Letter

Catalytic Asymmetric Carbonylation of Prochiral Sulfonamides via C-H Desymmetrization

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Catalytic Asymmetric Carbonylation of Prochiral Sulfonamides via C−H Desymmetrization

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ABSTRACT: An enantioselective oxidative C−H/N−H carbonylation process was developed in this work. A bimetallic Pd/Cu-based catalyst systems were found to catalyze enantioselective C(sp^2)−H carbonylation of prochiral arylsulfonamides via desymmetrization process in the presence of mono-N-protected amino acid ligands. This reaction provides a facile strategy to the stereoselective construction of the lactam-type products, such as isoindoline-1-ones and isoquinoline-1-ones, in good yields and enantioselectivities under balloon pressure with the mixture of CO/O_2. The reaction mechanism was rationalized by using density functional theory (DFT) study.

KEYWORDS: *C−H activation; enantioselective carbonylation; lactam; desymmetrization; palladium; DFT.*

Catalytic carbonylation is one of the most straightforward processes for oxo-synthesis and its asymmetric versions have been a great interest of synthetic chemists. [1] Although many studys on enantioselective carbonylation have been reported over the past decades, most of the them fall into the category of asymmetric carbonylation of alkenes under the promotion of specified chiral ligands, which was usually difficult to synthesize,[2] and more model reactions thereby in the context of enantioselective carbonylation are highly desired. In this regard, the thriving of C−H carbonylation[3] strategy and the tremendous success of enantioselective C−H functionalization[4] provided a new potential protocol for enantioselective carbonylation. For instance, Baudoin and co-workers have succeeded in an asymmetric palladium(0)-catalyzed intramolecular C(sp^3)−H carbamoylation of TMB-protected carbamoyl chloride in the presence of TADDOL-derived phosphine, with 75% yield of chiral *β*-lactam and 84% *ee*.[5] However, to the extent of our knowledge, this is the only study related to enantioselective C−H carbonylation reported up to now.

Lactams bearing medium rings, such as isoindolinone and isoquinolinone cores, are privileged structural unit in many natural products and bioactive compounds.[6] Furthermore, catalytic asymmetric synthesis of these valuable structures has been almost widely recognized as a challenge work and thus gained broad attentions.[7] Since Orito's pioneer work,[8] Pd-catalyzed C−H carbonylation of amines has been proved to be a highly powerful strategy for the construction of lactam; However, to the best of our knowledge, there is no reported study on the construction of chiral isoindolinone and isoquinolinone cores through the enantioselective carbonylation strategy. Herein, we report an enantioselective C−H/N−H carbonylation of prochiral sulfonamides, providing a new example for enantioselective carbonylation and an easily access to chiral isoindolinone and isoquinolinone cores. Gaunt's group has reported a series of pioneering work on the C−H

Scheme 1. C−H carbonylation of amines and design of asymmetric version.

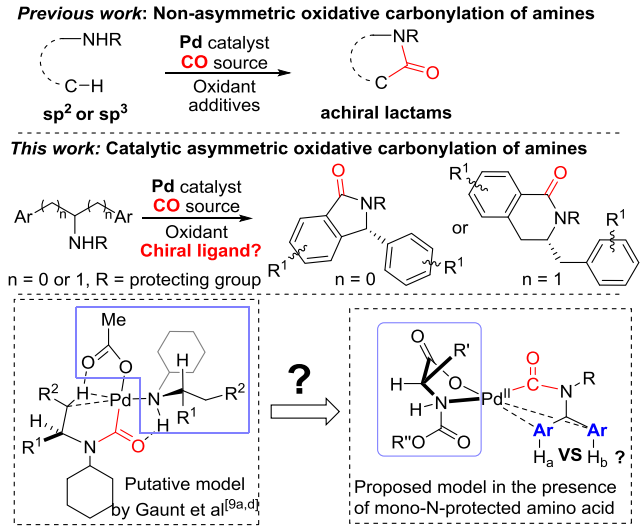
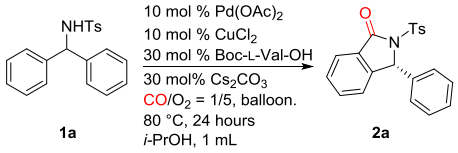


Table 1. Investigation of reaction parameters for asymmetric C(sp^2)–H carbonylation.

