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Hybrid Palladium Catalyst Assembled from Chiral Phosphoric Acid and Thioamide for Enantioselective β-C(sp^3)–H Arylation

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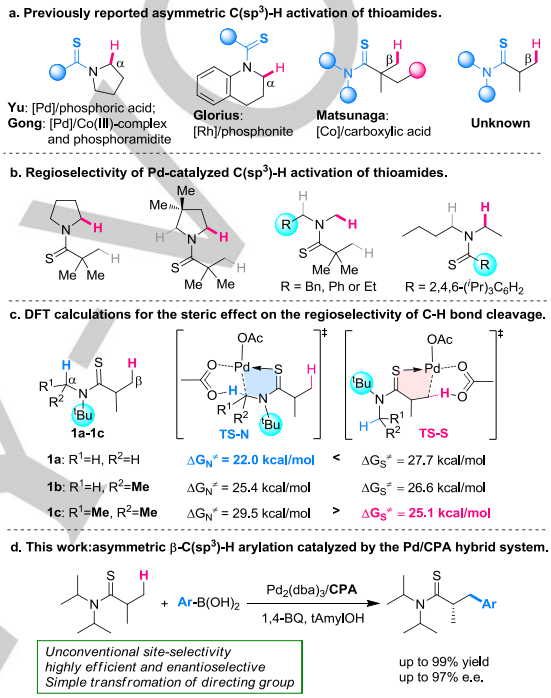
Abstract: A hybrid palladium catalyst assembled from chiral phosphoric acid (CPA) and thioamide shows a high capacity for enabling a highly efficient and enantioselective β-C(sp^3)–H functionalization of thioamides (up to 99% yield, 97% e.e.). A kinetic resolution of unsymmetrical thioamides via intermolecular C(sp^3)–H arylation can be achieved in high-levels of s-factor. Mechanistic investigations have revealed that stereocontrol is achieved by embedding the substrate in a robust chiral cavity defined by the bulky CPA with a neutral thioamide ligand.

Aliphatic C(sp^3)–H functionalization remains difficult due to high C–H bond energy (typically 90−100 kcal/mol), low acidity (estimated pKa = 45−60), and an unreactive molecular orbital profile.[1] It is a longstanding goal of chemists to achieve stereochemically controlled C(sp^3)–H functionalization. During the past decades, dozens of reactions have been developed by using the strategy of incorporating a functional group into substrates in either site- or stereoselective auxiliary-oriented bond cleavage enabled by transition metal catalysis.[2] The ability of sulfur atom to coordinate with transition metals has led to the use of sulfur-containing functional groups as directing groups in transition metal-catalyzed site-selective C–H functionalization.[3-4] As shown in Scheme 1a, Yu and coworkers reported an enantioselective amine α-C(sp^3)–H arylation of thioamides afforded by combining a chiral phosphoric acid (CPA) with a palladium catalyst.[4a] We found that a hybrid palladium catalyst containing a chiral Co(III)-complex anion and a chiral phosphoramidite ligand is highly efficient for a similar reaction, delivering up to 99% yields and 99% e.e.[4b] Using a chiral phosphoramidite ligand, Glorius and coworkers established an asymmetric Rh(I)-catalyzed amine α-arylation of 1,2,3,4-tetrahydroquinolines bearing a tert-butyl thioamide directing group.[4c] The Cp*Co(III)/chiral carboxylic acid catalyst system, together with the use of dioxazolone as the amidation reagent, switched the regioselection of C–H activation from the carbon adjacent to the nitrogen to the acyl side of the thioamide, allowing for the generation of chiral β-amidation products.[4d]



Scheme 1. The regioselectivity of asymmetric C(sp^3)−H functionalization reactions of thioamides.

Chiral β-aryl isobutyramides and their derivatives (γ-aryl isobutanol, β-aryl esters, etc.), which can be easily accessed from thioamides,[5] have frequently been encountered in bioactive compounds and pharmaceuticals.[6] Enantioselective desymmetrization of butyric thioamides would be a powerful method for the synthesis of these compounds, but has not yet been achieved by available strategies (Scheme 1a).[4] The formidable challenge is obviously arisen from the difficulty in the differentiation between a small α-methyl group and an even smaller α-hydrogen atom.[2f,7] We noticed that in previous studies on the Pd(II)-catalyzed N-α-C(sp^3)–H activation reactions, the C–H bond cleavage exclusively occurs at the most accessible site of the thioamide (Scheme. 1b).[4a,4b,8] These precedent observations imply that the site-selectivity in Pd(II)-catalyzed C(sp^3)–H activation might be modulated and switched by tuning the steric bulkiness of N-substituent of the thioamide. We initially carried out density functional theory (DFT) calculations to verify this speculation and found that an increase in steric hindrance at the α-position of the amide nitrogen (**1a**-**1c**) led to considerably higher activation barrier ($\Delta G_N^{\neq}$) of C–H activation at the carbon α to the nitrogen, via **TS-N**, and a comparable C–H activation barrier at β-

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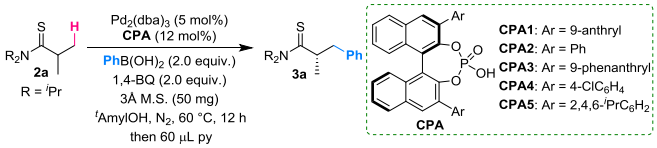
position of the thioamide, via **TS-S** ($\Delta G_S^{\neq}$). **TS-S** gets more favorable than **TS-N** as the N-substituents become bulkier (Scheme 1c, for details see Section 2.2 in SI). These theoretical predictions prompted us to posit that the incorporation of a bulky N, N-diisopropyl amine group into isobutyric thioamides might enable the Pd(II)-catalyzed β-C(sp^3)–H functionalization to achieve enantioselective desymmetrization (Scheme 1d).

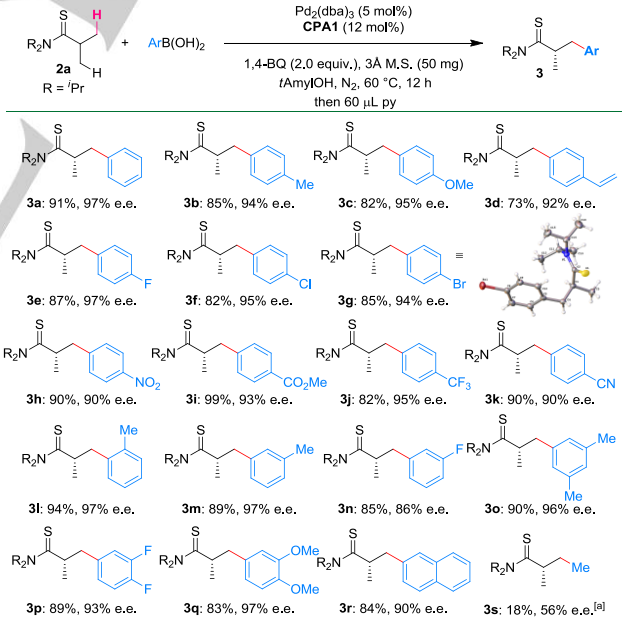
Table 1. Optimization of the desymmetrization of isobutyric thioamide **2a**.[a]



entry	conditions	yield (%)[b]	e.e. (%)[c]
1	**CPA1**	90 (91[d])	96
2	**CPA2**	64	13
3	**CPA3**	84	60
4	**CPA4**	60	23
5	**CPA5**	trace	-
6	without **CPA**	N.R.	-
7	without 3Å M.S.	82(83[d])	97
8	with 2.0 equiv. $KHCO_3$	51	86
9	2.0 equiv. 2,5-DMBQ	49	92
10	2.0 equiv. 2,6-DMBQ	60	91
11	2.0 equiv. thymoquinone	36	90
12	2.0 equiv. 2,5-DPBQ	49	92
13	2.0 equiv. 2,5-DTBQ	N.R.	-

[a] Standard conditions: thioamide **2a** (0.1 mmol, 1.0 equiv.), $PhB(OH)_2$ (0.2 mmol, 2.0 equiv.), $Pd_2(dba)_3$ (0.005 mmol, 5 mol%), **CPA** (0.012 mmol, 12 mol%) 1,4-BQ (0.2 mmol, 2.0 equiv.), ^{t}AmylOH (1.0 mL), 3 Å M.S. (50 mg), 60 °C, 12 h, then quenched with 60 μL pyridine. [b] Determined by ^{1}H NMR analysis of the crude products using trimethyl 1,3,5-benzenetricarboxylate as the internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Yield of the isolated product. 2,5-DMBQ = 2,5-dimethyl-1,4-benzoquinone. 2,6-DMBQ = 2,6-dimethyl-1,4-benzoquinone. 2,5-DPBQ = 2,5-diphenyl-1,4-benzoquinone. 2,5-DTBQ = 2,5-di-*tert*-butyl-1,4-benzoquinone.

The validation of the theoretical prediction commenced with the palladium-catalyzed asymmetric β-C(sp^3)–H arylation reaction between N, N-diisopropyl isobutyric thioamide (**2a**) and phenylboronic acid in the presence of catalytic amounts of sodium salts of anionic chiral Co^{III} complexes in combination with chiral phosphoramidite ligands, which was convinced to be highly efficient catalyst system for the enantioselective amine α-arylation of thioamides.[4b] However, only trace amounts of the desired product (**3a**) were detected (for details see Table S1 in SI). Next, we evaluated the chiral phosphoric acids (CPA), which have been proven to function as anionic ligands capable of inducing significant stereochemical outcomes in palladium catalyzed C–H functionalizations.[4a,9-10] The flexibly tunable steric environment by varying the 3- and 3'-substituents allows the CPA to discriminate the subtle difference between the methyl and a hydrogen atom and thus, various Akiyama-Terada phosphoric acids (CPA) were examined.[11] Both the catalytic activity and stereoselectivity of the palladium catalysts appeared to be highly sensitive to the 3- and 3'-substituents of CPA (Table 1, entries 1-5). Among the CPAs evaluated, **CPA1**, bearing 9-anthryl substituents at the 3- and 3'-positions, gave an excellent yield and stereochemical outcome (91% yield and 96% e.e., Table 1, entry 1), but the others resulted in significantly attenuated enantioselectivity (entries 2-4). Only trace amounts of the product (**3a**) were observed in the presence of **CPA5** with 2,4,6-triisopropylphenyl substituents (Table 1, entry 5) and no product was detected in the absence of the CPA, suggesting that the CPA participates in the cleavage of the C(sp^3)–H bond, presumably via the well-known concerted deprotonation-metalation (CMD) mechanism (Table 1, entry 6).[12] The absence of 3 Å molecular sieves and the addition of $KHCO_3$ as base both led to diminished yields (Table 1, entries 7 and 8 vs entry 1). Interestingly, substituents in the benzoquinone oxidants led to slightly lower enantioselectivity, but a significantly attenuated yield (Table 1, entries 9-13). These results suggest that the benzoquinone and the corresponding hydroquinone anion may not participate in the enantioselectivity-determining step. In our previous study, we demonstrated that the neutral phosphoramidite ligand can accelerate the C(sp^3)–H bond cleavage in the palladium-catalyzed α-arylation reactions of thioamides.[4b] We speculated accordingly, that an unidentified neutral ligand might exist and assist the Pd(II) catalyst to accelerate the C–H bond cleavage.



Scheme 2. Scope of coupling partners with isobutyric thioamides (**2a**). Standard conditions: thioamide **2a** (0.1 mmol, 1.0 equiv.), $ArB(OH)_2$ (0.2 mmol, 2.0 equiv.), $Pd_2(dba)_3$ (0.005 mmol, 5 mol%), **CPA1** (0.012 mmol, 12 mol%), 1,4-BQ (0.2 mmol, 2.0 equiv.), ^{t}AmylOH (1.0 mL), 3 Å M.S. (50 mg), 60 °C, 12 h, then quenched with 60 μL pyridine. The values beneath each structure indicate the yields of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a] Compound **3s** was obtained from the reaction with $MeB(OH)_2$ (1.0 mmol, 10.0 equiv.) at 100 °C, 24 h.

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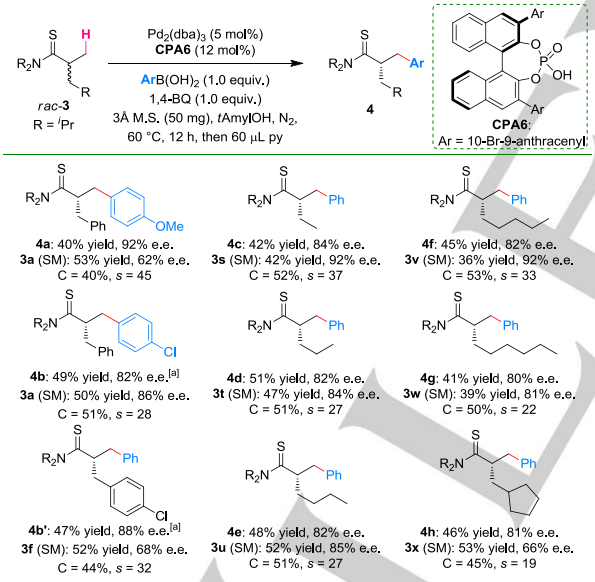
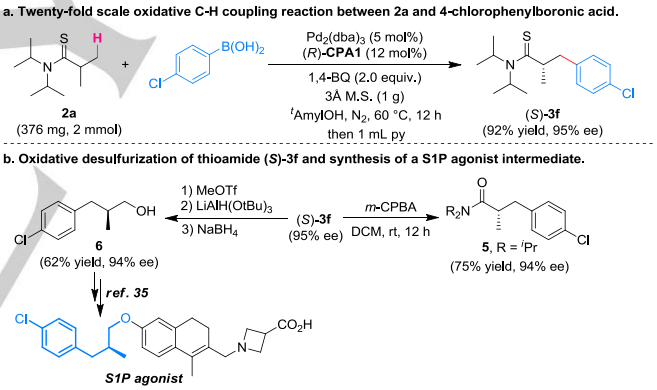
With the optimized reaction conditions in hand, the scope of the reaction was investigated with various coupling partners. Both electronically rich and deficient aryl boronic acids smoothly underwent the desymmetric C–H arylation and gave the coupling products in high yields and excellent enantioselectivities ranging from 86% to 97% e.e. (Scheme 2). A variety of functionalities, such as vinyl (**3d**), nitro (**3h**), ester (**3i**), trifluoromethyl (**3j**) and carbonitrile (**3k**) were compatible with the reaction conditions. The electronic feature of the substituent on the benzene ring of the aryl boronic acids did not exert considerable influence on the reaction performance as shown in the cases involving *para*-substituted phenyl boronic acids, all of which provided high yields and excellent levels of enantioselectivity (**3a-3k**). In addition, both *meta*- and *ortho*-methylphenyl boronic acids underwent a clean reaction, delivering the arylation products in high yields and with greater enantioselectivities than the *para*-methylphenyl boronic acid (**3l** and **3m** vs **3b**). However, a much diminished enantioselectivity was observed for *meta*-fluorophenyl boronic acid in comparison with the *para*-substituted isomer (**3n** vs **3e**). Disubstituted aryl and 2-naphthyl boronic acids were excellent substrates, leading to chiral coupling products with high yields and enantioselectivities (**3o-3r**), but the oxidative coupling reaction with a methyl boronic acid gave **3s** in only 18% yield and a relatively lower enantioselectivity. The absolute configuration of **3g** was assigned by single-crystal X-ray crystallography (See SI for details).



Scheme 3. Kinetic resolution of unsymmetrical thioamides. Standard conditions: thioamide **3** (0.1 mmol, 1.0 equiv.), $ArB(OH)_2$ (0.1 mmol, 1.0 equiv.), $Pd_2(dba)_3$ (0.005 mmol, 5 mol%), **CPA6** (0.012 mmol, 12 mol%), 1,4-BQ (0.1 mmol, 1.0 equiv.), tAmylOH (1.0 mL), 3 Å M.S. (50 mg), 60 °C, 12 h, then quenched by 60 μL pyridine. The values beneath each structure indicate the yields of isolated product. [a] 2.0 equiv. $ArB(OH)_2$ and 2.0 equiv. BQ were used. Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. $C=e.e._S/(e.e._S+e.e._R)$, $s= \ln[(1-C)(1-e.e._S)]/\ln[(1-C)(1+e.e._S)]$.

With the success in the enantioselective desymmetrization of isobutyric thioamides, we investigated the kinetic resolution of unsymmetrical thioamides.[13] Compared with the desymmetrization reaction, the kinetic resolution requires the recognition of different enantiomers in a racemic mixture.[2f] Although kinetic resolution has been established in $C(sp^2)$–H activation,[14] only a few examples can be found in $C(sp^3)$–H substrates,[9f,15] particularly even fewer in intermolecular $C(sp^3)$–H activation.[16] However, the use of identical conditions in the kinetic resolution of N,N-diisopropyl-2-methyl-3-phenyl-propanethioamide (**3a**) failed to give satisfactory results (for details see Table S2 in SI). Re-evaluation of CPAs identified **CPA6** to be a more stereoselective co-catalyst, enabling the reaction giving the desired diarylation products with high levels of enantioselectivity (**4a**, 92% e.e. and **4b**, 82% e.e.), accompanied with the recovered **3a** in 62% e.e. and 86% e.e. respectively (Scheme 3). The kinetic resolution of a structurally diverse range of thioamides proceeded well, giving the corresponding products with high enantioselectivity. The oxidative coupling reaction between *rac*-**3f** and phenylboronic acid led to the diarylation product **4b'**, the enantiomer of **4b**, in 88% e.e. More significantly, primary alkyl-substituted substrates could be resolved with high s-factor values (**4c-4g**, for details see Table S3 in SI). **CPA6** can even differentiate an ethyl group from the methyl group as shown in the thioamide *rac*-**3s** with high enantioselectivites of both the starting material and the corresponding product (s-factor = 37). The cyclopentyl-substituted thioamide (**3x**) also reacted smoothly, giving high enantioselectivity for the product and 66% e.e. for the recovered **3x**.



Scheme 4. Scale-up reaction and synthetic applications.

To elucidate the practicality of this transformation, a twenty-fold scale oxidative C–H coupling reaction between **2a** and 4-chlorophenylboronic acid was successfully carried out to afford (*S*)-**3f** in 92% yield and with 95% e.e. (Scheme 4a). Diversification of the β-arylation product to incorporate other important functional groups was achieved through simple chemical modifications. The product (*S*)-**3f** (95% ee) was readily converted into an amide (**5**) with 94% e.e. by treatment with *m*-CPBA.[17] Methylation and subsequent reduction of (*S*)-**3f** provided an aldehyde, which was then treated with $NaBH_4$ to furnish the chiral alcohol **6** with 94% e.e.[5] The chiral alcohol **6** can be easily converted into a S1P agonist using known methods (Scheme 4b).[6d]

To understand the successful role of Pd in combination with CPA in the reaction, both mass spectrometry analysis and DFT calculations were conducted. We designed a stoichiometric stepwise reaction and monitored the reaction process by

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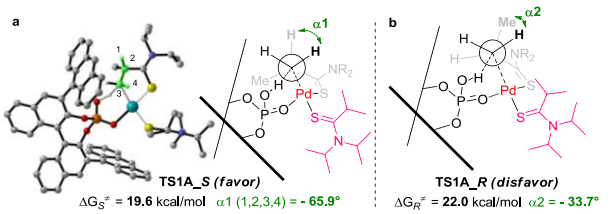
electrospray ionization mass spectrometry (ESI-MS, for details see Section 2.1 in SI).[18] The experiments suggest that CPA is able to facilitate the C–H activation to generate the palladation intermediates. In the C–H activation step, two thioamides (**2a**) coordinate to the palladium, one undergoing β-C–H activation and the other acting as a neutral ligand at the beginning of reaction. Accompanying with the reaction undergoing, the product **3a** grows and gradually replaces the substrate **2a** to be the neutral ligand (Figure S43).



Scheme 5. Stereocontrol model rationalizing the origin of the enantioselectivity.

Based on the intermediates identified by HRMS, we calculated diastereomers of the transition states to elucidate the origin of the enantioselectivity (Scheme 5 and Section 2.2 in SI). These studies reveal that **TS1A_*S***, which yields the (*S*)-product, is 2.4 kcal/mol lower in energy than **TS1A_*R***, which yields the (*R*)-product. The origin of the preference can be found by measuring the corresponding dihedral angle, α1 (highlighted in green in Scheme 5). A larger angle (α1 = - 65.9°) found in **TS1A_*S*** reveals the structure to engage in a staggered transition state (Scheme 5a). In contrast, the corresponding dihedral angle of **TS1A_*R***, α2 is - 33.7°, which leads to an unfavorable structure with stronger torsional strain (Scheme 5b). We also considered the transition state, which is assisted by a molecule of product (**3a**) instead of substrate (**2a**) as the neutral ligand (Figure S48 in SI). The similar results imply that the chirality of thioamide **3a** does not affect much on the selectivity. Further examination of structures of these transition states shows that the substrate adjusts its structure to fit the shape of the catalyst, and consequently, the excellent stereocontrol is achieved here presumably by embedding the substrate in a chiral robust cavity defined by the bulky CPA and the neutral ligand (**2a** or **3a**). In this scenario, it is not surprising that the e.e. value appears to be sensitive to the nature of the CPA (Figure S49 in SI).

In summary, a Pd-catalyzed enantioselective β-C(sp^3)–H functionalization of thioamides has been developed using a chiral phosphoric acid as a chiral auxiliary. The employment of a bulky diisopropylamine auxiliary allows switching the regioselectivity from the carbon adjacent to the nitrogen atom to the acyl side. The MS studies and DFT analysis elucidate the role of the bulky CPA and the assistance of thioamide ligand, which could define a robust chiral cavity to achieve a high level of stereocontrol.

Acknowledgements

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Keywords: palladium catalysis • chiral phosphoric acid • C(sp^3)–H arylation• thioamides

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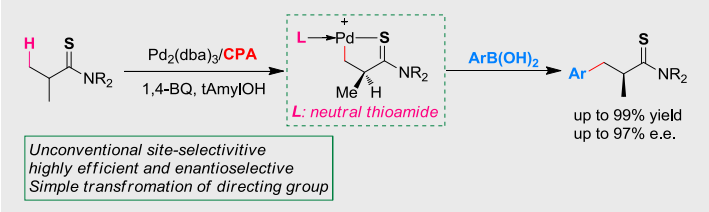

A Pd-catalyzed enantioselective β-C(sp^3)–H functionalization of thioamides has been developed using a chiral phosphoric acid as a chiral auxiliary. ESI-MS studies and DFT analysis elucidate the role of the bulky CPA and the assistance of thioamide ligand, which could define a robust chiral cavity to achieve a high level of stereocontrol.

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Hybrid Palladium Catalyst Assembled from Chiral Phosphoric Acid and Thioamide for Enantioselective β-C(sp^3)–H Arylation