Enantioselective *para*-C(sp²)-H Functionalization of Alkyl Benzene Derivatives via Cooperative Catalysis of Gold/Chiral Bronsted Acid

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Supporting Information Placeholder

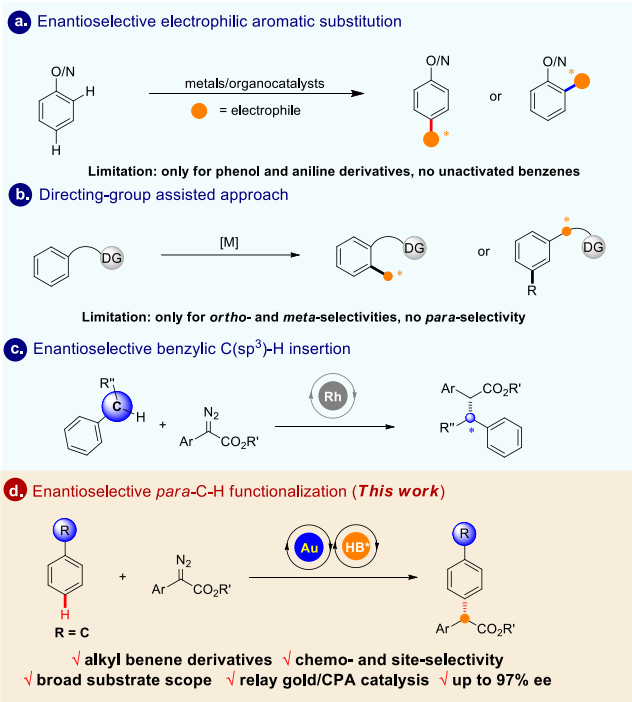
ABSTRACT: Herein, we developed an asymmetric *para*-C(sp²)-H bond functionalization of alkyl benzene derivatives via cooperative catalysis of gold and chiral phosphoric acid, leading to synthetically useful diaryl chiral centers. In this transformation, chiral phosphoric acid, ligand, and molecular sieves were all crucial for enantioselectivity control. The salient features of this protocol include mild conditions, high efficiency, readily available starting materials, highly chemo- and site- as well as enantioselective aromatic C−H functionalization, broad substrate scope, and extensive applications of the chiral products. The mechanistic studies showed that one gold complex and two CPAs might be involved in the chiral induction.

Direct aromatic C-H bond functionalization of arenes represents one of the most integral approaches for the synthesis of natural products, pharmaceuticals, agrochemicals, fine chemicals and polymers.[1] Although many efforts have been devoted to this field, the enantioselective version is rarely explored.[2] Classical electrophilic substitution, named Friedel-Crafts reaction, is the most straightforward strategy for enantioselective C(sp²)-H bond functionalization of phenyl rings. However, the substrates are limited to the arenes with strong electron-donating groups, such as phenol and aniline derivatives (Scheme 1a).[3] Recently, the directing group (DG) assisted strategy offers an alternative to achieve enantioselective *ortho*-, and *meta*-, selective C(sp²)-H bond functionalization of phenyl rings, but DG is too far to control the enantioselectivity of the *para*-position.[4] To date, highly enantioselective *para*-C-H bond functionalization of benzene derivatives is still significantly challenging, especially the ones without electronic bias such as alkyl benzenes.

Metal-carbenes are versatile intermediates, which are widely employed in synthetic chemistry due to their unique reactivities.[5] The insertion of metal-carbenes into C-H bonds has be used in *para*-selective C(sp²)-H bond functionalization of arenes.[6] In 2015, Zhu and Zhou disclosed an elegant asymmetric *para*-C−H bond functionalization of anilines with α-aryl-α-diazoacetates via the combination of achiral rhodium complex and a chiral phosphoric acid (CPA). In 2021, Xu et al. achieved a *para*-selective C(sp²)−H allylation of anilines with arylvinyl diazoacetates under a chiral rhodium (I) complex. However, rhodium catalysts favored benzylic C(sp³)-H functionalization other than C(sp²)−H bonds of alkyl benzene due to the lower bond dissociation energies of benzylic carbon-hydrogen bonds.[7] Che and Davies, et al. have demonstrated a variety of asymmetric Rh-catalyzed benzylic C-H insertion of alkyl benzenes (Scheme 1c). The development of new catalytic modes is vital to achieve slectively C(sp²)−H insertion in alkyl arenes.