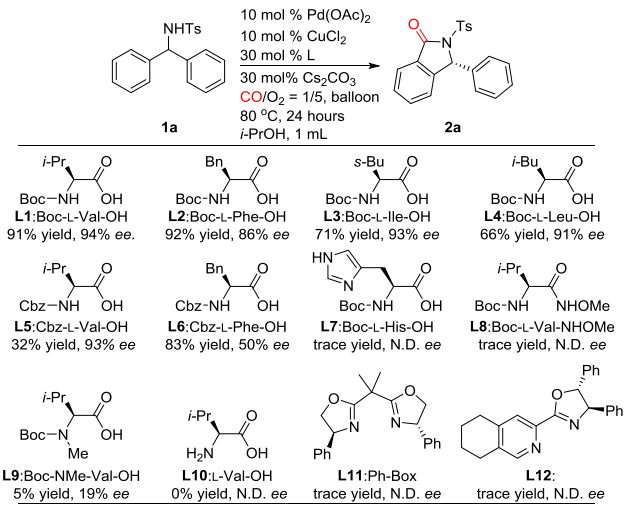


Entry	Variation from standard condition	Yield (%)[b] 1a	2a	*ee*
1[a]	none	trace	>95(91)	94
2	Without $Pd(OAc)_2$	>99	N.R.[c]	N.D.[d]
3	Without $CuCl_2$	>95	Trace	N.D.
4	$PdCl_2$ instead of $Pd(OAc)_2$	77	23	95
5	$(PPh_3)_2PdCl_2$ instead of $Pd(OAc)_2$	>99	N.R.	N.D.
6	2.0 equivalent $CuCl_2$ instead of oxygen under 1/5 mixture of CO/N_2	>95	trace	N.D.
7	10 equivalent $(CH_2O)_n$ instead of carbon monoxide under oxygen atmosphere	>95	trace	N.D.
8	Without Cs_2CO_3	>99	N.R.	N.D.
9	*i*-Pr_2NEt or 2,6-lutidine instead of Cs_2CO_3	>99	N.R.	N.D.
10	60 mol% Cs_2CO_3 was used	54	Trace	N.D.
11	Carried out at 60 ℃	49	50	95
12	Carried out at 40 ℃	>95	Trace	N.D.
13	CO/Air = 1/1	80	16	N.D.
14	CO/Air = 1/5	69	31	N.D.
15	CO/O_2 = 1/2	52	45	N.D.

[a] The standard reaction was carried out at 0.1 mmol scale with 10 mol% $Pd(OAc)_2$, 10 mol% $CuCl_2$, 30 mol% Boc-L-Val-OH and Cs_2CO_3 in 1 mL *i*-PrOH, the partial pressure ratio of CO/O_2 was 1/5 and the reaction was refluxed at 80 ℃ for 24 hours. [b] Determined by ^1H NMR analysis with CH_2Br_2 as an internal standard, the value in parentheses shows the isolated yield. [c] N.R.= no reaction. [d] N.D.= not determined.

carbonylation of simple amines,[9] and proposed a plausible model that both the carboxylate ion and another amine molecule play key role in the reaction. We questioned whether it is feasible to use amino acid derived ligands instead of both amine and carboxylate ion moieties in their model to design an enantioselective C–H carbonylation protocol (Scheme 1). In fact, mono-N-protected amino acids (MPAA) has been frequently used as magic ligands in Pd-catalyzed enantioselective desymmetric functionalization of C–H bonds since the pioneering works of Yu's group.[10] Meanwhile, the MPAA also proved to be effective ligands in promoting palladium-catalyzed C(sp^2)–H carbonylation.[11] However, enantioselective version of C(sp^2)–H carbonylation that promoted by MPAA ligands has not been reported yet. To test our hypothesis, we initiated our study using tosyl-protected diarylmethylamine (**1a**) as the substrate and evaluated a series of conditions (Table S1-S6 of Supporting Information), The optimized

