Organic LETTERS

Letter

pubs.acs.org/OrgLett

Iridium-Catalyzed Asymmetric Hydrogenation of Ketones with Accessible and Modular Ferrocene-Based Amino-phosphine Acid (f-Ampha) Ligands

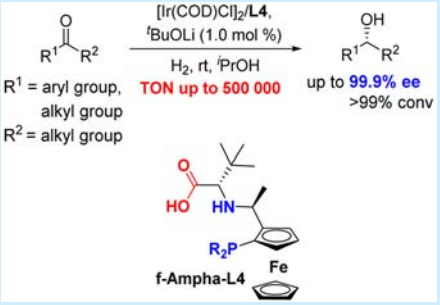
Jianfei Yu,[†,§] Jiao Long,[†,§] Yuhong Yang,[‡] Weilong Wu,[†] Peng Xue,[†] Lung Wa Chung,*[,‡] Xiu-Qin Dong,*[,†] and Xumu Zhang*[,‡,†]

[†]College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei 430072, P. R. China

[‡]Department of Chemistry, South University of Science and Technology of China, Shenzhen, Guangdong 518055, P. R. China

Supporting Information

ABSTRACT: A series of tridentate ferrocene-based amino-phosphine acid (f-Ampha) ligands have been successfully developed. The f-Ampha ligands are extremely air stable and exhibited excellent performance in the Ir-catalyzed asymmetric hydrogenation of ketones (full conversions, up to >99% ee, and 500 000 TON). DFT calculations were performed to elucidate the reaction mechanism and the importance of the −COOH group. Control experiments also revealed that the −COOH group played a key role in this reaction.



Catalytic asymmetric hydrogenation is a powerful and economically feasible method for the construction of chiral organic compounds.[1] Chiral alcohols are important building blocks in many pharmaceuticals.[2] Asymmetric hydrogenation of prochiral unfunctionalized ketones is one of the most straightforward methods to access them.[3] This powerful synthetic method was demonstrated in Noyori's [$RuCl_2$(diphosphine)-(diamine)] catalytic system with excellent results.[4] Encouraged by this fundamental study, numerous ligands were successfully developed for the asymmetric hydrogenation of simple ketones.[5] Most of these ligands are sensitive to air and are synthesized via multistep complicated reactions with expensive chemical reagents, which limit their application. Therefore, the development of more efficient and practical ligands in terms of excellent enantioselectivity and activity, tolerance of wide range of functional groups, good air stability, and ease of preparation remains challenging in asymmetric catalysis. Herein, we successfully developed tridentate ferrocene-based amino-phosphine acid (f-Ampha) ligands by introducing easily accessible chiral amino acids to the ferrocenylphosphine motif (Figure 1). The highly modular f-Ampha ligands exhibited excellent performance in Ir-catalyzed asymmetric hydrogenation of simple ketones affording chiral alcohols (full conversions, almost all products up to >99% ee, TON up to 500 000). Density functional theory (DFT) calculations revealed that the carbonyl group of the −COOH group in f-Ampha ligands coordinated with iridium, and the −OH group was involved with the formation of O−H··· substrate interaction with a new catalytic bifunctional mode. Control experiments identified the importance of the −COOH group (Figure 2).

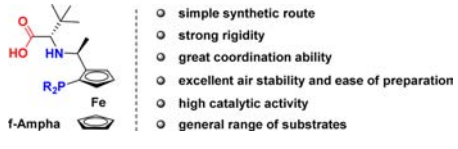


Figure 1. Ferrocene-based f-Ampha ligands.

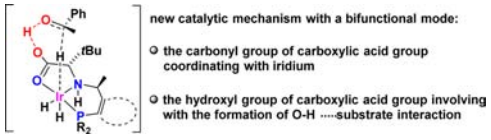


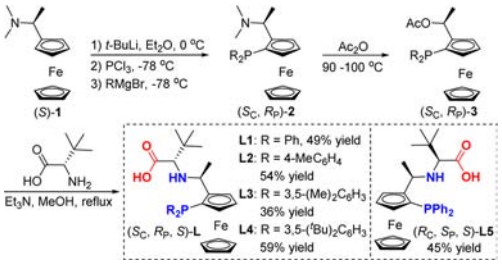
Figure 2. Key transition state for Ir/f-Ampha-catalyzed asymmetric hydrogenation of ketone.

The novel f-Ampha ligands **L1**−**L5** with high air stability were easily prepared via a simple synthetic route (Scheme 1).[6−8] Starting from commercially available (*S*)-Ugi's amine **1**, a one-pot sequential reaction provided aminophosphines (S_C, R_P)-**2** efficiently.[6] The acetates (S_C, R_P)-**3** were obtained in high yields by heating the solution of (S_C, R_P)-**2** in acetic anhydride.[7] (S_C, R_P)-**3** reacted with amino acid (*S*)-2-amino-3,3-dimethylbutanoic acid via condensation generating ligands **L1**−**L4**.[8] Ligand **L5** was synthesized to investigate the relationship between the stereoselectivity and configuration of the ligand, which is the diastereoisomer of ligand **L1**.

Received: December 27, 2016
Published: January 17, 2017

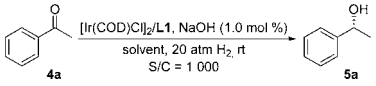
DOI: 10.1021/acs.orglett.6b03862
Org. Lett. 2017, 19, 690−693

Scheme 1. Synthetic Route of f-Ampha Ligands L1−L5



With the f-Ampha ligand **L1** in hand, we started our investigation by evaluating its catalytic effect in the asymmetric hydrogenation of acetophenone **4a** as the model substrate with the catalyst generated *in situ* by mixing $[Ir(COD)Cl]_2$ with ligand **L1** (S/C = 1000) in various solvents. As shown in Table 1, the solvent greatly affected this transformation. Excellent results were observed in toluene, DCM, and ^{i}PrOH (>99% conversion, 93−94% ee, entries 1−2, 6). Moderate enantioselectivities were obtained in THF, EtOH, and 1,4-dioxane (84−89% ee, entries 3, 5, 7). ^{i}PrOH was the best solvent in terms of reactivity and enantioselectivity (entry 6). We also obtained the same result when the catalyst loading was reduced to 0.01 mol % (S/C = 10 000, entry 8).

Table 1. Screening Solvents for Asymmetric Hydrogenation of Acetophenone 4a[a]

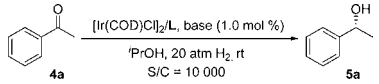


entry	solvent	conv (%)[b]	ee (%)[c]
1	toluene	>99	93
2	CH_2Cl_2	>99	93
3	THF	>99	89
4	MeOH	NR	NA
5	EtOH	<5	84
6	^{i}PrOH	>99	94
7	1,4-dioxane	95	87
8[d]	^{i}PrOH	>99	94

[a]Reaction conditions: 0.2 mmol scale, [substrate] = 0.2 M, 0.05 mol % $[Ir(COD)Cl]_2$, 0.105 mol % **L1**, 1.0 mol % NaOH, 1.0 mL of solvent, rt (25−30 °C). [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis. [d]S/C = 10 000. NR = no reaction. NA = not available.

Subsequently, different bases were screened for this transformation catalyzed by Ir-**L1** (S/C = 10 000) in ^{i}PrOH (Table 2). Moderate enantioselectivities were observed in the presence of ^{t}BuOK, K_2CO_3, and Cs_2CO_3 (78−89% ee, 97 to >99% conversions, entries 1, 4−5). ^{t}BuONa, MeONa, and ^{t}BuOLi provided excellent results (94−96% ee, >99% conversions, entries 2−3, 6), and ^{t}BuOLi was identified as the best choice with 96% ee. This reaction cannot occur without a base (entry 7), which revealed the significance of the base, although it is not clear whether the base truly acts as the cocatalyst or activates the Ir−Cl complex or ligand to form an active Ir-ligand complex. The promising results encouraged us to investigate the ligand effects of **L1**−**L5**. The results revealed that the substituents on the P atom had an important effect on the enantioselectivity. Increasing the size of the substituents on the P atom was beneficial to improve the enantioselectivity (entries 8−10). Ligand **L4** with the sterically hindered 3,5-di-*tert*-phenyl group afforded >99% ee and >99% conversion (entry 10). No reaction was observed when ligand **L5** was applied in this reaction. It indicated the importance of configuration matching for the reactivity and enantioselectivity.

