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Ligand-Accelerated Palladium(II)-Catalyzed Enantioselective Amination of C(sp^2)−H Bonds

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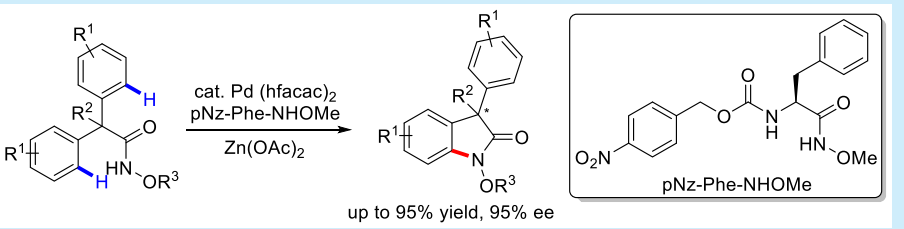

ABSTRACT: The first example of the Pd(II)-catalyzed enantioselective amination of aryl C−H bonds is reported. The key to the successful realization of this asymmetric catalytic transformation was the identification of mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligands, which promote reactivity under mild conditions and control enantioselectivity. The counteranions in the solvent medium, hexafluoroacetylacetate and acetate, were also found to play key roles in stereocontrol and reactivity enhancement.

Optically pure nitrogen-containing heterocycles are common structural motifs in a wide variety of biologically active natural products and pharmaceuticals (Figure 1).[1] Synthesizing such chiral nitrogen compounds in a fast, efficient, and convenient manner still represents a significant challenge in organic synthesis.[2] Transition-metal-catalyzed stereoselective C−H amination methods have recently attracted significant attention from the synthetic community due to the unique atom and step economies of such processes.[3] However, it is still a significant challenge to achieve high levels of chemo- and stereoselectivity in these transformations among the omnipresent less active C−H bonds.[4] One approach to enantioselective C−H amination has been metallonitrene catalysis,[3f−l] in which several chiral catalysts derived from rhodium,[5] copper,[6] ruthenium,[7] manganese,[8] and iridium[9] have been developed for asymmetric nitrene C−H insertion in inter- and intramolecular contexts. An alternative approach, enantioselective inner-sphere transition-metal-catalyzed C−H amination, which involves the formation of an enantioenriched metallocycle arising from stereospecific C−H cleavage, is appealing due to the distinct chemoselectivity patterns of such reactions, but it remains underdeveloped.[10] In particular, all known catalytic systems normally work only for C(sp^3)−H bonds, especially the relatively activated benzylic and allylic C−H bonds, and transition-metal-catalyzed asymmetric C-(sp^2)−H amination still remains to be demonstrated,[11] probably due to the nonselective attack of the easily generated nitrogen-centered radical to aryl rings. Herein we report the first example of the Pd(II)-catalyzed enantioselective amination of C(sp^2)−H bonds, in which mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligands promote reactivity under mild conditions and provide high levels of stereoinduction. Hexafluoroacetylacetate and acetate counteranions were also found to play key roles in stereocontrol and reactivity enhancement.

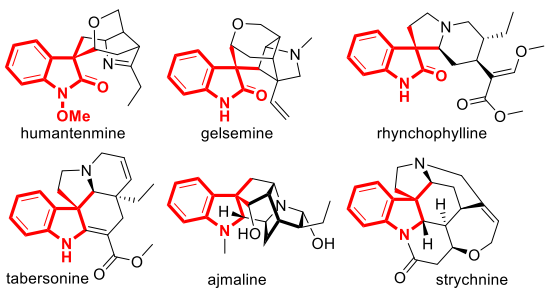

Figure 1. Sampling of natural products and pharmaceuticals containing chiral indolines and indoline-2-ones.

To begin our study, we first sought to identify an appropriate nitrogen-based directing group/reaction partner. We reasoned that a higher nucleophilicity of the nitrogen species would lead to stronger coordination to the palladium-

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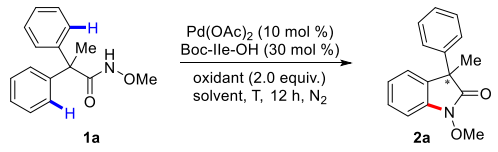
(II) center and thus decrease the possibility of nitrogen-centered radical attack. Thus our optimization efforts commenced with *N*-methoxy-2,2-diphenylpropanamide **1a** as the model substrate in the presence of a catalytic amount of palladium diacetate (10 mol %) at 100 °C (Scheme 1).