Homogenous gold catalysis[8] has attracted much attention because gold complexes offer very unique reactivity and selectivity compared to other commonly used noble metals in carbene chemistry. Recently, several gold-catalyzed C(sp²)-H functionalization

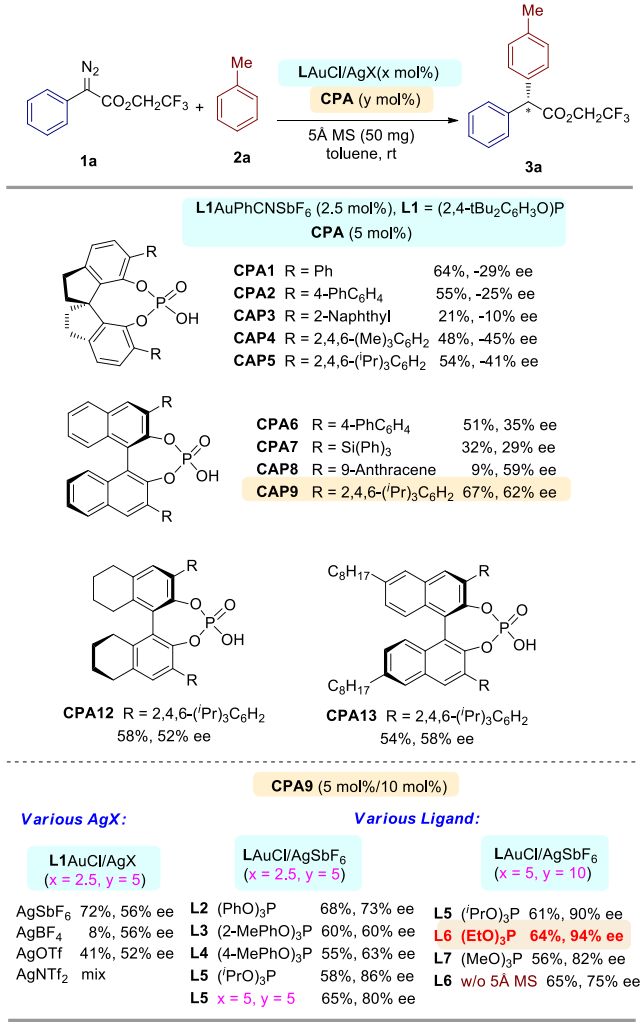
Scheme 1. State-of-the-art enantioselective C-H functionalization of phenyl rings.



of arenes,[9] such as phenol, aniline, anisole, with α-diazoesters have been developed, because gold-carbene can serve as gold-stabilized cation that favours the aromatic C(sp²)−H functionalization of arenes.[9,10] However, the enantioselective version is challenging as the key step for both rate-determination and chiral induction is the formation of final product from enols via proton transfer assisted by water as proton shuttle, in which the gold complex is leaving or far away from the chiral carbon center on the basis of previous

mechanistic studies.[9c,9h] Given the fact that chiral phosphoric acid (CPA) is an excellent proton shuttle[11] and compatible with many metal catalysts,[12] we assumed that the asymmetric of *para*-C(sp^2)–H bond functionalization of alkyl benzenes with diazoesters might be achieved via cooperative catalysis of gold and CPA. Herein, we present the first highly enantio-selective *para*-C(sp^2)-H bond functionalization of alkyl benzene derivatives with diazoesters (Scheme 1d). This strategy provided a facile access to chiral diarylacetate motifs, which are ubiquitous subunits in natural products, bioactive molecules, and functional materials.[13]

Table. 1 Optimization of reaction conditions[a]

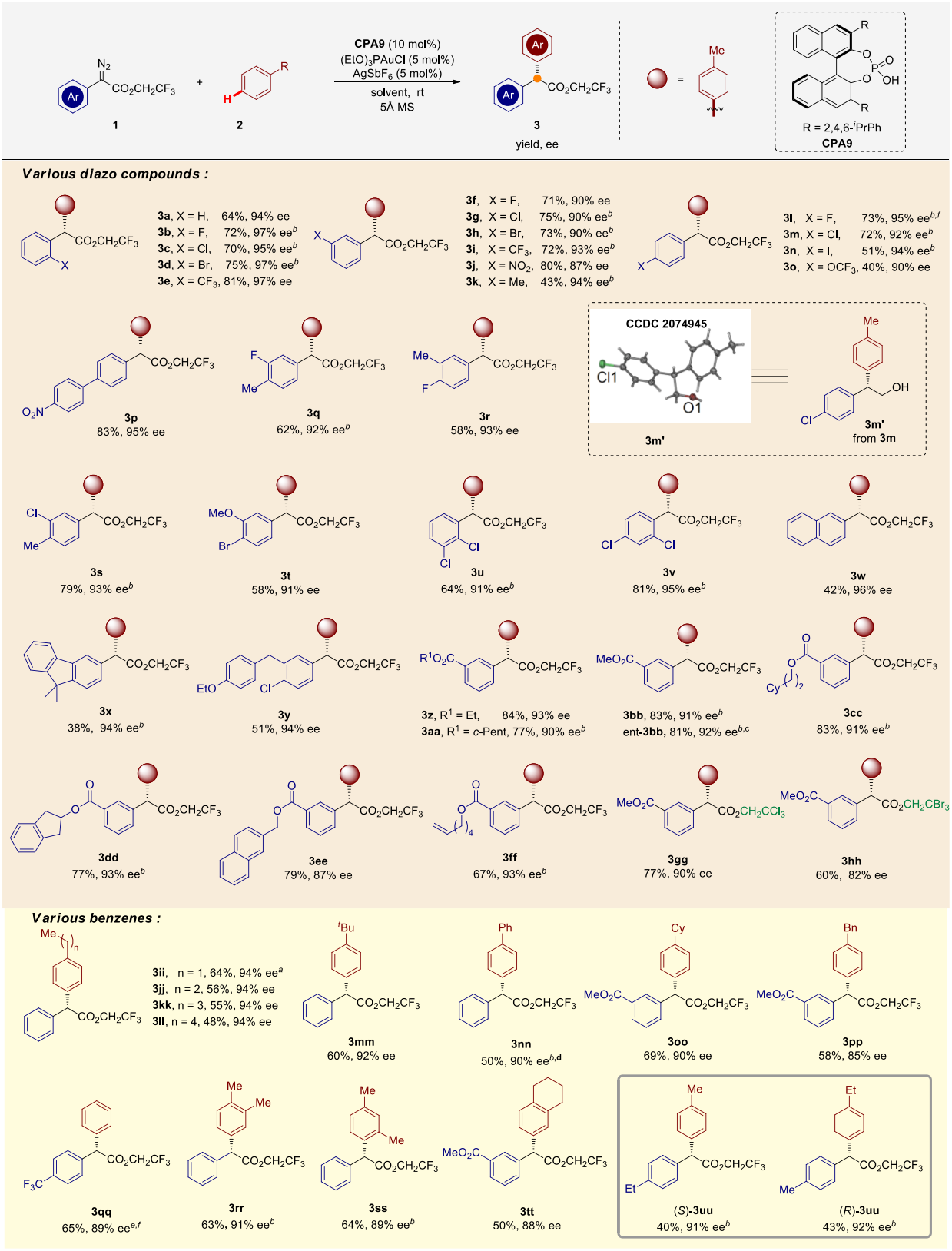


[a]Unless otherwise specified, all reactions were performed with LAuCl/AgX (x mol%), CPA (y mol%), **1a** (0.1 mmol), 5Å MS (50 mg) in 1.5 mL of toluene at 25 °C. Isolated yields are provided. The ee was determined by HPLC.

We optimized the reaction conditions for the asymmetric para-C-H alkylation with trifluoroethyl *α*-aryl-*α*-diazoesters **1a** and toluene **2a** as the model substrates (Table 1). The reaction proceeded smoothly when it was conducted at room temperature in the presence of 2.5 mol % **L1**AuPhCNCl/$AgSbF_6$ and 5 mol % spiro chiral phosphoric acid **CPA1** as catalysts with 5 Å molecular sieve (MS) as additive, delivering the desired *para*-selective C-H bond functionalization product **3a** in 64% yield with 29% ee. This result indicated that the cooperative catalysis of gold and CPA was promising for achieving high enantioselectivity. After screening various spiro CPAs (**CPA1-CPA5**), only moderate enantioselectivities were obtained (10-45% ee). The 1,1'-bi-2-napthol (BINOL) derived CPAs (**CPA6-CPA13**) were also examined, and **CPA9** (TRIP) with two 3,3'-di(2,4,6-isopropylphenyl) moieties, gave the highest yield as well as enantioselectivity (67% yield, 62% ee). Using **CPA9** as the chiral proton shuttle, then we screened various gold catalysts. The reaction efficiency was improved when the ligand benzonitrile was removed (72% yield, 56% ee). Counter anion effect is very important in gold catalysis and was also observed in this reaction. Evaluation of various silver salts revealed that the $AgSbF_6$ exhibited the best efficiency and enantioselectivity. The use of a smaller phosphite ligand, $(PhO)_3P$ (**L2**) for gold catalyst improved the enantioselectivity to 73% ee. Other substituted phenyl phosphite ligand (**L3** and **L4**) reduced the enantioselectivity to 60% ee and 63% ee, respectively. These results indicated that the steric hindrance of phophite ligand was crucial for the stereoselectivity. To our delight, the combination of **L5**AuCl/$AgSbF_6$ and **CPA9** gave the desired product **3a** in 58% yield with 86% ee. If the catalytic amount of **L5**AuCl/$AgSbF_6$ was increased to 5 mol%, the enantioselectivity was decreased to 80% ee, which showed the ratio of the amount of gold catalysts and CPAs affected the catalytic efficiency and enantioselectivity. When the amount of **CPA9** was raised to 10 mol% with 5 mol% **L5**AuCl/$AgSbF_6$ (gold/CPA being 1:2), 90% ee was obtained. Gratifyingly, the use of smaller ligand, triethylphosphite (**L6**), improved the performance (64% yield, 94% ee). However, the smallest trimethylphosphite (**L7**) reduced the yield (56%) and enantioselectivity (82%). It was noteworthy that 5Å MS had a strong effect on the enantioselectivity. The ee dropped to 75% in the absence of 5Å MS.

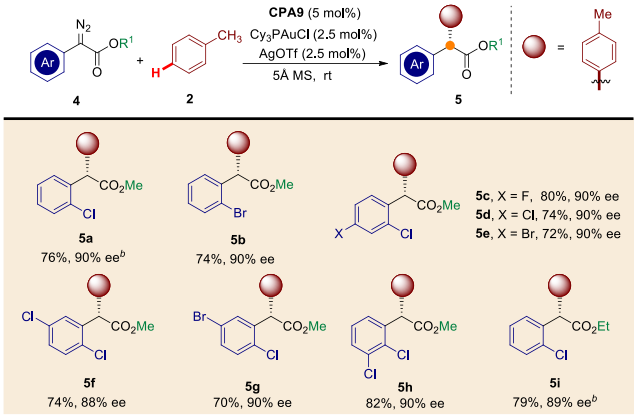
Using the optimal reaction conditions, we tested the substrate scope of this asymmetric *para*-C(sp^2)-H functionalization. First, we used toluene **2a** to investigate the scope of trifluoroethyl *α*-aryl diazoesters **1**. As shown in Scheme 2, the reactions of toluene with diazoesters **1** with different substitutes on *para*-, *meta*- and *ortho*-positions of phenyl ring were carried out smoothly, affording the corresponding chiral 1,1-diaryl compounds **3a**-**3v** in moderate to good yield (40-83%) and excellent enantio-selectivity (90-97% ee). Substituents on *ortho*-position of the aryl ring of the α-aryl-α-diazoacetates had a little bit positive effect on enantioselectivity due to the steric hindrance, while substituents at the *para*- and *meta*-positions showed a negligible impact on the enantioselectivity. Diazo compounds **1** with a fused ring, such as 2-naphthyl and 9*H*-fluorenyl, were also suitable substrates for this C-H alkylation reaction and gave the corresponding products (**3w** and **3x**) in satisfied yields and enantioselectivities. The benzyl substituted α-aryl α-diazoacetate also worked, leading to the corresponding product **3y** in 51% yield with 94% ee. Various ester groups, such as alkyl, cycloalkyl, indanyl, benzyl, and alkenyl, were installed on the phenyl ring of diazoesters, which were still the suitable substrates for this reaction and afforded the *para*-C-H functionalization products **3z**-**3ff** in good yield (67-84%) with excellent enantioselectivity (87-93%). Notably, all these reactions were chemo- and site-specific, in which neither benzylic C-H insertion nor cyclopropanation was observed. The reserved *ent*-**3bb** was obtained in the similar yield and enantioselectivity by switching (*R*)-**CPA9** to (*S*)-**CPA9**. The aryldiazoacetates with other electron-withdrawing ester moieties, such as 2, 2, 2-trichloroethyl and 2, 2, 2-tribromoethyl exhibited slightly lower yields and enantioselectivities (**3gg** and **3hh**). Unfortunately, diazoacetates with alkyl ester group, e.g. methyl, ethyl, were not applicable in this transformation under this catalytic conditions due to the weaker eletrophilicity of the forming gold-carbene. The absolute configuration of chiral 1,1-diaryl-*β*-alcohol (*S*)-**3m'**, which was obtained from the reduction of product (*S*)-**3m** , was determined by single-crystal X-ray analysis, and all of the other products **3** were tentatively assigned accordingly.