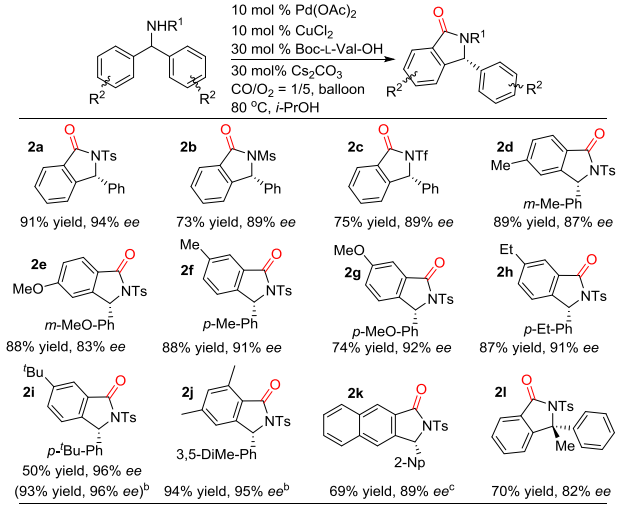
Scheme 2. Effect of ligands on the reactivity and enantioselectivity.



standard condition was 0.1 M **1a** in *i*-PrOH with 10 mol % $Pd(OAc)_2$, 10 mol % $CuCl_2$, 30 mol % Boc-L-Val-OH and 30mol % Cs_2CO_3 at 80 ℃ under a balloon atmospheric of CO/O_2(1/5 in v/v) mixture. 91% isolated yield and 94% *ee* of **2a** was obtained after refluxing for 24 hours under this standard condition (Table 1, entry 1). Table 1 showed representative results for the enantioslective C–H carbonylation of prochiral arylsulfonamide **1a** to isoindolinone **2a**. For example, the reaction almost didn't work in the absence of either $Pd(OAc)_2$, $CuCl_2$, or Cs_2CO_3 (Table 1, entry 2-3 and 8). Replacing $Pd(OAc)_2$ with $PdCl_2$ diminished the yield of **2a** to 23%, while the *ee* value slightly increased to 95% (Table 1, entry 4). $[(PPh_3)_2PdCl_2]$ showed no catalytic activity in this reaction (Table 1, entry 5). A trace amount of product was detected when using 2.0 equivalents of $CuCl_2$ as the oxidant under a balloon atmospheric of CO/N_2(1:5 in v/v) gas mixture (Table 1, entry 6). Replacing carbon monoxide with 10 equivalents of paraformaldehyde also leaded to trace amount of yiel. When it comes to using other bases, K_2CO_3 or Na_2CO_3, the yield was decreased to 37% and 6% respectively, while the *ee* values maintained at 93-94%. Notably, 95% *ee* was acquired in the sacrifice of reaction efficiency (50% yield) when the reaction temperature was decreased to 60 ℃. Gas mixture of CO/O_2 proved to be more efficient than CO/Air. A suitable partial pressure ratio of CO/O_2 range from 1/3 to 1/10, the conversion of **1a** suffered from any change either increase or decrease, of the ration of CO/O_2. (Table 1, entry 13-15; Supporting Information, Table S4). Based on our experimental observations, increasing the ratio of CO lead to black dust quickly during the reaction, that is the result of the strong reducing effect of CO against Pd(II). In addition, lowering the concentration of CO would slow down the carbonyl insertion step of the reaction.

The influence of electronic and substituent effect of mono-N-protected amino acid on the reactivity and enantioselectivity was studied under the optimized condition (Scheme 2). Generally, most of the commercial mono-N-protected amino acids evaluated in this reaction showed improvement on the Pd/Cu co-catalyzed enantioselective desymmetric C–H carbonylation of diarylsulfonamide, resulting up to 91% isolated yield and

Scheme 3. Scope of diarylsulfonamides for the enantioselective C(sp^2)−H carbonylation.

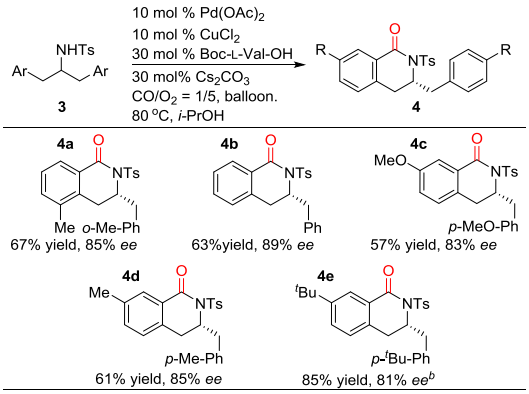


[a] Unless otherwise specified, the reaction was carried out at 0.3 mmol scale with 10 mol% $Pd(OAc)_2$, 10 mol% $CuCl_2$, 30 mol% Boc-L-Val-OH and 30 mol% Cs_2CO_3 in 3 mL *i*-PrOH, the partial pressure ratio of CO/O_2 was 1/5 and the reaction was refluxed at 80 ℃ for 24 hours. [b] CO/O_2 = 1/7, reflux at 80 ℃ for 48 hours. [c]: reflux for 72 hours.

94% *ee* of **2a**, except Boc-L-Phe-OH and Cbz-L-Phe-OH, which decreased the *ee* of **2a** to 83% and 50% *ee* respectively. These results indicated that both the substituents on the backbone and the protecting group of amino acid ligands involved in the enantiocontrol state. Boc-L-His-OH showed no activation on the reactivity, that might be due to the competitive coordination of imidazolyl toward metal center. When using unprotected amino acid **L10** or replacing the carboxyl with an *N*-methoxyamide group (**L8**), the carbonylation almost did not take place. Methyl instead of hydrogen on the nitrogen of ligand (**L9**) was detrimental to both the yield (5%) and *ee* (19%). Other commercial chiral azo ligands such as Ph-Box (**L11**) and **L12** showed no improvements on this C−H carbonylation reaction. These experimental results indicated that both the mono-N-protected amino and acid moieties are essential to the reactivity of this C−H carbonylation approach.

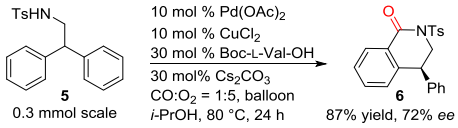
With the optimized condition in hand, we next investigated the scope and limitations of the Pd/Cu co-catalyzed enantioselective carbonylation reaction. As demonstrated in Scheme 3, The carbonylation reactivity was obviously affected by the protecting group of nitrogen and substituents on the phenyl of substrates. For instance, Ms- or Tf- protected diphenylmethylsulfonamide provided enantiomer enriched isoindolinones with slightly lower *ee* values and yields. *Meta*-substituted (Me-, MeO- for example) substrates exerted exclusive site selectivity, giving **2d** and **2e** in 87% and 83% *ee* respectively with good yields. *Para*-substituted substrates afforded corresponding carbonylated products **2f-2h** in high yields (74-88%) and good enantioselectivities (> 91% *ee*). For a strong electric-donating and sterically hindered group, *t*-butyl for instance, providing **2i** in 96% *ee* but only giving 50% yield. When changed the partial pressure ratio of CO/O_2 to 1/7 and extended the reaction time to 48 hours, the yield of **2i** increased to 93% and *ee* value matained at 96%. 3,5-Dimethyl

Scheme 4. Scope of diarylmethylsulfonamides for the enantioselective C(sp^2)−H carbonylation.



[a] Unless otherwise specify, the reaction was carried out at 0.3 mmol scale with 10 mol% $Pd(OAc)_2$, 10 mol% $CuCl_2$, 30 mol% Boc-L-Val-OH and 30 mol% Cs_2CO_3 in 3 mL *i*-PrOH, the partial pressure ratio of CO/O_2 was 1/5 and the reaction was refluxed at 80 ℃ for 24 hours. [b] CO/O_2 = 1/7, reflux at 80 ℃ for 24 hours.

Scheme 5. Enantioselective carbonylation of Ts-protected 2,2-diphenylethylsulfonamide 5.