Scheme 1. Preliminary Studies on Asymmetric C(sp^2)−H Amination



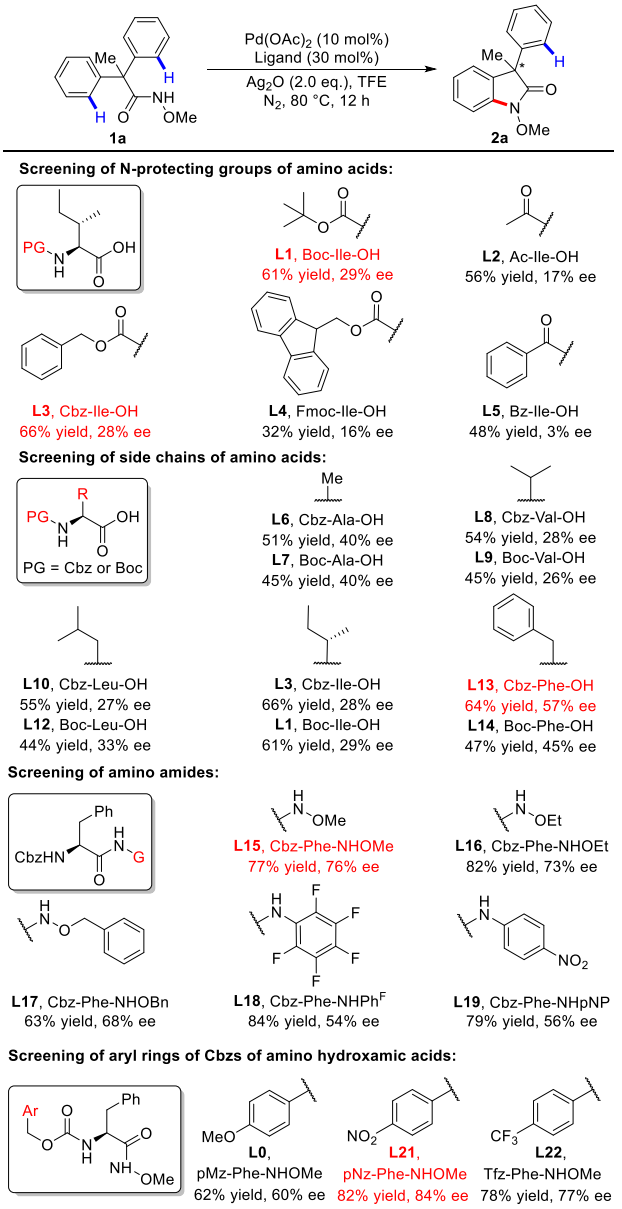
$AgOAc/CuCl_2$, DCE, no ligand, 100°C: 46%;
$AgOAc/CuCl_2$, DCE, 100°C: 49%, rac;
Ag_2O, TFE, 100°C: 71%, 26% ee;
Ag_2O, TFE, 80°C: 61%, 29% ee.

Whereas the desired product **2a** was obtained in 46% yield with $AgOAc/CuCl_2$ as the oxidation system in 1,2-dichloroethane (DCE) according to a published report,[12] the addition of a chiral ligand, monoprotected amino acid (MPAA) Boc-L-Ile-OH (**L1**), led to a racemic product in comparable yield. Interestingly, the replacement of the Ag/Cu bimetallic oxidant with silver oxide (Ag_2O) in trifluoroethanol (TFE) with the addition of Boc-L-Ile-OH as a ligand to accelerate the reaction gave a higher yield of 71%. To our delight, in this case, the amination product **2a** was obtained with 26% ee. Decreasing the reaction temperature to 80 °C gave a slightly enhanced enantioselectivity (29% ee) with a somewhat lower yield.