Scheme 2. Enantioselective C-H bond functionalization of arenes with 2, 2, 2-trifluoroethyl α-aryl-α-diazoesters.[a]



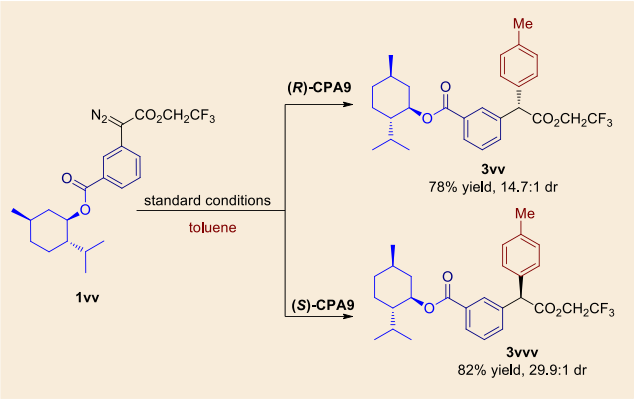
[a]Unless otherwise specified, all reactions were performed with $(EtO)_3PAuCl$ (5 mmol%), $AgSbF_6$ (5 mmol%), (*R*)-**CPA9** (10 mmol%), **1** (0.2 mmol), 5Å MS (100 mg) in 3 mL of toluene derivatives **2** at 25 °C. Isolated yields are provided. The ee was determined by HPLC. [b]The ee of the alcohol **3'** via C-H alkylation and reduction. [c](*S*)-**CPA9** was used instead of (*R*)-**CPA9**. [d]Arenes (5 equiv) was used in CH_2Cl_2 (3 mL). [e]$(EtO)_3PAuCl/AgSbF_6$ (7.5 mol%). [f]1.0 mmol scale.

Scheme 3. Various alkyl α-aryl-α-diazoesters. [a]



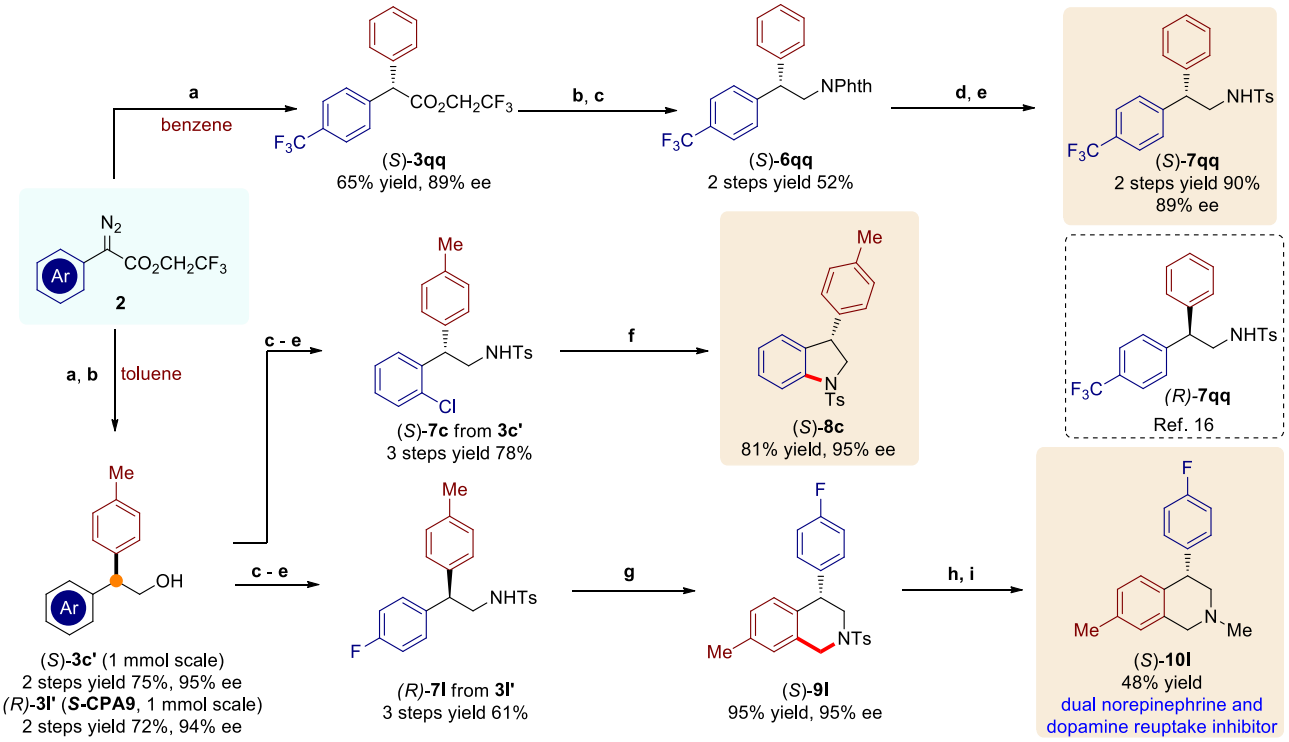
[a]Unless otherwise specified, all reactions were performed with Cy_3PAuCl (2.5 mmol%), AgOTf (2.5 mmol%), (*R*)-**CPA9** (5 mmol%), **4** (0.2 mmol), 5Å MS (100 mg) in 3 mL of toluene at 25 °C. Isolated yields are provided. The ee was determined by HPLC. [b]The ee of the alcohol **5'** via C-H alkylation and reduction.

