Organic LETTERS

Letter

pubs.acs.org/OrgLett

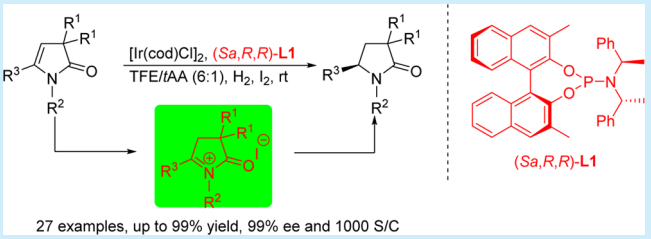
Iridium-Catalyzed Asymmetric Hydrogenation of β,γ-Unsaturated γ-Lactams: Scope and Mechanistic Studies

Qianjia Yuan,[†] Delong Liu,*[,‡] and Wanbin Zhang*[,†,‡]

[†]School of Chemistry and Chemical Engineering and [‡]School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. China

Supporting Information

ABSTRACT: An efficient asymmetric hydrogenation of β,γ-unsaturated γ-lactams using an iridium−phosphoramidite complex is reported. The chiral γ-lactams were obtained in excellent yields and enantioselectivities (up to 99% yield and 99% ee). The mechanistic studies indicated that the reduced products were obtained via the hydrogenation of the *N*-acyliminium cations, generated from β,γ-unsaturated γ-lactams, which was verified by ^{1}H NMR analysis. The reaction was carried out at a reduced catalyst loading of 0.1 mol %, and the reduced products can be transformed to two potential bioactive compounds. A new route is provided for the synthesis of chiral γ-lactams.



γ-Lactams, bearing chiral 5-carbon atoms, exist as key structural elements in many natural products and bioactive molecules and are useful building blocks for the total synthesis of natural products and chiral auxiliaries (Figure 1).[1] For these reasons,

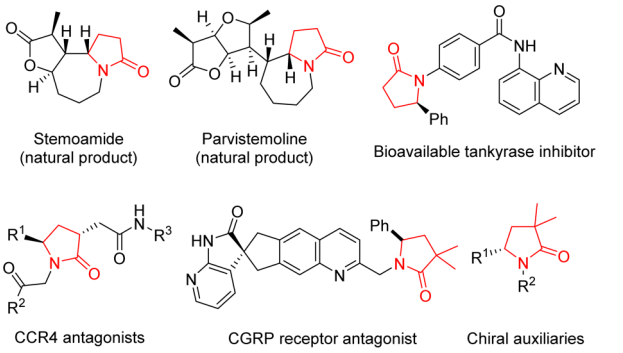
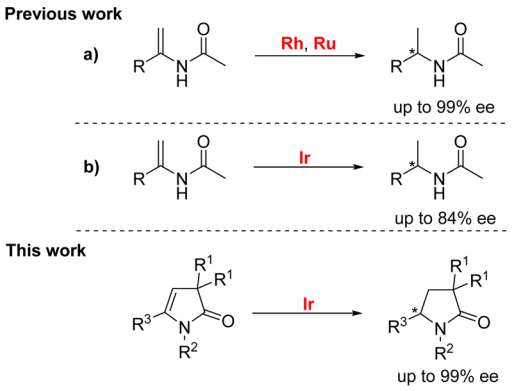


Figure 1. Representative structures of natural products, bioactive molecules, and chiral auxiliaries containing a 5-substituted γ-lactam moiety.

the development of efficient methodologies for the enantioselective synthesis of γ-lactam derivatives has attracted much attention.[2] However, no reports on the asymmetric hydrogenation of β,γ-unsaturated γ-lactams for the preparation of chiral γ-lactams have been published.