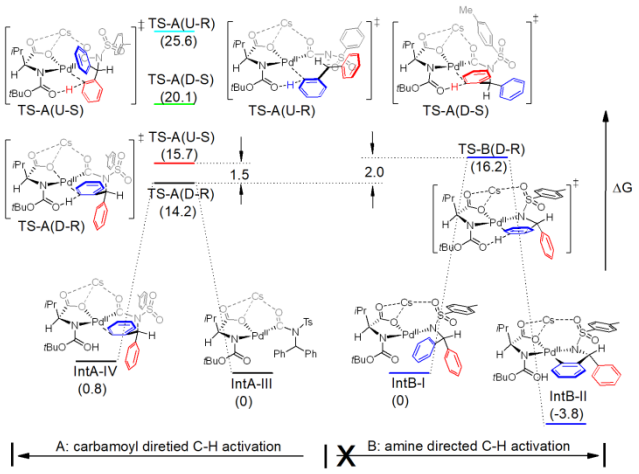


substituted product **2j** also obtained in 94% yield and 95% *ee* in the same way as **2i** did. For Ts-protected di(2-naphthyl)-methylsulfonamide **1k**, unsatisfactory site selectivity compromised the yield of **2k** to 69% at 89% *ee*. In addition, **2l**, with a chiral quaternary carbon stereo center, acquired in 70% yield and 82% *ee*.

To further test the application of our catalytic enantioselective C−H carbonylation system, we next applied the standard reaction condition to the carbonylation of Ts-protected dibenzylmethylsulfonamides.[12] As the results shown in Scheme 4, isoquinolinones **4a-4e** were obtained in moderate to good yields under the optimized condition mentioned above, the corresponding *ee* values distributed from 83% to 89%. Ts-protected 2,2-diphenylethan-1-sulfonamide **5** converted to 4-phenyl substituted isoquinolinones **6** in 87% yield and even low to 72% *ee*. These results indicated that the bigger cyclic transient state in the C−H activation step for isoquinolinones formation prejudiced the stereo control and resulted to poor enantioselectivity. Fortunately, we obtained the single crystal diffraction data of **2e**, **2k**, **4a** and **6** from the corresponding enantiopure samples (>99% *ee* obtained through a recrystallization from *i*-PrOH). It should be noted that the phenyl on the C4 position of **6** stretched toward to the up side of the isoquinolinone plane as shown in Scheme 5, while the phenyl on the C3 position of isoquinolinone **4a-4e** pointed to the down side.

For the reaction mechanism, there are two possible pathways for the asymmetric C−H activation of sulfonamide to chiral lactams according to references: A) carbamoyl directed C−H activation or B) amine directed C−H activation (Scheme 6). Yu and co-workers proposed a reasonable transient state

Scheme 6. Free energy profiles for enantioselective C−H activation of sufulamide 1a. [a]



[a] Activation free energies are given in kcal/mol. The Gibbs energy of **intA-III** and **intB-I** were set to zero for each protocol respectively.

model for the mono-N-protected amino acid promoted enantioselective desymmetric C−H functionalization before, combining experiments and DFT calculations.[13] Herein, we conducted a DFT study to compare the activation free energy of the C−H activation step between these two different protocols. As shown in Scheme 6, the lowest activation energy of carbamoyl directed C−H activation was calculated to be 14.2 kcal/mol (**TS-A(D-R)**), while the amine directed C−H activation calculated to 16.2 kcal/mol (**TS-B(D-R)**; that is, 2.0 kcal/mol higher than **TA-A(D-R)**). This result supported a carbamoyl directed C−H activation protocol. A complete catalytic cycle was proposed based on it (the Supporting information, Scheme S1). For the driving force of enantioselectivity, four different transition states were simulated for the transition from carbamoyl-Pd species (**int-III**) to Pd tether bicycle species (**int-IV**). In the transition state **TS-A(D-*R*)** and **TS-A(D-*S*)**, activating C−H bond was oriented blow the Pd coordination plane, whereas in **TS-A(U-*S*)** and **TS-A(U-*R*)**, the activating C−H bond was oriented upward. The lower energy state for *S*-enantiomer (**TS-A(U-*S*)**) was calculated to be 15.7 kcal/mol, which is 1.5 kcal/mol higher than **TS-A(D-*R*).** The energy difference elucidated the origin of *R*-enantiomer selective carbamoyl directed C−H carbonylation protocol. Transition state models of carbamoyl-Pd oriented C−H activation for sulfonamide **4a** and **6** also simulated and optimized under the same theoretical model and basis set (see Supporting Information, Figure S2(B, C)). The free Gibbs energy of **TS-4a(D-*S*)** was calculated to be 1.8 kcal/mol higher than **TS-4a(D-*R*)**; **TS-6-*R*** calculated to 2.5 kcal/mol higher than **TS-6-*S***. These were consistent with the experiment results.

