an important method for accessing enantiopure scaffolds. However, all these methods lead to the generation of asymmetric *tertiary* carbon centers.[16] Since the formation of asymmetric *quaternary* carbon centers[17] is very important, recent focus of many research groups is devoted to the development of catalytic asymmetric variants that generate quaternary carbon centers.[18,19] However, most of these reactions require either cyclic imines[18] or specially designed substrates.[19] In this regard, the newly developed method is valuable. Moreover, the hydroxyl group could provide a functional handle for further functionalizations.

In summary, we have discovered the catalytic enantioselective hydroamination–hydroarylation of alkynes under the catalysis of a $Au^I$/chiral Brønsted acid binary system. The method is very general and works well for a range of pyrrole-based aromatic amines and, therefore, may open unprecedented opportunities in diversity-oriented synthesis (DOS) for the development of enantioselective relay[20] catalytic branching cascade reactions.[21] In addition, the work presented herein could be considered as an advanced complement to Pictet–Spengler (type) reactions, because the formation of quaternary carbon centers through the condensation of aromatic amines with carbonyl compound is highly challenging and mostly limited to tryptamines.[19,22] Further investigations on expanding the scope of this reaction are currently underway in our laboratory.

## Experimental Section

### Representative procedure

At room temperature, (*S*)-TRIP (10 mol%) and (Johnphos)AuMe (5 mol%) in DCE (2 mL) were added to a flame-dried screw-capped vial equipped with a magnetic stir bar, and the reaction mixture was stirred for 30 min. To this reaction mixture, alkynol (0.15 mmol) was added followed by the aromatic amine (0.15 mmol) under argon atmosphere. The reaction vial was fitted with a cap, evacuated, back-filled with argon, and stirred at a specified temperature (72 h). The reaction mixture was diluted with ethyl acetate and filtered through a plug of silica gel. The filtrate was concentrated and thus the obtained residue was purified by silica gel column chromatography using petroleum ether/EtOAc as an eluent to afford analytically pure final compounds. All racemic samples were synthesized by using (Johnphos) AuCl (5 mol%) and AgOTf (5 mol%) catalysts following the same reaction conditions (reaction time of 24 h).

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**Keywords:** Brønsted acids · enantioselectivity · gold · hydroamination · hydroarylation

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# COMMUNICATION

**Synthetic Methods**

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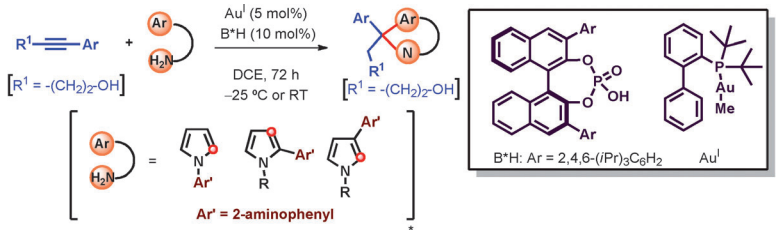
## Gold(I)/Chiral Brønsted Acid Catalyzed Enantioselective Hydroamination–Hydroarylation of Alkynes: The Effect of a Remote Hydroxyl Group on the Reactivity and Enantioselectivity




**Enantioinduction**: The catalytic enantioselective hydroamination–hydroarylation of alkynes by using a ($R_3P$)AuMe/(*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate ((*S*)-TRIP) binary catalyst system is reported (see scheme). The OH group in the alkyne tether is essential to obtain the pyrrole-embedded aza-heterocyclic scaffolds bearing a quaternary carbon center in high yields and enantioselectivities.