Transition-metal-catalyzed asymmetric hydrogenation reactions hold a prominent position in organic synthesis because of their operational simplicity, high atom economy, and low environmental impact.[3,4] Asymmetric hydrogenations of enamides catalyzed by Rh and Ru complexes bearing chiral phosphine ligands are elegant and efficient methods for the enantioselective synthesis of chiral amides (Scheme 1a).[3b,e] In

Scheme 1. Asymmetric Hydrogenation of Enamides



these hydrogenation reactions, the carbonyl group of the enamide in the substrate is required in order to obtain high enantioselectivity by forming a chelate complex with the metal of the catalyst in the transition state.[3b] The asymmetric hydrogenation of cyclic enamides, i.e., unsaturated lactams, catalyzed by Rh and Ru complexes has not been reported, possibly due to the inability of the carbonyl group of the enamide in the cyclic species to coordinate with the metal center of the catalyst. In contrast to Rh and Ru diphosphine complexes, Ir-based catalysts do not require a coordinating group in close proximity to the C=C bond and, therefore, enable the hydrogenation of a much wider range of alkenes.[5] The Ir-catalyzed asymmetric hydrogenation of enamides has been realized with moderate enantioselectivities (Scheme 1b);[6]

Received: January 18, 2017

DOI: 10.1021/acs.orglett.7b00171
Org. Lett. XXXX, XXX, XXX−XXX

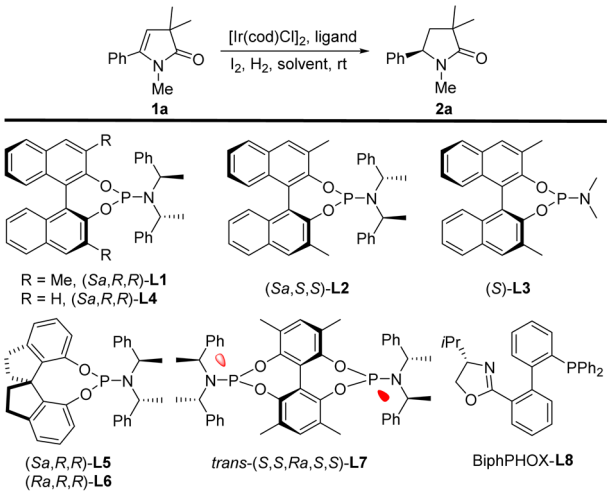
however, first direct asymmetric hydrogenation of endocyclic enamides is yet to be reported and still remains a challenge.

Our group has long been interested in developing novel substrates and catalytic systems for the asymmetric hydrogenations.[7] In continuation of these studies, we here report the first asymmetric hydrogenation of β,γ-unsaturated γ-lactams catalyzed by an iridium−phosphoramidite complex for the synthesis of chiral γ-lactam derivatives in excellent yields and enantioselectivities (Scheme 1).

Compound **1a** was selected as a model substrate because γ-lactams bearing 3,3-dimethyl substituents are also useful building blocks for the synthesis of bioactive molecules and chiral auxiliaries.[1b,i] Additionally, it can be readily prepared and is relatively stable. Studies to elucidate optimal reaction conditions for the asymmetric hydrogenation of **1a** using a privileged phosphoramidite ligand **L1** were undertaken (Table 1).[8] The reaction solvent has a significant influence on the reaction conversion and product enantioselectivity.[9] Notably, I_2 was paramount to the success of the hydrogenation reaction and has been used successfully in several iridium-catalyzed asymmetric hydrogenation reactions.[10] Finally, the ratio of TFE to *tert*-amyl alcohol was tested (entries 1−5). When the ratio of TFE/*t*AA was adjusted to 6:1 (v/v), 94% ee and full conversion were obtained (entry 4). Other binaphthyl phosphoramidite ligands including our newly prepared ligand **L2**, reported ligands **L3** and **L4**, and chiral spiro phosphoramidite ligand **L5** and **L6** were also tested, and all were inferior to **L1** (entries 6−10 vs 4). Our previously developed D_2-symmetric biphenyl phosphoramidite ligand **L7**, which has provided excellent behavior in asymmetric catalysis, displayed unsatisfactory results for this reaction (entry 11).[11] Axially unfixed P,N-ligand **L8**, which has provided excellent results in iridium-catalyzed asymmetric hydrogenations of exocyclic α,β-unsaturated carbonyl compounds, was almost unreactive (entry 12).[7a,b,d] Reactions with P,N-ligand (*S*)-*t*Bu-PHOX and diphosphine ligand (*S*)-BINAP gave poor conversions and enantioselectivities (entries 13 and 14).

With the optimized reaction conditions in hand, a variety of β,γ-unsaturated γ-lactams were tested (Scheme 2). First, the influence of the substituted group R^2 on the nitrogen atom of the substrate was examined. The reduction of **1** bearing *N*-Bn (benzyl), *N*-PMB (4-methoxybenzyl), or *N*-DMPM (3,4-dimethoxybenzyl) groups gave the corresponding products with better enantioselectivities than those bearing *N*-Me or *N*-

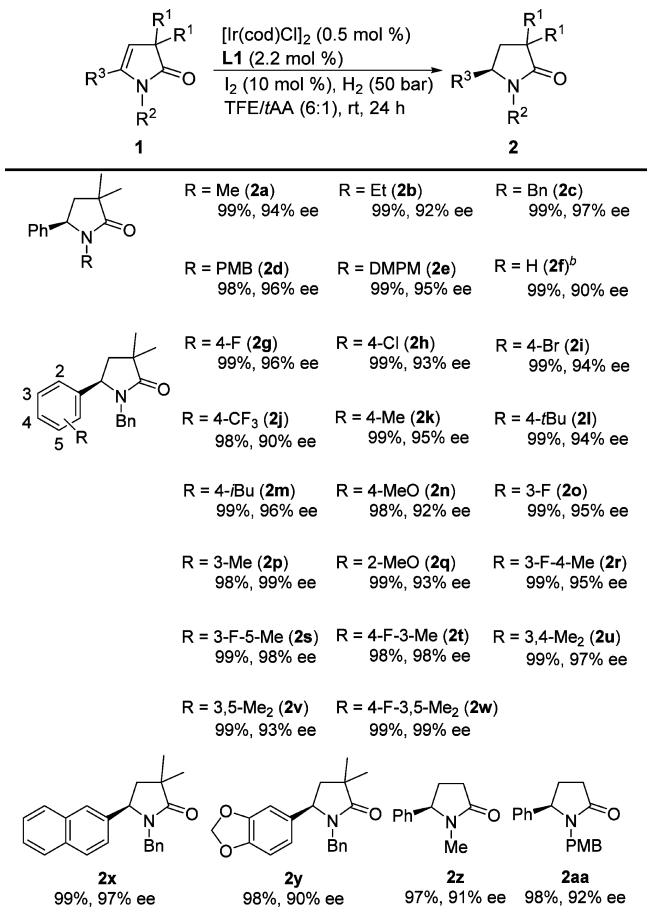
Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	solvent (v/v)	conv[b] (%)	ee[c] (%)
1	**L1**	TFE/*t*AA (1:1)	69	72 (*R*)
2[d]	**L1**	TFE/*t*AA (2:1)	89	89 (*R*)
3	**L1**	TFE/*t*AA (4:1)	>99	91 (*R*)
4[e]	**L1**	TFE/*t*AA (6:1)	>99	94 (*R*)
5[f]	**L1**	TFE/*t*AA (8:1)	>99	86 (*R*)
6[e]	**L2**	TFE/*t*AA (6:1)	>99	80 (*R*)
7[e]	**L3**	TFE/*t*AA (6:1)	61	16 (*R*)
8[e]	**L4**	TFE/*t*AA (6:1)	28	38 (*R*)
9[e]	**L5**	TFE/*t*AA (6:1)	>99	62 (*S*)
10[e]	**L6**	TFE/*t*AA (6:1)	>99	51 (*R*)
11[e,g]	**L7**	TFE/*t*AA (6:1)	45	9 (*S*)
12[e,g]	**L8**	TFE/*t*AA (6:1)	<5	−
13[e,g]	(*S*)-*t*Bu-PHOX	TFE/*t*AA (6:1)	17	<5
14[e,g]	(*S*)-BINAP	TFE/*t*AA (6:1)	26	<5

[a]Reaction was conducted on a 0.2 mmol scale in 2.0 mL of the solvent under 50 bar H_2 at rt for 24 h in the presence of $[Ir(cod)Cl]_2$ (0.5 mol %), ligand (2.2 mol %), and I_2 (10 mol %). [b]Determined by ^1H NMR analysis. [c]Determined by chiral HPLC analysis. [d]TFE/*t*AA (1.4 mL + 0.7 mL). [e]TFE/*t*AA (1.8 mL + 0.3 mL). [f]TFE/*t*AA (1.6 mL + 0.2 mL). [g]Ir/ligand = 1:1.1. cod = 1,5-cyclooctadiene. TFE = 2,2,2-trifluoroethanol. *t*AA = *tert*-amyl alcohol.