Scheme 4. Control experiments. [a]



[a]Standand conditions: **1vv** (0.2 mmol), $(EtO)_3PAuCl$ (5 mmol%), $AgSbF_6$ (5 mmol%), **CPA9** (10 mmol%) and 5Å molecular sieves (MS) 100 mg in 3.0 mL of toluene at room temperature. The dr was determined by HPLC of the alcohols **3aa'** via C-H alkylation and reduction.

Scheme 5. Scale-up reaction and synthetic application.



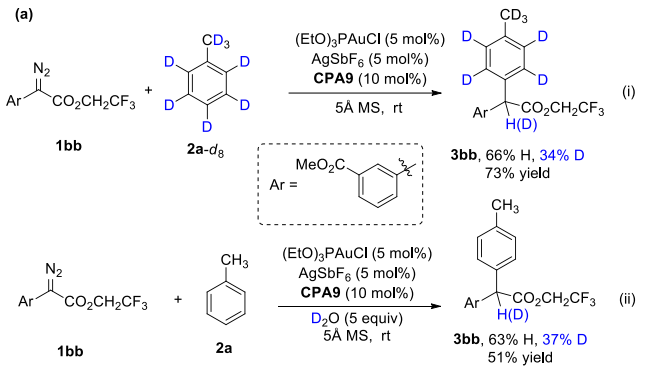
Reaction conditions: a) $(EtO)_3PAuCl/AgSbF_6$ (5 mol% or 7.5 mol%), **CPA9** (10 mol%), 5ÅMS, rt. b) $LiAlH_4$ (1.5 equiv), THF, 0 °C. c) Phthalimide (2.5 equiv), PPh_3 (2.5 equiv), DIAD (2.5 equiv), THF, 0 °C to rt. d) $N_2H_4{\cdot}H_2O$, MeOH, 80 °C. e) TsCl (2.0 equiv), Et_3N (2.0 equiv), DCM, rt. f) $Pd(OAc)_2$ (5 mol%), RuPhos (10 ml%), K_2CO_3 (1.4 equiv), 1,4-dioxane, MeOH, 110 °C. g) Paraformaldehyde (1.2 equiv), TFA, 80 °C. h) Mg (6.0 equiv), MeOH, sonication, 30 °C. i) HCHO (37% in H_2O), MeOH, 30 °C, $NaBH_4$.

We also investigated the C-H functionalization reactions of various toulene derivatives **1** with diazoacetate **2**. The reactions of mono-alkyl or mono-aryl substituted benzenes **1** with 2, 2, 2-trifluoroethyl diazoesters **2** proceeded smoothly, affording the corresponding *para*-selective C-H functionalization products **3ii-3pp** in moderate to good yield (48-69%) with excellent enantioselectivity (85-94% ee). Notably, no C(sp^3)-H insertion of secondary benzylic, tertinary benzylic, double benylic position was detected, indicating that this approach was highly chemoselective. Gratifyingly, the unsubstituted benzene was also applicable to this transformation and the corresponding product **3qq** was obtained in 65% yield with 89% ee. The substituents at *ortho*- and *meta*-position on the aryl ring of toluene had a negligible effect on the enantioselectivity (**3rr**−**3ss**). Arene with a fused ring, such as tetrahydronaphthalene, was also a suitable substrate in this transformation, affording the *para*-C-H functionalization product **3tt** in excellent

enantioselectivity (88% ee). Interestingly, (*S*)-**3uu** was obtained in 40% yield with 91% ee via the reaction of toluene with α-(4-ethylphenyl)-α-diazoester, while the enantioisomer (*R*)-**3uu** could be given in similar efficiency and enantioselectivity by the reaction of ethylbenzene with α-(4-methylphenyl)-α-diazoester under the same condition. This results showed this reaction could afford two enantioisomers with one chiral catalytic system.

Furthermore, we investigated the reaction of alkyl diazoesters with toluene. After screening the conditions, the best result was observed under 2.5 mol% $Cy_3PAuCl/AgOTf$, 5 mol% (*R*)-**CPA9**, and 5Å MS at room temperature (Scheme 3, for more details, see supporting information Table S2). The reactions of methyl diazoesters **4** equipped with various substituents on phenyl ring and toluene **2a** proceeded smoothly and afforded the desired *para*-C-H functionalization products **5a-5h** in 70-82% yields with excellent stereoselectivities (88-90% ee). The bulkier ester moiety did not affect the efficiency and enantioselectivity in this transformation (**5i**).

To investigate the match/mismatch effect of this reaction, (*R*)-**CPA9** and (*S*)-**CPA9** were separately employed as the catalyst for the reaction of toluene with (-)-menthol derived diazo compound **1vv.** As shown in Scheme 4, the C-H functionalization products **3vv** and **3vvv** with reversed diastereoselectivities were obtained, indicating that the enantioselectivity of this reaction was controlled by the catalyst rather than the chiral substrate.



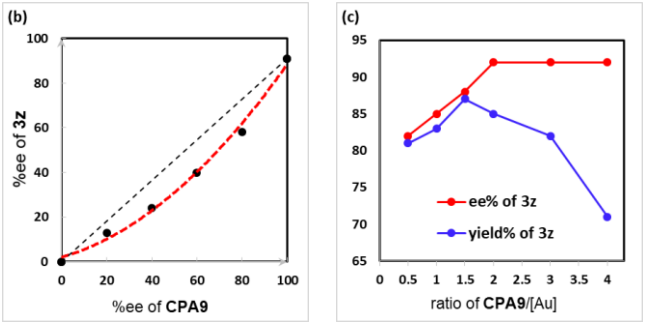
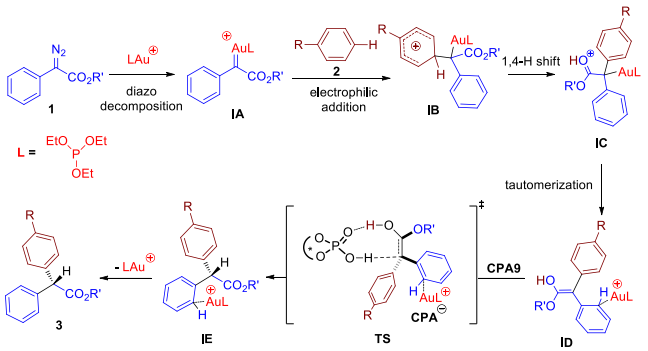


Figure 1. Mechanistic experiments. (a) Deuterium-labeling experiments. (b) Nonlinear effects with different %ee of **CPA9**. (c) Ees and yields of **3z** with different ratio of **CPA9**/[Au] ([Au] is keeping 5 mol%).

This enantioselective *para*-C-H bond functionalization of toluene derivatives was easy scale-up. Two 1 mmol scale sequential C-H alkylation/reduction reactions were carried out, furnishing the corresponding alcohol (S)-**3c'** in 75% yield with 95% ee and (R)-**3l'** in 72% yield with 94% ee. To exhibit the promising applications of this transformation in organic synthesis, further transformations of these chiral 1,1-diaryl esters **3** or alcohols **3'** were also performed (Scheme 5). The chiral *β,β*-diarylamine **6qq**, which is present in various biologically and pharmacologically active molecules for the treatment of disorders of the central nervous system,[14] was obtained from **3qq** via successive reduction and Mitsunobu reaction without any loss of enantioselectivity.[15] The protecting group of amine of **6qq** was easily switched to tosyl and **7qq** was obtained in 90% yield with 89% ee. **7qq** was further determined to have the (*S*)-configuration according to the specific rotation.[16] Furthermore, (*S*)-**7c** was smoothly cyclized under Pd-catalyzed intramolecular amination conditions,[17] delivering the chiral indoline (*S*)-**8c** in excellent yield, which was also often found in structurally related drugs and natural products.[18] Chiral tetrahydroisoquinoline (*S*)-**10l** , which was a dual norepinephrine and dopamine reuptake inhibitor[19], could be efficiently accessed from (*R*)-**3l'**, keeping the ee intact through Pictet−Spengler reaction, Ts-deprotection and methylation.[20]

To further gain insights into the mechanism of this enantioselective C-H bond functionalization, several experiments were conducted. As shown in Figure 1a, the deuterium-labeling experiments for the reaction of **1bb** and toluene were performed. When deuterated toluene **2a**-d_8 was employed, the *para*-selective C-H bond alkylation product **3bb** was obtained with 34% deuterium at the chiral *α*-position (eq i). The similar product **3bb** with 37% deuterium incorporation was obtained in the presence of a stoichiometric amount of D_2O (eq ii). These results indicated that the hydrogen atom on the chiral α-position did not come exclusively from the *para*-position of toluene, but derived partly from the water in the solvent via the stepwise process, which was consistent with the previous mechanistic studies. We observed a clear negative nonlinear effects[21] between the ee's of chiral catalyst (**CPA9**) and product **3z**, indicating that the catalytic species in the step of chiral induction might employ more than one chiral phosphoric acid (Figure 1b). We also tested the effects of the ratio of **CPA9** and the gold catalyst on the enantioselctivity. As shown in Figure 1c, the ee% of product **3z** was increased along with the increasing ratio of CPA9/[Au] until 2. If the ratio was greater than two, the excess chiral phosphoric acid could not improve the enantioselectivity. This result indicated the key catalytic species might contain two **CPA9** and one gold for the enantioselective control. The dropped yield might be attributed to the weak coordination between gold complex and the excess **CPA9**, which deactivated the activity of gold catalytic species.

Scheme 6. Proposed Mechanism.



On the basis of the above mentioned experiments and previous mechanistic studies of gold-carbene and chiral proton shuttle, we proposed the following reaction pathway (Scheme 6). The electrophilic gold-carbene intermediate **IA** generated from the decomposition of the diazoester **1** reacts with the phenyl ring of **2** to form the gold-contained cationic intermediate **IB**, which proceeds an intramolecular 1,4-H transfer to generate **IC**. Subsequently, the intermediate **IC** undergoes an isomerization to the enol **ID** through 1,3-migration of the $(EtO)_3PAu^+$ to the phenyl ring. The following 1,3-proton shift and deauration of **ID** produce the final product **3**. The chiral induction occurs in this step of the formation of **IE** from **ID**, in which the chiral phosphoric acid **CPA9** assists the 1,3-proton

shift via a proton shuttle model (**TS**). Another **CPA** molecule/anion is also employed in the transition state, which has a few effect on the enantioselectivity.

In conclusion, we have developed the first highly enantioselective *para*-C(sp^2)-H functionalization of non-active benzene derivatives with diazo compounds via cooperative catalysis of achiral gold complex and chiral phosphoric acid, leading to the synthetically useful 1,1-diaryl chiral motif. This reaction features mild conditions, readily available starting materials, enantioselective aromatic C-H functionalization, broad substrate scope as well as diverse synthetic applications of the products. The mechanistic studies show that the chiral induction might involve one gold complex and two CPAs. This protocol would broaden the applications of gold catalysts in asymmetric C-H bond functionalization and carbene transfer reactions.[22]

ASSOCIATED CONTENT

Supporting Information
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AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful for the generous financial support from the NSFC (Nos. 21971066, 22171088) and the STCSM (18JC1412300).

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(22) During preparation of our manuscript, we became aware that the Sun group had developed an asymmetric *para*-selective C-H functionalization of anisole derivatives. They reported one example of the reaction of toluene, but the ee is only 40%: Xu, G.; Huang, M.; Zhang, T.; Shao, Y.; Tang, S.; Cao, H.; Zhang, X.; Sun, J. Asymmetric Arylation of Diazoesters with Anisoles Enabled by Cooperative Gold and Phosphoric Acid Catalysis. https://doi.org/10.1021/acs.orglett.2c00709.

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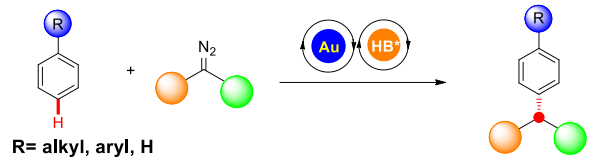

R= alkyl, aryl, H

√ unactivited arenes √ relay gold/CPA catalysis √ mild conditions
√ 60 examples √ chemo- and site-selectivity √ up to 97% ee