In summary, we have developed a novel Pd/Cu co-catalyzed enantioselective C−H carbonylation of prochiral sulfonamides to optically enriched isoindolinones and isoquinolinones based on a desymmetrization strategy. It is the first example of direct enantioselective oxidative carbonylation of C−H/N−H bonds promoted by readily available mono-N-protected amino acid ligands. The reaction was simply handled under a mixture atmosphere of carbon monoxide and oxygen at balloon pressure. This enantioselective process has the potential to be used in the asymmetric synthesis and pharmaceutical fields because of its mild reaction conditions. In addition, a plausible enantioselective carbamoyl-Pd oriented C−H activation mechanism was proposed based on the computational study.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. At DOI: 10.1021/acscatal.xxxx.

Experimental procedures, characterization of products and spectroscopic data (PDF); Crystallographic data for **2e** (CIF); Crystallographic data for **2k** (CIF); Crystallographic data for **4a** (CIF); Crystallographic data for **6** (CIF)

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Notes

The authors declare no competing financial interests.

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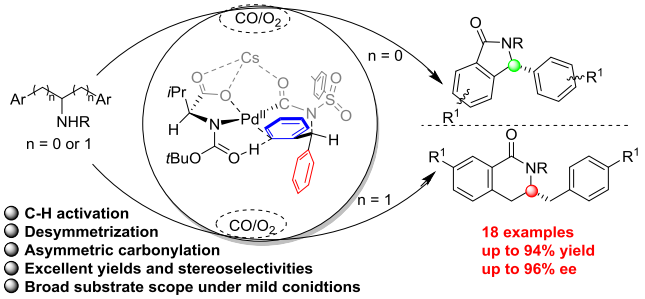
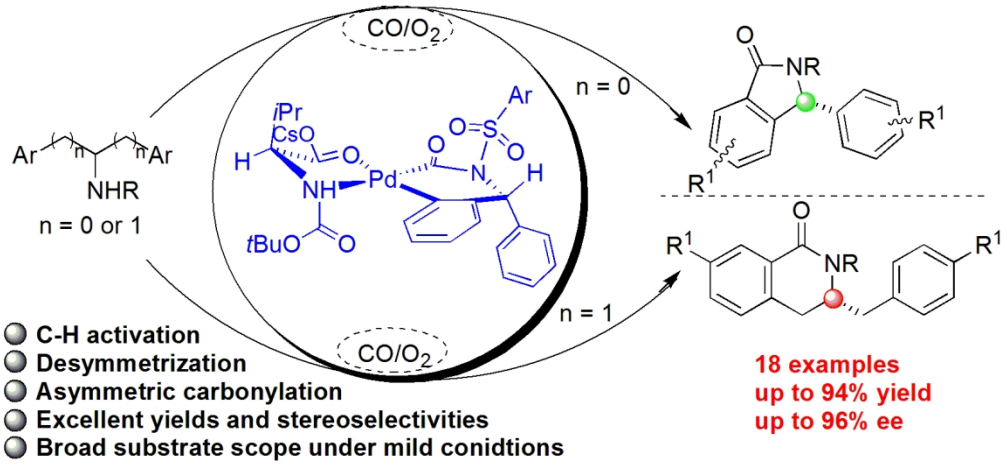

CO/O2
Cs
iPr
Pd
tBuO
Ar
NHR
n = 0 or 1
n = 0
n = 1
NR
R1
C-H activation
Desymmetrization
Asymmetric carbonylation
Excellent yields and stereoselectivities
Broad substrate scope under mild conidtions
18 examples
up to 94% yield
up to 96% ee



C-H Desymmetrization

144x65mm (300 x 300 DPI)