Scheme 2. Substrate Scope[a]



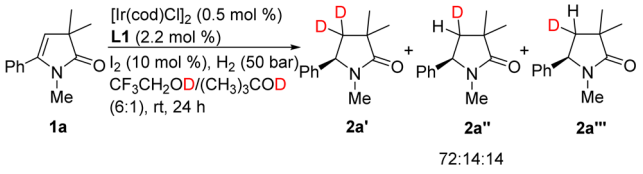
[a]Reaction was conducted on **1** (0.2 mmol) in TFE/*t*AA (6:1 v/v, 2.1 mL) under 50 bar H_2 at rt for 24 h, in the presence of $[Ir(cod)Cl]_2$ (0.5 mol %), **L1** (2.2 mol %), and I_2 (10 mol %). Isolated yield. ee was determined by chiral HPLC analysis. [b]Reaction solvent is HFIP/*t*AA (2:1 v/v, 2.1 mL). HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

DOI: 10.1021/acs.orglett.7b00171
Org. Lett. XXXX, XXX, XXX−XXX

Et groups (**2c**–**e** vs **2a** and **2b**). The reaction of **1** bearing a free *N*-H group could also afford the corresponding product **2f** with 90% ee. Benzyl was selected as the nitrogen atom substituent for the examination of substrates bearing different 5-substituted R^3 groups. When R^3 was a phenyl group bearing electron-withdrawing F, Cl, Br, or CF_3 substituents or electron-donating Me, *t*Bu, *i*Bu, or MeO substituents at the *para*-position, the reduced products **2g**–**n** were obtained in high enantioselectivities and excellent yields. With a F or Me substituent at the *meta*-position of the phenyl ring, the related reduced products **2o** and **2p** were obtained in 95% and 99% ee, respectively. A substrate with a MeO substituent at the *ortho*-position of the phenyl ring, gave the reduced product **2q** in 93% ee. Substrates with two or three substituents located at different positions of the phenyl ring were reduced in 93–99% ee (**2r**–**w**). A substrate substituted with a fused-ring aryl, 2-naphthyl, gave the reduced product **2x** in 97% ee. A substrate with a 3,4-methylenedioxy group on the phenyl ring was reduced in 90% ee (**2y**). *β*,*γ*-Unsaturated *γ*-lactams with no substituents at the 3-position isomerized easily to their corresponding *α*,*β*-unsaturated *γ*-lactams,[12] hydrogenation of which gave racemic products. Therefore, asymmetric hydrogenation of *β*,*γ*-unsaturated *γ*-lactams with no substituents at the 3-position was a more challenging problem. To our delight, using our catalytic system the reduced products **2z** and **2aa** could be obtained with 91% and 92% ee, respectively. The absolute configuration of **2i** was determined as *R* by means of X-ray crystallography. In addition, other types of enamides were also tested with the optimized reaction conditions.[9]

To gain insight into the reaction mechanism, a deuterium-labeling experiment was conducted (Scheme 3). The use of CF_3CH_2OD/*t*BuOD (6:1) as the reaction solvent afforded *β*-deuterated products **2a′**, **2a″**, and **2a‴** in a ratio of 72:14:14.

Scheme 3. Deuterium-Labeling Experiment

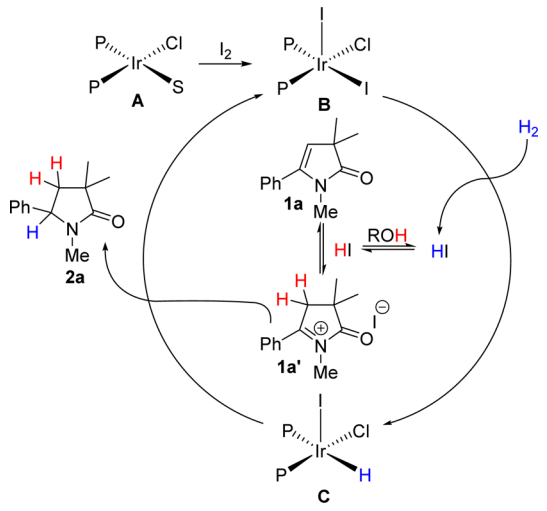


On the basis of the above experimental results, a catalytic cycle for the iridium-catalyzed asymmetric hydrogenation of *β*,*γ*-unsaturated *γ*-lactams has been proposed (Scheme 4). The oxidative addition of I_2 to Ir(I) precursor **A** generates the Ir(III) complex **B**.[10a] Heterolytic cleavage of H_2 generates Ir(III)–H species **C** and HI. In the presence of HI, the *N*-acyliminium cation **1a′** is generated via protonation and isomerization of *β*,*γ*-unsaturated *γ*-lactam **1a**, which was verified by ^{1}H NMR analysis.[9] Hydride transfer from complex **C** to the *N*-acyliminium cation **1a′** may proceed via an outer sphere mechanism to give the reduced product **2a** and regenerate the Ir(III) complex **B**.

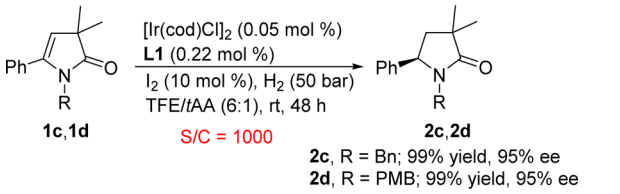
To evaluate the efficiency of our developed catalytic system, a ratio of S/C = 1000 was tested, and the reduced products **2c** and **2d** were both obtained in 95% ee with quantitative yields in 48 h (Scheme 5).

To demonstrate the potential of this simple and highly efficient catalytic asymmetric hydrogenation, further transformations of the reduced products were carried out as shown in Scheme 6. Compound **2d** was transformed to compound **2f**

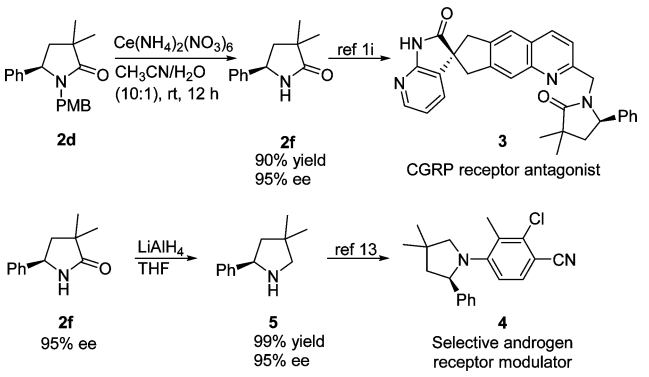
Scheme 4. Proposed Reaction Mechanism



Scheme 5. Efficiency of the Catalytic System



Scheme 6. Transformations of the Product 2d



easily via removal of the *N*-protecting group in 90% yield and without a loss in enantioselectivity. Compound **3**, a potential CGRP receptor antagonist, can be synthesized from **2f**.[1i] Compound **2f** was readily converted into **5** by reduction. Potential selective androgen receptor modulator **4** can be readily prepared from **5**.[13]

In summary, an asymmetric hydrogenation of *β*,*γ*-unsaturated *γ*-lactams for the preparation of chiral *γ*-lactams was realized using an iridium–phosphoramidite complex. The chiral *γ*-lactams were obtained in excellent yields and enantioselectivities (up to 99% yield and 99% ee). Deuterium-labeling experiments indicated that the reduced products were obtained via the hydrogenation of the *N*-acyliminium cations, generated from *β*,*γ*-unsaturated *γ*-lactams, rather than directly obtained by the hydrogenation of the latter. The *N*-acyliminium cationic intermediate was verified by ^{1}H NMR analysis. The reaction was also successful at a reduced catalyst loading of 0.1 mol %. Potential CGRP receptor antagonist **3** and potential selective

DOI: 10.1021/acs.orglett.7b00171
Org. Lett. XXXX, XXX, XXX–XXX

androgen receptor modulator **4** could be prepared from the reduced products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra, HPLC data, crystal data, and crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00171.

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra, HPLC data, and crystal data (PDF)

Crystallographic data for compound **2i** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dlliu@sjtu.edu.cn.

*E-mail: wanbin@sjtu.edu.cn.

ORCID

Wanbin Zhang: 0000-0002-4788-4195

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by the National Natural Science Foundation of China (Nos. 21232004, 21372152, 21472123, and 21672142), Program of Shanghai Subject Chief Scientists (No.14XD1402300), and the Instrumental Analysis Center of SJTU for characterization.

■ REFERENCES

(1) (a) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571. (b) Davies, S. G.; Dixon, D. J.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron: Asymmetry* **2002**, *13*, 647. (c) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355. (d) Kwan, C.-Y.; Harrison, P. H. M.; Kwan, T. K. *Vasc. Pharmacol.* **2003**, *40*, 35. (e) Newhouse, B.; Allen, S.; Fauber, B.; Anderson, A. S.; Eary, C. T.; Hansen, J. D.; Schiro, J.; Gaudino, J. J.; Laird, E.; Chantry, D.; Eberhardt, C.; Burgess, L. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5537. (f) Liu, H.; He, X.; Phillips, D.; Zhu, X.; Yang, K.; Lau, T.; Wu, B.; Xie, Y.; Nguyen, T. N.; Wang, X. Compounds and Compositions as Inhibitors of Cannabinoid Receptor 1 Activity. WO2008076754, June 26, 2008. (g) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908. (h) Bregman, H.; Chakka, N.; Guzman-Perez, A.; Gunaydin, H.; Gu, Y.; Huang, X.; Berry, V.; Liu, J.; Teffera, Y.; Huang, L.; Egge, B.; Mullady, E. L.; Schneider, S.; Andrews, P. S.; Mishra, A.; Newcomb, J.; Serafino, R.; Strathdee, C. A.; Turci, S. M.; Wilson, C.; DiMauro, E. F. *J. Med. Chem.* **2013**, *56*, 4320. (i) Stump, C. A.; Quigley, A. G.; Theberge, C. R.; Wood, M. R. CGRP Receptor Antagonists. U.S. Patent 0,275,017, Sep 18, 2014. (j) Tan, S. W. B.; Chai, C. L. L.; Moloney, M. G.; Thompson, A. L. *J. Org. Chem.* **2015**, *80*, 2661.

(2) Selected reviews: (a) Royer, J., Ed. *Asymmetric Synthesis of Nitrogen Heterocycles*; Wiley-VCH: Weinheim, 2009. (b) Martelli, G.; Orena, M.; Rinaldi, S. *Curr. Org. Chem.* **2014**, *18*, 1373. (c) Ye, L.-W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem.* **2014**, *12*, 1833.

(3) Selected reviews: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) de Vries, J. G., Elsevier, C. J., Eds. *Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, 2007. (c) Börner, A., Ed. *Phosphorus Ligands in Asymmetric Catalysis*; Wiley-VCH: Weinheim, 2008. (d) Blaser, H.-U., Federsel, H.-J., Eds. *Asymmetric Catalysis on Industrial Scale*, 2nd ed.; Wiley-VCH: Weinheim, 2010. (e) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713. (f) Zhang, Z.; Butt, N.; Zhang, W. *Chem. Rev.* **2016**, *116*, 14769.

(4) Selected recent papers: (a) Lyubimov, S. E.; Rastorguev, E. A.; Petrovskii, P. V.; Davankov, V. A. *Russ. Chem. Bull.* **2012**, *61*, 2322. (b) Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G.; Tang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 4235. (c) Liu, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 1978. (d) Bernasconi, M.; Müller, M.-A.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 5385. (e) Lagaditis, P. O.; Sues, P. E.; Sonnenberg, J. F.; Wan, K. Y.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 1367. (f) Dub, P. A.; Henson, N. J.; Martin, R. L.; Gordon, J. C. *J. Am. Chem. Soc.* **2014**, *136*, 3505. (g) Li, Y.; Yu, S.; Wu, X.; Xiao, J.; Shen, W.; Dong, Z.; Gao, J. *J. Am. Chem. Soc.* **2014**, *136*, 4031. (h) Yu, C.-B.; Huang, W.-X.; Shi, L.; Chen, M.-W.; Wu, B.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2014**, *136*, 15837. (i) Wang, Q.; Huang, W.; Yuan, H.; Cai, Q.; Chen, L.; Lv, H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 16120. (j) Peters, B. K.; Zhou, T.; Rujirawanich, J.; Cadu, A.; Singh, T.; Rabten, W.; Kerdphon, S.; Andersson, P. G. *J. Am. Chem. Soc.* **2014**, *136*, 16557. (k) Kuwano, R.; Hashiguchi, Y.; Ikeda, R.; Ishizuka, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 2393. (kl) Lu, L.-Q.; Li, Y.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2015**, *137*, 2763. (m) Li, W.; Schlepphorst, C.; Daniliuc, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2016**, *55*, 3300. (n) Kita, Y.; Hida, S.; Higashihara, K.; Jena, H. S.; Higashida, K.; Mashima, K. *Angew. Chem., Int. Ed.* **2016**, *55*, 8299. (o) Ma, W.; Zhang, J.; Xu, C.; Chen, F.; He, Y.-M.; Fan, Q.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 12891. (p) Shevlin, M.; Friedfeld, M. R.; Sheng, H.; Pierson, N. A.; Hoyt, J. M.; Campeau, L.-C.; Chirik, P. J. *J. Am. Chem. Soc.* **2016**, *138*, 3562. (q) Touge, T.; Arai, T. *J. Am. Chem. Soc.* **2016**, *138*, 11299. (r) Li, M.-L.; Yang, S.; Su, X.-C.; Wu, H.-L.; Yang, L.-L.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2017**, *139*, 541.

(5) Selected a review: Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402.

(6) (a) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem. - Eur. J.* **2004**, *10*, 4198. (b) Erre, G.; Enthaler, S.; Junge, K.; Addis, D.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 1437.

(7) Selected papers: (a) Tian, F.; Yao, D.; Liu, Y.; Xie, F.; Zhang, W. *Adv. Synth. Catal.* **2010**, *352*, 1841. (b) Liu, Y.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 2203. (c) Chen, J.; Liu, D.; Butt, N.; Li, C.; Fan, D.; Liu, Y.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 11632. (d) Liu, Y.; Gridnev, I. D.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 1901. (e) Hu, Q.; Zhang, Z.; Liu, Y.; Imamoto, T.; Zhang, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 2260. (f) Chen, J.; Zhang, Z.; Liu, D.; Zhang, W. *Angew. Chem., Int. Ed.* **2016**, *55*, 8444. (g) Hu, Q.; Chen, J.; Zhang, Z.; Liu, Y.; Zhang, W. *Org. Lett.* **2016**, *18*, 1290.

(8) (a) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486. (b) Zhang, Z.; Xie, F.; Yang, B.; Yu, H.; Zhang, W. *Chin. J. Org. Chem.* **2011**, *31*, 429. (c) Yuan, Q.; Zhang, W. *Chin. J. Org. Chem.* **2016**, *36*, 274.

(9) See details in the Supporting Information.

(10) (a) Wang, D.-W.; Wang, X.-B.; Wang, D.-S.; Lu, S.-M.; Zhou, Y.-G.; Li, Y.-X. *J. Org. Chem.* **2009**, *74*, 2780. (b) Guo, C.; Sun, D.-W.; Yang, S.; Mao, S.-J.; Xu, X.-H.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 90 and references cited therein.

(11) (a) Yang, B.; Xie, F.; Yu, H.; Shen, K.; Ma, Z.; Zhang, W. *Tetrahedron* **2011**, *67*, 6197. (b) Yu, H.; Xie, F.; Ma, Z.; Liu, Y.; Zhang, W. *Adv. Synth. Catal.* **2012**, *354*, 1941. (c) Yu, H.; Xie, F.; Ma, Z.; Liu, Y.; Zhang, W. *Org. Biomol. Chem.* **2012**, *10*, 5137. (d) Wu, X.; Xie, F.; Ling, Z.; