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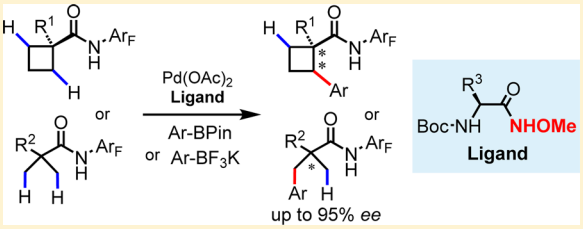
Palladium(II)-Catalyzed Enantioselective C(sp^3)−H Activation Using a Chiral Hydroxamic Acid Ligand

Kai-Jiong Xiao, David W. Lin, Motofumi Miura, Ru-Yi Zhu, Wei Gong, Masayuki Wasa, and Jin-Quan Yu*

Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

ABSTRACT: An enantioselective method for Pd(II)-catalyzed cross-coupling of methylene β-C(sp^3)−H bonds in cyclobutanecarboxylic acid derivatives with arylboron reagents is described. High yields and enantioselectivities were achieved through the development of chiral mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligands, which form a chiral complex with the Pd(II) center. This reaction provides an alternative approach to the enantioselective synthesis of cyclobutanecarboxylates containing α-chiral quaternary stereocenters. This new class of chiral catalysts also show promises for enantioselective β-C(sp^3)−H activation of acyclic amides.



1. INTRODUCTION

Enantioselective functionalization of prochiral unactivated C−H bonds remains a significant challenge. Although carbenoid and nitrenoid insertion[1,2] as well as metal insertion[3] processes have been developed to enantioselectively functionalize prochiral C−H bonds, the scope of substrates and transformations falls short of the standard demonstrated in other areas of asymmetric catalysis. In particular, both intra-[4,5] and intermolecular[6−13] enantioselective C−H activation reactions are still limited to a few classes of substrates. Alternative approaches of C−H activation followed by asymmetric carbometalation or hydrometalation to construct chiral centers have also met with difficulties.[14]

Building on the stereomodel of palladium-catalyzed diastereoselective C−H oxygenation,[15] our laboratory has further developed diverse enantioselective C(sp^2)−H functionalization reactions that include cross-coupling with organoboron reagents,[7] olefination,[8] oxidation,[9] and iodination[10] using chiral mono-N-protected amino acid (MPAA) ligands. The ability of MPAA ligands to accelerate or enable[16] palladium(II)-catalyzed C−H functionalization reactions is crucial for achieving high enantioselectivities. This approach has also been applied to the enantioselective functionalization of prochiral C(sp^3)−H bonds. Using a MPAA ligand, the first intermolecular example was reported for the alkylation of methyl C−H bonds in 38% yield and 37% ee.[7a] This was later followed by the cross-coupling of methylene C−H bonds in cyclopropanecarboxylic acid derivatives with arylboron reagents.[11] Keys to the development of this method were the use of an electron-deficient amide as a weakly coordinating directing group[17] on the cyclopropane substrate and development of a novel chiral MPAA ligand, featuring a bulky and electron-deficient carbamate which was essential for achieving high enantioselectivity. However, this method was limited to the functionalization of relatively acidic[18] cyclopropyl C−H bonds, and more broadly applicable methods for enantioselective functionalization of less reactive C(sp^3)−H bonds have remained elusive. To address this issue, the design and synthesis of novel chiral ligands are currently needed.

Enantiopure cyclobutanes are important structural features found in many bioactive natural products (Figure 1).[19] Many

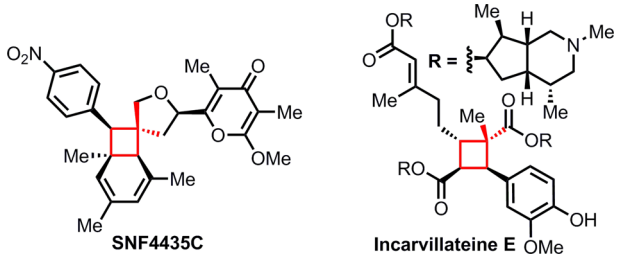


Figure 1. Natural products containing cyclobutanes with chiral quaternary stereocenters.