To improve the reaction efficiency and enantioselectivity, we next focused on the optimization of the chiral ligand. First, as shown in Scheme 2, varying the *N*-protecting group on isoleucine (**L1**−**5**) showed that *tert*-butyloxycarbonyl (Boc, **L1**) and benzyloxycarbonyl (Cbz, **L3**) afforded similar ee values. Accordingly, a variety of amino acids protected by either Boc or Cbz were examined, which revealed that Cbz-L-Phe-OH (**L13**) gave the best result of 57% ee. (For more details, see the Supporting Information.) Inspired by a previous report in which the replacement of the carboxylic acid with the more strongly coordinating hydroxyamic acid group improved the stereoselectivity,[13] we next converted several *N*-monoprotected amino acid analogs containing a hydroxyamic acid group. Consistent with our hypothesis, we were pleased to find that the *O*-methylhydroxamic acid derivative (**L15**), henceforth referred to as a mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligand,[13] dramatically enhanced the enantioselectivity to 76% ee. Electron-withdrawing *N*-aryl amides gave comparatively lower ee values (**L18** and **L19**). Finally, an examination of the electronic effects of the aryl ring on the Cbz-protecting group revealed that the presence of a strongly electron-withdrawing *p*-NO_2 (**L21**) substituent further improved the ee value to 84%.

Next, we reasoned that the nature of the counteranion in the parent metal salt was likely to also play a key role in governing the reactivity and enantioselectivity. Hence, we next examined different kinds of palladium(II) salts in order to identify the best counteranion for this asymmetric amination. As shown in Table 1, the palladium catalyst with hexafluoroacetylacetonate (hfacac) as the counteranion gave a higher ee of 92%, albeit with a significantly lower yield of 43% (entry 3). Considering the decreasing yield due to the absence of acetate (entries 1−3), a variety of acetates were investigated with $Pd(hfacac)_2$ as the catalyst, which showed that 15 mol % of $Zn(OAc)_2$ gave **2a** in 80% yield with 94% (entries 4−6; for more details, see the Supporting Information). Extending the reaction time to 24 h increased the yield to 86% with a slightly reduced ee value (entry 7). Ag_2O was found to be only sparingly soluble in the reaction solvent, and it accumulated on the sides of the reaction vessel. We speculated that this was impeding the reoxidation of Pd(0) to Pd(II). Hence, 30 mol % of dibenzyl phosphate (DBP) was added as a phase-transfer catalyst to bring Ag^+ into the solution phase,[14] which further increased the yield to 90% (entry 10). Finally, changing the solvent from TFE to pentafluoropropanol (PFP) afforded a 95% yield of **2a** with an excellent ee value (95%) (entry 11). In addition, a slight lower yield was obtained without a decline in ee when

Scheme 2. Pd(II)-Catalyzed Enantioselective C(sp^2)−H Amination: Screening of Ligands[a]



[a]Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), ligand (30 mol %), Ag_2O (2.0 equiv), TFE (1.5 mL), N_2, 80 °C, 12 h. Isolated yield. The ee value was determined by chiral HPLC analysis.

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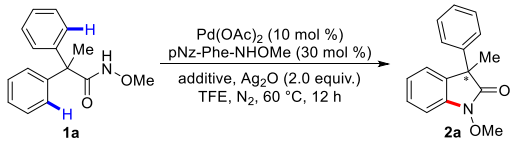
Table 1. Pd(II)-Catalyzed Enantioselective C(sp^2)−H Amination: Optimization of Conditions[a]



entry	[Pd]	additive (mol %)	yield (%)	ee (%)
1	$Pd(OAc)_2$		85	86
2	$Pd(acac)_2$		69	89
3	$Pd(hfacac)_2$		43	92
4	$Pd(hfacac)_2$	$Cu(OAc)_2$ (10)	70	92
5	$Pd(hfacac)_2$	$Zn(OAc)_2$ (10)	77	94
6	$Pd(hfacac)_2$	$Zn(OAc)_2$ (15)	80	94
7[b]	$Pd(hfacac)_2$	$Zn(OAc)_2$ (15)	86	92
8[b]	$Pd(hfacac)_2$	$Zn(OAc)_2$ (15)/DBP (10)	93	94
9[b]	$Pd(hfacac)_2$	DBP (10)	60	92
10[b]	$Pd(hfacac)_2$	$Zn(OAc)_2$ (15)/DBP (30)	90	95
11[b,c]	$Pd(hfacac)_2$	$Zn(OAc)_2$ (15)/DBP (30)	95	95
12[b,c]	$Pd(acac)_2$	$Zn(OAc)_2$ (15)/DBP (30)	92	95