Table 2. Screening Bases and Ligands for Asymmetric Hydrogenation of Acetophenone 4a[a]

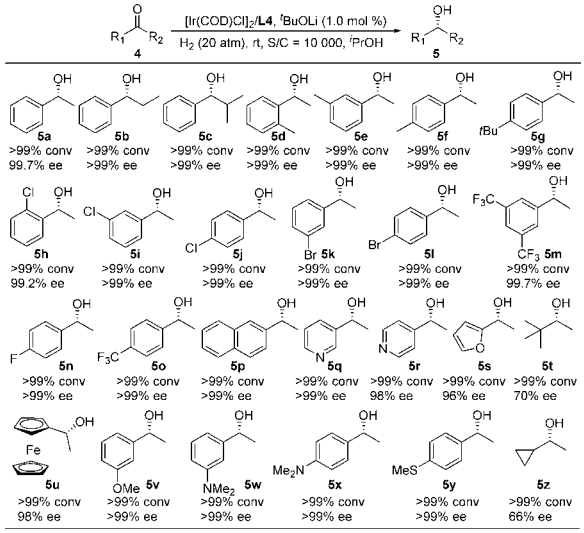


entry	base	ligand	conv (%)[b]	ee (%)[c]
1	^{t}BuOK	**L1**	>99	89
2	^{t}BuONa	**L1**	>99	94
3	MeONa	**L1**	>99	94
4	K_2CO_3	**L1**	97	89
5	Cs_2CO_3	**L1**	>99	78
6	^{t}BuOLi	**L1**	>99	96
7	–	**L1**	NR	NA
8	^{t}BuOLi	**L2**	>99	96
9	^{t}BuOLi	**L3**	>99	98
10	^{t}BuOLi	**L4**	>99	>99
11	^{t}BuOLi	**L5**	NR	NA

[a]Reaction conditions: 2.0 mmol scale, 0.005 mol % $[Ir(COD)Cl]_2$, 0.0105 mol % ligand, 1.0 mol % base, 2.0 mL of ^{i}PrOH, rt (25−30 °C). [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis. NR = no reaction. NA = not available.

Having established the optimal reaction conditions (Ir-**L4**/20 atm H_2/1.0 mol % ^{t}BuOLi, S/C = 10 000/rt), we explored various simple ketones to evaluate the substrate scope. The results are summarized in Scheme 2. A series of alkyl aryl ketones were hydrogenated affording chiral alcohols with excellent results (almost all products up to >99% ee, >99% conversions). Alkyl aryl ketones (**4a**−**4p**, **4v**−**4y**) containing different substitution patterns (*ortho*-, *meta*-, *para*-) at the phenyl ring were hydrogenated smoothly, regardless of their electronic properties (electron-neutral, electron-rich, electron-deficient). It is worth mentioning that heterocyclic substrates (**4q**−**4s**) also proceeded

Scheme 2. Asymmetric Hydrogenation of Various Ketones with Catalyst Ir-L4[a]



[a]Reaction condition was the same with Table 2, for substrates **4q**−**4u**, **4y**−**4z**: S/C = 1000. The conversion was determined by ^{1}H NMR analysis; the ee was determined by GC or HPLC analysis.