methods have been developed for the asymmetric synthesis of chiral cyclobutanes.[20] However, the enantioselective construction of cyclobutanes with chiral quaternary stereocenters[21] is still limited.[20a,b] Although elegant methods to construct quaternary stereocenters on cyclobutyl rings have been recently reported by Toste[20d] and Stoltz,[20f] but these methods are applicable to the synthesis of cyclobutanones only. We envisioned that a Pd(II)-catalyzed enantioselective C−H functionalization of cyclobutanecarboxylic acid derivatives could offer a new and complementary method.[22] Herein we report the first example of enantioselective coupling of cyclobutanes with arylboron reagents using a chiral mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligand

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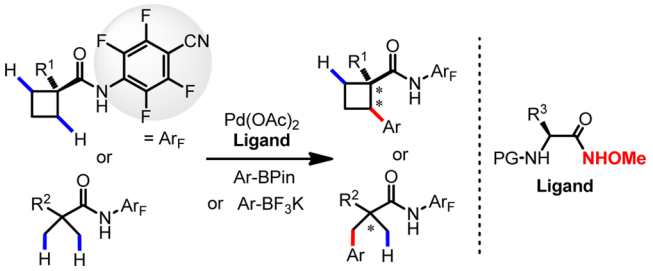
(Scheme 1), providing a new route for the synthesis of cyclobutanes with chiral quaternary stereocenters. The

Scheme 1. Enantioselective C(sp^3)−H Activation via Desymmetrization of Prochiral C−H Bonds

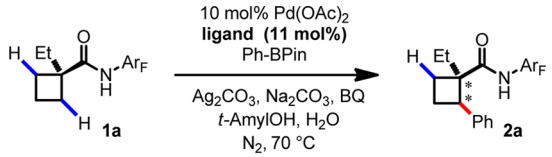


feasibility of using this ligand to achieve enantioselective C(sp^3)−H activation of prochiral gem-dimethyl groups is also demonstrated.

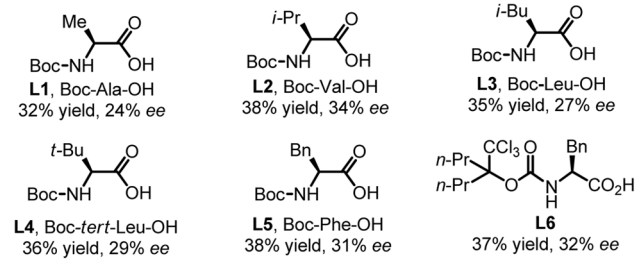
2. RESULTS AND DISCUSSION

We began our studies by investigating the reactivity of 1-ethyl-1-cyclobutanecarboxylic acid derivative **1a** with an electron-deficient amide directing group. Initially we focused on the C−H cross-coupling reactions with phenylboronic acid pinacol ester using mono-*N*-protected amino acid (MPAA) ligands (Table 1). Modest yields and enantioselectivities of the C−H coupling reactions were obtained using commercially available MPAA ligands such as *N*-Boc-leucine (**L1**−**5**). Surprisingly, chiral MPAA ligand **L6**, which gave enantioselectivities in excess of 90% ee with a broad range of cyclopropanecarboxylic

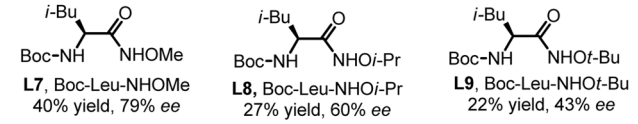
Table 1. Screening of Ligands[a,b]



Mono-protected amino acids



***O*-Alkylhydroxamic acid ligands**



[a]Reaction conditions: substrate **1a** (0.1 mmol), Ph−BPin (2.0 equiv), $Pd(OAc)_2$ (10 mol %), ligand (11 mol %), Ag_2CO_3 (1.5 equiv), Na_2CO_3 (2.0 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), *t*-AmylOH (0.5 mL), N_2, 70 °C, 24 h. [b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase.

acid substrates,[11] gave a significantly lower yield (37%) and enantioselectivity (32% ee) with the cyclobutanecarboxylic acid substrate **1a**.

Reasoning that modifying the electronic property of the ligand might enhance the stereoselection, we sought to replace the anionic carboxylate group of the ligand with a more Lewis basic counterpart. Inspired by our previous finding that the *O*-methylhydroxamic acid group is highly efficient in facilitating Pd(II)−catalyzed C−H bond activation,[23,24] we converted *N*-Boc-leucine to the corresponding *O*-methylhydroxamic acid **L7**. The stronger coordination between this ligand and the Pd(II) center could also further rigidify the transition state and improve the stereoselection. We were pleased to observe that **L7** in fact provided a significant boost in enantioselectivity (79% ee). This motivated us to screen other *O*-alkylhydroxamic acids; however, increasing the steric bulk of hydroxamate protecting group (**L8**−**9**) led to a marked decrease in enantioselectivity.

To further explore the effect of ligand structure on yield and enantioselectivity, a wide range of MPAHA ligands was prepared (Table 2). A number of different amine protecting groups were screened (**L10**−**14**); however, only reductions in enantioselectivities were observed. Ligands containing different α-substituents were also prepared and screened. Ligands featuring aromatic side chains appeared to give the superior enantioselectivities (**L18** and **L19**), so a series of different aromatic side chains were screened (**L20**−**25**, see Supporting Information (SI) for ligand screening data). Remarkably, the (2,6-diphenyl)phenylalanine *O*-methylhydroxamic acid ligand **L22** gave a significant boost to both yield and ee. Since this type of ligands can be readily synthesized by our *ortho*-C-H coupling reaction directed by the sulfonamide group (see SI), we prepared various 2,6-disubstituted phenylalanine-derived ligands (**L22**−**25**) for optimization. Of the ligands prepared, the [2,6-di(4-fluorophenyl)]phenylalanine *O*-methylhydroxamic acid ligand **L25** gave the best yield and enantioselectivity of 67% and 88%, respectively. The use of the parent amino acid ligand bearing the same backbone as **L25** gave significantly lower yield and ee (38% yield, 45% ee), demonstrating the distinct property of hydroxamic acid ligands for inert C(sp^3)−H activation.

Encouraged by the improved yields and ee's using this new hydroxamic acid ligand, we began to systematically optimize the reaction conditions. Among the bases screened, sodium carbonate gave the best yield and enantioselectivity (see Table S1). Examination of reagent stoichiometries led to the observation that 2.5 equiv of silver(I) carbonate gave the optimum yield and enantioselectivity (Table S2). Solvent effects and palladium source were also examined to reveal that 2-methyl-2-butanol (*t*-AmylOH) and palladium(II) acetate were the optimal solvent and palladium source (Tables S3 and S4). Finally, a screen of amide directing groups found that the 4-cyano-2,3,5,6-tetrafluoroaryl group (Ar_F) gave the best ee (Table S5). Altogether, these optimized reaction conditions resulted in cross-coupling yield of 75% and enantioselectivity of 92% ee.

With the optimized reaction conditions in hand, we explored the substrate scope of this method (Table 3). The reaction was found to work well with a variety of arylboronic acid pinacol esters (**2a**−**m**). Trifluoromethyl- or fluoro- phenylboronic acid pinacol esters are amenable to the reaction conditions (**2e**−**g**). Functional groups such as aryl chlorides and bromides (**2h**, **2i**), esters (**2j**), ethers (**2k**), and anilides (**2l**) are well tolerated.

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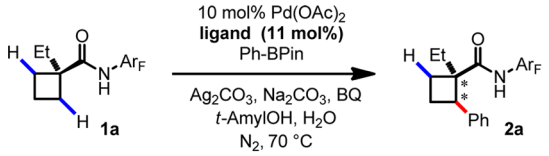
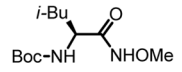
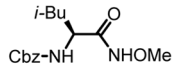
Table 2. Development of MPAHA Ligands[a,b]



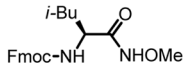
Screening of *N*-Protecting groups



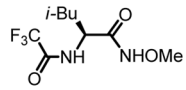
L7, Boc-Leu-NHOMe
40% yield, 79% *ee*



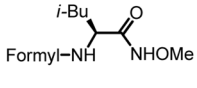
L10, Cbz-Leu-NHOMe
25% yield, 78% *ee*



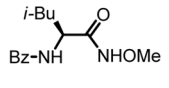
L11, Fmoc-Leu-NHOMe
39% yield, 79% *ee*



L12, CF_3CONH-Leu-NHOMe
41% yield, 69% *ee*

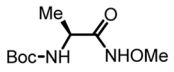


L13, Formyl-Leu-NHOMe
38% yield, 40% *ee*

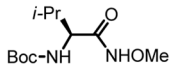


L14, Bz-Leu-NHOMe
19% yield, 0% *ee*

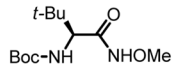
Boc-protected NHOMe ligands



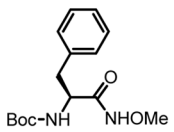
L15, Boc-Ala-NHOMe
33% yield, 74% *ee*



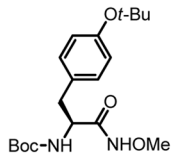
L16, Boc-Val-NHOMe
43% yield, 80% *ee*



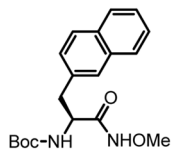
L17, Boc-*tert*-Leu-NHOMe
37% yield, 68% *ee*



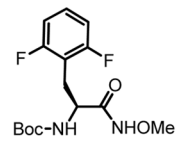
L18, Boc-Phe-NHOMe
45% yield, 82% *ee*



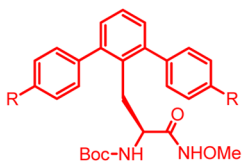
L19, Boc-Tyr(*t*-Bu)-NHOMe
40% yield, 80% *ee*



L20, Boc-2-Nal-NHOMe
38% yield, 80% *ee*



L21, 53% yield, 83% *ee*

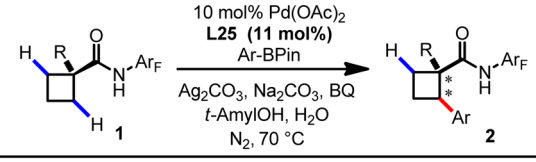


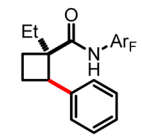
L22-L25

L22, R = H
65% yield, 87% *ee*
L23, R = Ph
59% yield, 84% *ee*
L24, R = OMe
43% yield, 81% *ee*
L25, R = F
67% yield, 88% *ee*

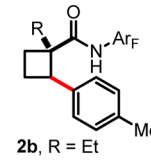
[a]Reaction conditions as described in Table 1. [b]The yield and ee were determined as described in Table 1.

Table 3. Substrate Scope[a,b]

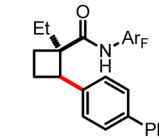




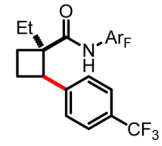
2a
75% yield, 92% *ee*



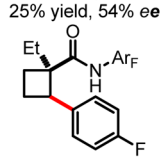
2b, R = Et
70% yield, 92% *ee*
2c, R = H (120 °C)
25% yield, 54% *ee*



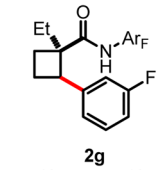
2d
71% yield, 91% *ee*



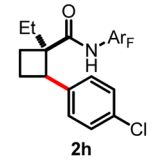
2e
59% yield, 89% *ee*



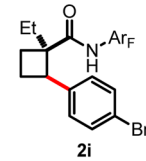
2f
62% yield, 90% *ee*



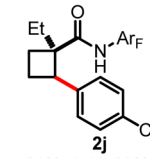
2g
53% yield, 87% *ee*



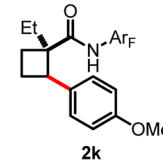
2h
55% yield, 89% *ee*



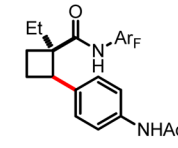
2i
49% yield, 86% *ee*



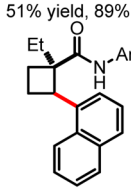
2j
51% yield, 89% *ee*



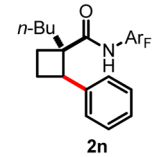
2k
66% yield, 90% *ee*



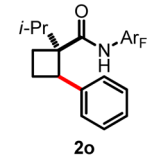
2l
57% yield, 93% *ee*



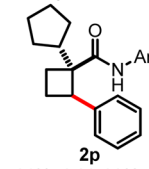
2m
56% yield, 90% *ee*



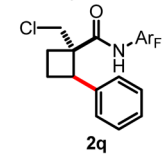
2n
72% yield, 88% *ee*



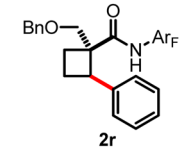
2o
77% yield, 95% *ee*



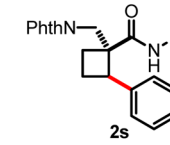
2p
61% yield, 92% *ee*



2q
65% yield, 84% *ee*



2r
76% yield, 95% *ee*



2s
68% yield, 81% *ee*

[a]Reaction conditions: substrate **1** (0.1 mmol), Ar−BPin (2.0 equiv), $Pd(OAc)_2$ (10 mol %), **L25** (11 mol %), Ag_2CO_3 (2.5 equiv), Na_2CO_3 (2.0 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), *t*-AmylOH (0.5 mL), N_2, 70 °C, 24 h. [b]Isolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase.

Although the presence of an α-hydrogen to amide carbonyl group decreased the yield and ee (**2c**), the reaction worked well with various 1-substituted 1-cyclobutanecarboxylic acid derivatives (**2n**−**s**). The enantioselective cross-coupling of *n*-butyl substituted substrate gave 72% yield and 88% ee (**2n**). Sterically hindered 1-(isopropyl)-1-cyclobutane (**2o**) and 1-(cyclopentyl)-1-cyclobutane (**2p**) substrates are functionalized in high yield and ee, demonstrating that this reaction can be used to prepare highly sterically congested quaternary all-carbon stereocenters on cyclobutanes. Heteroatom substituents such as halogens (**2q**), oxygen (**2r**), and nitrogen (**2s**) are tolerated on the exocyclic alkyl side chain of the cyclobutane substrate. These substituents are amenable for further synthetic elaborations thereby broadening the diversity of the products. Although the current scope of the cyclobutane substrates for C−H activation is still limited to relatively simple scaffold, asymmetric syntheses of these products via other methods would require the use of a wide range of substrates to incorporate different aryl groups.

Treatment of **2o** with conc. HCl resulted in removal of the auxiliary to give the carboxylic acid product **3** in 94% yield (Scheme 2). The absolute configuration of **2r** was also determined to be (1*R*,2*R*) by X-ray crystallographic analysis, providing information for understanding the origin of enantioselectivity (Figure 2).

A preliminary examination of acyclic $C(sp^3)$−H activation substrates was also conducted using the geminal dimethyl substrate **4a** (Table 4). We found through a preliminary ligand screening (see SI) that, using the α-amino-*O*-methylhydroxamic acid ligand **L7** and the newly optimized reaction conditions, cross-coupling of **4a** proceeded with an aryltri-

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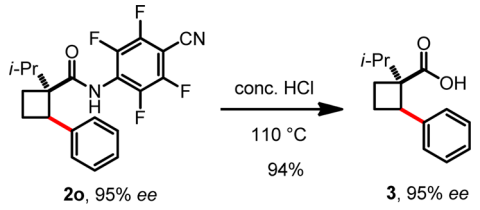
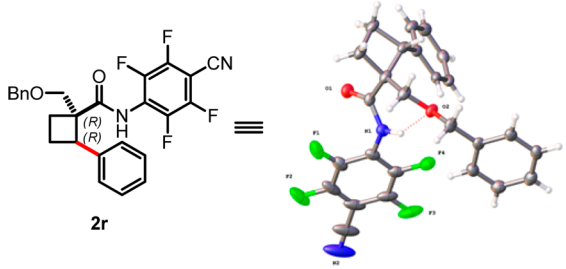
Scheme 2. Auxiliary Cleavage



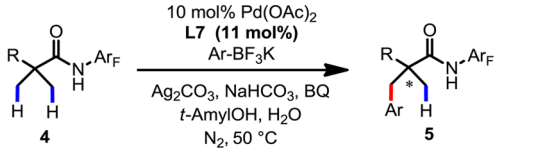
2o, 95% *ee* **3**, 95% *ee*

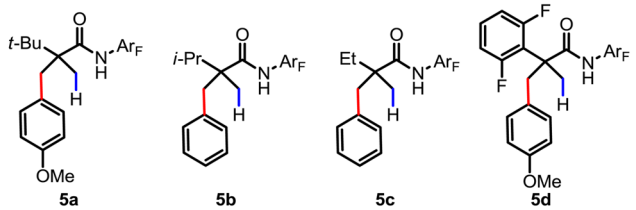


2r

Figure 2. Absolute Configuration of **2r**.

Table 4. Desymmetrization of Prochiral Methyl Groups[a,b]





5a 61% yield, 80% *ee* **5b** 36% yield, 35% *ee* **5c** 32% yield, 29% *ee* **5d** 47% yield, 61% *ee*

[a]Reaction Conditions: substrate **4** (0.1 mmol), Ar-BF_3K (2.0 equiv), $Pd(OAc)_2$ (10 mol %), **L7** (11 mol %), Ag_2CO_3 (2.0 equiv), $NaHCO_3$ (3.0 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), *t*-AmylOH (0.5 mL), N_2, 50 °C, 72 h. [b]Isolated yield. The ee values were determined by HPLC analysis on a chiral stationary phase.

fluoroborate coupling partner in moderately good yield (61%) and enantioselectivity (80% ee). Other less hindered substrates **5b–d** gave lower ees under the same conditions (Table 4). These preliminary results suggest that MPAHA ligands could be potentially applicable to the enantioselective functionalization of prochiral methyl C–H bonds.

3. CONCLUSION

In summary, intermolecular enantioselective functionalization of C(sp^3)–H bonds are demonstrated with amide substrates derived from cyclobutanecarboxylic acids. The key to the success of this method was the discovery of a new class of chiral ligands, MPAHA, which were derived from mono-*N*-protected amino acids. These chiral MPAHA ligands have also shown promise for further development of new methods for stereoselective functionalization of acyclic unactivated C-(sp^3)–H bonds.

4. EXPERIMENTAL SECTION

General Precedure for the Enantioselective C(sp^3)–H Activation of Cyclobutanecarboxylic Acid Derivatives (Table 3). Substrate **1** (0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), Ar-BPin (2.0 equiv), **L25** (0.11 equiv), Ag_2CO_3 (2.5 equiv), Na_2CO_3 (2.0 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), and *t*-AmylOH (0.5 mL) were added into a 10 mL sealed tube. The reaction vessel was evacuated and backfilled with nitrogen (×3). The reaction mixture was heated to 70 °C for 24 h under vigorous stirring. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite, eluting with EtOAc. The filtrate was concentrated under vacuum, and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to give the desired product. The ee value was determined on a Hitachi LaChrom HPLC system using commercially available chiral columns.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

yu200@scripps.edu

Notes

The authors declare no competing financial interest.

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