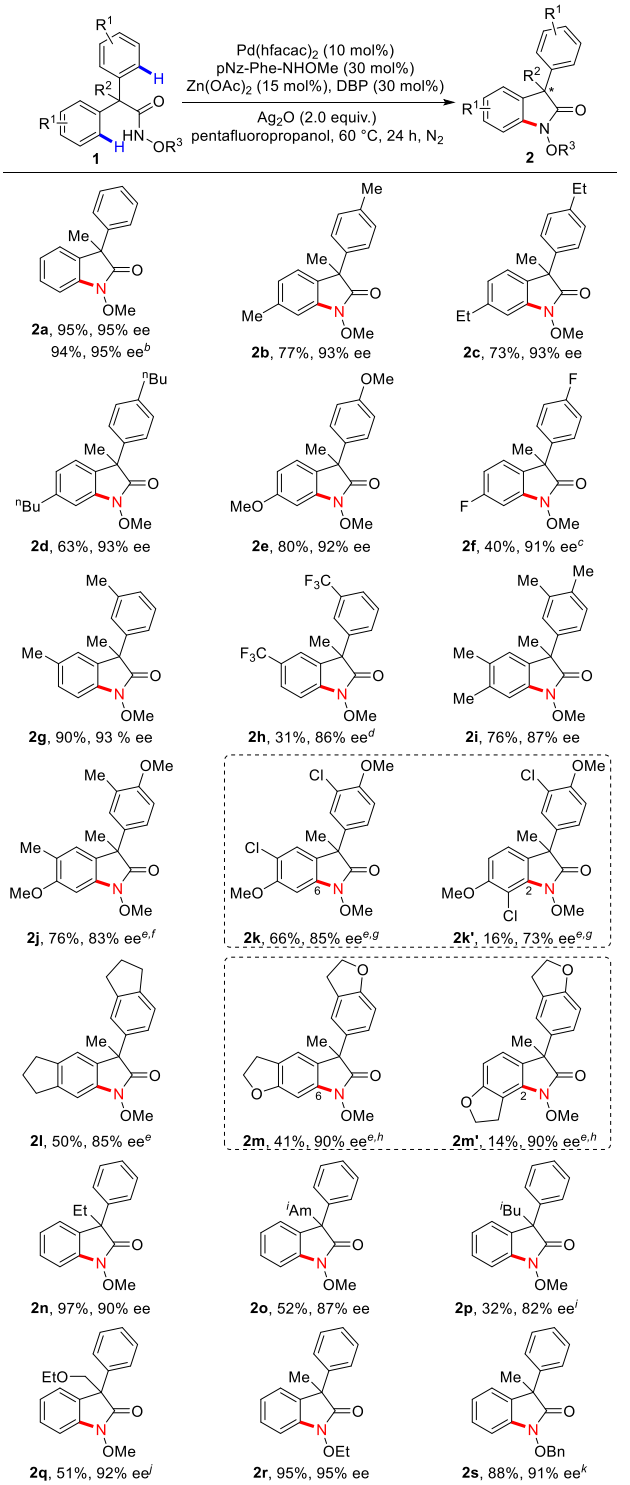
[a]Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), pNz-Phe-NHOMe (30 mol %), additive, Ag_2O (2.0 equiv), TFE (2.5 mL), N_2, 60 °C, 12 h. Isolated yield. The ee value was determined by chiral HPLC analysis. [b]24 h. [c]PFP was used as the solvent.

$Pd(acac)_2$ (acac = acetylacetonate) was used as the catalyst instead of $Pd(hfacac)_2$ under the optimized conditions (entry 12).

With the optimized reaction conditions in hand, a collection of *N*-methoxy-2,2-diphenylpropanamides **1** were subjected to the enantioselective C−H amination conditions, affording the corresponding lactams **2** with high enantioselectivities. As shown in Scheme 3, potential substituent effects on the aryl rings of the *N*-methoxyamides **1** were examined, and the results revealed that both electron-donating groups (alkyl, methoxy) and electron-withdrawing groups (F, Cl, CF_3) on the aryl rings were well tolerated in this transformation. Whereas *N*-methoxyamides with electron-donating substituents (**2b−e**) gave the chiral lactams in good yields with excellent ee values, unsurprisingly, substrates with electron-withdrawing groups on the aryl rings (**2f** and **2h**) afforded the cyclized products in moderate yields with good ee values. A variety of meta-substituted substrates could be smoothly cyclized to afford the corresponding lactams, although mixtures of two expected regioisomers were obtained in some cases (**2k** and **2m**). Bicyclic amides afforded the corresponding tricyclic products (**2l** and **2m**), also with good enantioselectivities. To our satisfaction, when the α-methyl group was replaced with ethyl, isoamyl, and isobutyl (R^2) groups, these substrates underwent cyclization to afford the desired products **2n−p**, whereas the reactivity and enantioselectivity of such substrates decreased as the steric hindrance increased. The presence of a heteroatom on the alkyl chain was also compatible in this reaction with a similar ee (92%), albeit with a lower yield (**2q**). Lastly, the examination of the O-substituents (R^3) on the hydroxyamic amides showed that Et and Bn groups gave almost the same results as the Me group (**2r** and **2s**).

The absolute configuration of **2n** was confirmed to be R by X-ray crystallographic analysis (Figure 2). To demonstrate the potential practical utility of this novel asymmetric transformation, product **2a** was transformed into other nitrogen heterocycles (Scheme 4). In particular, the treatment of **2a**

Scheme 3. Pd(II)-Catalyzed Enantioselective C(sp^2)−H Amination: Substrate Scope[a]



[a]Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), pNz-Phe-NHOMe (30 mol %), $Zn(OAc)_2$ (15 mol %), DBP (30 mol %), Ag_2O (2.0 equiv), PFP (2.5 mL), N_2, 60 °C, 12 h. Isolated yield. The ee value was determined by chiral HPLC analysis. [b]1 mmol scale. [c]$Pd(OAc)_2$ (10 mol %) was used as a catalyst without $Zn(OAc)_2$. [d]80 °C, 96 h. [e]$Pd(acac)_2$ (10 mol %) was used as the catalyst. [f]50 °C, 48 h. [g]AgOAc (15 mol %) was used as the acetate source, and Tfz-Phe-NHOMe (30 mol %) was used as the ligand. [h]30 h. [i]65 °C. [j]36 h. [k]TFE was used as the solvent.

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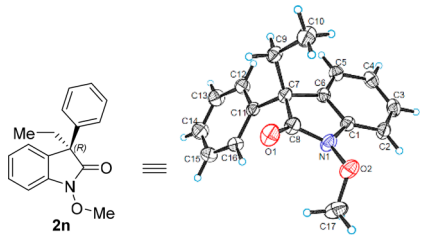
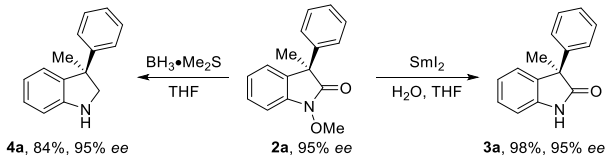


Figure 2. ORTEP (35% ellipsoid) in the X-ray crystal structure of **2n**.

Scheme 4. Transformations of Lactam 2a



with SmI_2 led to the selective cleavage of the N−OMe bond to afford indoline-2-one (**3a**) in 98% yield. The stronger reducing reagent $BH_3{\cdot}SMe_2$ transformed **2a** to indoline **4a** in 84% yield in a single step. Notably, the quaternary chiral center on the *N*-methoxyindoline-2-one was maintained without any loss of enantiomeric purity.

In summary, we have developed an enantioselective amination via Pd(II)-catalyzed asymmetric C(sp^2)−H activation. The key to the successful realization of this asymmetric catalytic reaction was the discovery of chiral MPAHA ligands, which promoted both the reactivity and the enantioselectivity. The counteranions, hexafluoroacetylacetate and acetate, were also found to play crucial roles in the reaction. Further exploration of asymmetric C(sp^2)−H bonds to enable chiral azacycles motifs is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02216.

Experimental procedures, spectral and analytical data, X-ray crystal data, and copies of ^1H and ^{13}C NMR and HPLC spectra for new compounds (PDF)

Accession Codes

CCDC 2006081 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

§X.-F.C. and F.F. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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