DOI: 10.1021/acs.orglett.6b03862
Org. Lett. 2017, 19, 690−693

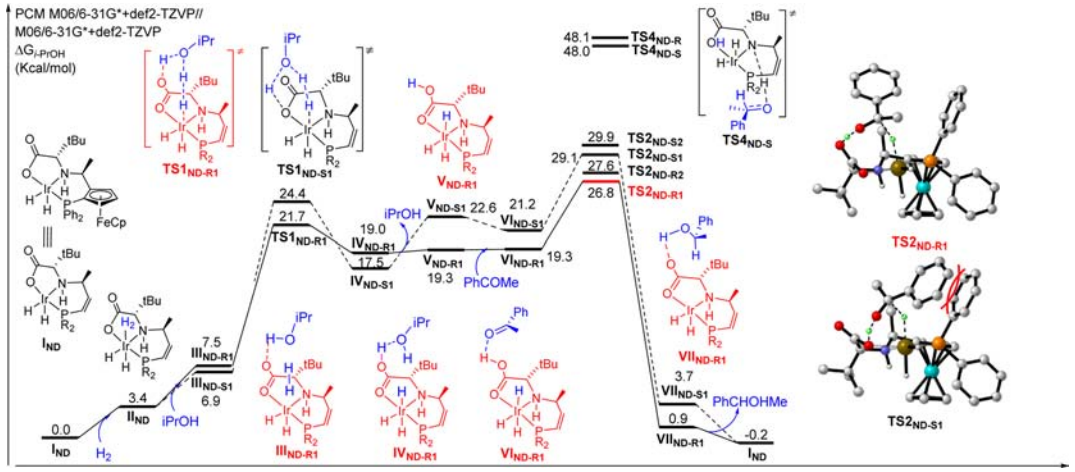


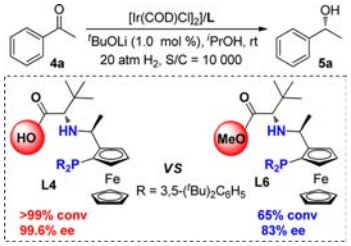
Figure 3. Free energy profile for the key reaction pathways of the Ir-catalyzed asymmetric hydrogenation in solution by M06/6-31G*+def2-TZVP method.

efficiently with >99% conversion and 96 to >99% ee. The challenging aliphatic substrates *tert*-butyl (**4t**) and cyclopropyl (**4z**) methyl ketone also worked well with moderate enantioselectivities (66−70% ee). To our delight, ferrocene-substituted ketone (**4u**) reacted smoothly to produce chiral ferrocene-substituted alcohol (**5u**) with 98% ee, which is an important skeleton for the construction of chiral ligands.

To shed light on the reaction mechanism, systematic DFT (M06/6-31G*+def2-TZVP method) calculations have been carried out by using the **L1** ligand and substrate acetophenone **4a**.[9a,b,10] Our calculations suggest that the most favorable pathway initiates with a Ir(III)-dihydride complex ($\mathbf{I_{ND}}$, Figure 3), which is derived from reaction of the Ir(I) precursor, **L1**, the base, and one H_2 molecule along with dissociation of the COD ligand (Scheme S1). Then, another H_2 molecule coordinates to $\mathbf{I_{ND}}$ to form $\mathbf{II_{ND}}$. The carboxylate group and metal facilitate heterolytic H_2 cleavage[9c] with assistance of one alcohol molecule (as a proton relay) to give an active Ir(III)-trihydride intermediate $\mathbf{V_{ND}}$. The barrier for this step is about 21.7−24.4 kcal/mol in ^{i}PrOH solution (while the barrier is dramatically increased to 33.6−34.5 kcal/mol without the proton relay). Moreover, four conformers for the Ir(III)-trihydride intermediate were found: $\mathbf{V_{ND}}$, $\mathbf{V_{NU}}$, $\mathbf{V_{NDF}}$, and $\mathbf{V_{NUF}}$ (Figure S2).[11] $\mathbf{V_{ND}}$ (i.e., $\mathbf{V_{ND\text{-}R1}}$ and $\mathbf{V_{ND\text{-}S1}}$) is the most reactive one for the subsequent rate- and enantio-determining hydrogenation. The substrate coordinates to $\mathbf{V_{ND\text{-}R1}}$ to form a H-bond in $\mathbf{VI_{ND\text{-}R1}}$. Afterward, stepwise transfers of proton from the acidic $-CO_2H$ group with hydride from the Ir−H part to the substrate[9c] (outer-sphere mechanism) occur. The pathway via $\mathbf{TS2_{ND\text{-}R1}}$ leading to the (*R*)-alcohol has the lowest barrier. More steric repulsion between the Ph part of the substrate and the ferrocene part (Figure 4) in the (*S*)-form transition states than the (*R*)-form transition states leads to the observed enantioselectivity (the computed ee value: 96% at 300 K). After the product dissociates, $\mathbf{I_{ND}}$ is regenerated for the next catalytic cycle. Another outer-sphere pathway through stepwise transfer from the less acidic N−H group requires much higher barriers (about 48.0 kcal/mol, Figure S5) and should be excluded. These results suggest the key role of the carboxylic acid group of the ligand for this hydrogenation.

In order to further investigate the role of the −COOH group of the f-Ampha ligand, we synthesized ligand **L6** by replacing the −COOH group with methyl ester. Poor conversion and moderate enantioselectivity were observed under the same conditions (65% conversion, 83% ee, Scheme 3) in the Ir/**L6**-catalyzed asymmetric hydrogenation of acetophenone **4a**. The −COOH group of f-Ampha ligand played an important role in this transformation. Our calculations showed that the free energy difference between two enantio-determining (*R*- and *S*-) transition states is reduced to 0.3 and 1.0 kcal/mol if the carboxylate group in ligands **L1** and **L4** are esterified, respectively.

Scheme 3. Control Experiments



The Ir-**L4** complex was very stable and exhibited high catalytic activity. When the catalyst loading was decreased to 0.0002 mol % (S/C = 500 000), the asymmetric hydrogenation of acetophenone **4a** on a 12.0 g scale proceeded well providing product **5a** with full conversion and >99% ee within 60 h at rt (Scheme 4).

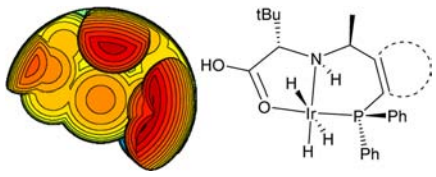
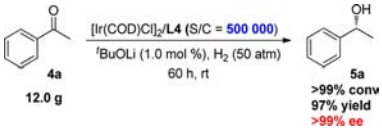


Figure 4. Steric map[9d] for intermediate $\mathbf{V_{ND\text{-}R1}}$ (the top view from the ligand; red (more bulky) and green (less bulky)). The ferrocene part is simplified for clarity.

Scheme 4. Asymmetric Hydrogenation of 4a with High S/C



DOI: 10.1021/acs.orglett.6b03862
Org. Lett. 2017, 19, 690−693

In summary, we successfully developed a series of new tridentate f-Ampha ligands with high air stability. They exhibited excellent performance in Ir-catalyzed asymmetric hydrogenation of simple ketones affording chiral alcohols (full conversions, almost all products up to >99% ee, TON up to 500 000). And the DFT calculations showed that the carbonyl group of the −COOH group in f-Ampha ligands coordinated with iridium, and the −OH group was involved with the formation of O−H···substrate interaction with a new catalytic bifunctional mode. Control experiments identified the importance of the −COOH group. Our f-Ampha ligands are extremely easily accessible and highly stable with a low cost, which motivates us to explore their application in other asymmetric reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03862.

Experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xumu@whu.edu.cn.
*E-mail: xiuqindong@whu.edu.cn.
*E-mail: oscarchung@sustc.edu.cn.

ORCID

Lung Wa Chung: 0000-0001-9460-7812
Xumu Zhang: 0000-0001-5700-0608

Author Contributions

§J.Y. and J.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the grant from Wuhan University (203413100003), the support of the Important Sci-Tech Innovative Project of Hubei Province (2015ACA058), the National Natural Science Foundation of China (Grant No. 21372179, 21432007, 21473086, 21502145), and the Shenzhen Peacock Program (KQTD20150717103157174).

■ REFERENCES

(1) Selected examples: (a) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer: Berlin, 1989; Vol. *5*, p 115. (b) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 1993; p 1. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2. (d) Ohkuma, T.; Noyori, R. In *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. *2*, p 25. (e) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (f) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. (g) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (h) *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007. (i) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(2) Selected examples: (a) Rogawski, M. A.; Löscher, W. *Nat. Rev. Neurosci.* **2004**, *5*, 553. (b) Almeida, L.; Soares-Da-Silva, P. *Neurotherapeutics* **2007**, *4*, 88. (c) Creighton, C. J.; Ramabadran, K.; Ciccone, P. E.; Liu, J.; Orsini, M. J.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4083. (d) Cui, J. J.; Tran-Dubé, M.; Shen, H.; Nambu, M.; Kung, P.-P.; Pairish, M.; Jia, L.; Meng, J.; Funk, L.; Botrous, I.; McTigue, M.; Grodsky, N.; Ryan, K.; Padrique, E.; Alton, G.; Timofeevski, S.; Yamazaki, S.; Li, Q.; Zou, H.; Christensen, J.; Mroczkowski, B.; Bender, S.; Kania, R. S.; Edwards, M. P. *J. Med. Chem.* **2011**, *54*, 6342.

(3) Selected examples: (a) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (b) Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288. (c) Li, W.; Sun, X.; Zhou, L.; Hou, G.; Yu, S.; Zhang, X. *J. Org. Chem.* **2009**, *74*, 1397. (d) Xie, J.-H.; Bao, D.-H.; Zhou, Q.-L. *Synthesis* **2015**, *47*, 460.

(4) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Hashiguchi, S.; Noyori, R. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Doucet, H.; Ohkuma, T.; Murata, K.; Yok-ozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703. (d) Ohkuma, T.; Koi-zumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529.

(5) Selected examples: (a) Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173. (b) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. (c) Henschke, J. P.; Burk, M. J.; Malan, C. G.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300. (d) Hu, A.; Ngo, H. L.; Lin, W. *Org. Lett.* **2004**, *6*, 2937. (e) Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Sandoval, C.; Noyori, R. *J. Am. Chem. Soc.* **2006**, *128*, 8724. (f) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 14960. (g) Hedberg, C.; Källström, K.; Arvidsson, P. I.; Brandt, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2005**, *127*, 15083. (h) Jolley, K. E.; Zanotti-Gerosa, A.; Hancock, F.; Dyke, A.; Grainger, D. M.; Medlock, J. A.; Nedden, H. G.; Le Paih, J. J. M.; Roseblade, S. J.; Seger, A.; Sivakumar, V.; Prokes, I.; Morris, D. J.; Wills, M. *Adv. Synth. Catal.* **2012**, *354*, 2545. (i) Jiang, Y.-T.; Jiang, Q.-Z.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817. (j) Yamamura, T.; Nakatsuka, H.; Tanaka, S.; Kitamura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9313. (k) Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7329. (l) Wu, W.; Liu, S.; Duan, M.; Tan, X.; Chen, C.; Xie, Y.; Lan, Y.; Dong, X.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 2938. (m) Clarke, M. L.; Díaz-Valenzuela, M. B.; Slawin, A. M. Z. *Organometallics* **2007**, *26*, 16. (n) Phillips, S. D.; Fuentes, J. A.; Clarke, M. L. *Chem. - Eur. J.* **2010**, *16*, 8002.

(6) Nie, H.-F.; Yao, L.; Li, B.; Zhang, S.-Y.; Chen, W.-P. *Organometallics* **2014**, *33*, 2109.

(7) (a) Gischig, S.; Togni, A. *Organometallics* **2004**, *23*, 2479. (b) Chen, W.-P.; Mbafor, W.; Roberts, S. M.; Whittall, J. *J. Am. Chem. Soc.* **2006**, *128*, 3922.

(8) (a) Hu, X.-P.; Chen, H.-L.; Zheng, Z. *Adv. Synth. Catal.* **2005**, *347*, 541. (b) Zhou, Z.-M.; Zhang, Y.-M. *Synth. Commun.* **2005**, *35*, 2401.

(9) (a) See computational details in Supporting Information. Our mechanism is qualitatively supported by M06-L and B3LYP-D3 methods (Tables S2, S4, and S6). (b) Cheng, G.-J.; Zhang, X.; Chung, L. W.; Xu, L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2015**, *137*, 1706. (c) Tan, X.; Wang, G.; Zhu, Z.; Ren, C.; Zhou, J.; Lv, H.; Zhang, X.; Chung, L. W.; Zhang, L.; Zhang, X. *Org. Lett.* **2016**, *18*, 1518. (d) Falivene, L.; Credendino, R.; Poater, A.; Petta, A.; Serra, L.; Oliva, R.; Scarano, V.; Cavallo, L. *Organometallics* **2016**, *35*, 2286.

(10) Recent computational studies on hydrogenation of ketones: (a) Hayes, J. M.; Deydier, E.; Ujaque, G.; Lledós, A.; Malacea-Kabbara, R.; Manoury, E.; Vincendeau, S.; Poli, R. *ACS Catal.* **2015**, *5*, 4368. (b) Geilen, F. M.; Engendahl, B.; Hölscher, M.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2011**, *133*, 14349. (c) Zuo, W.; Prokopchuk, D. E.; Lough, A. J.; Morris, R. H. *ACS Catal.* **2016**, *6*, 301. (d) Liu, Y.; Gridnev, I. D.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 1901. (e) Dub, P. A.; Gordon, J. C. *Dalton Trans.* **2016**, *45*, 6756.

(11) ND, NU, NDF, and NUF representative orientation of the NH group downward (D), upward (U), downward with a facial coordination (DF), and upward with a facial coordination (UF), respectively.

DOI: 10.1021/acs.orglett.6b03862
Org. Lett. 2017, 19, 690−693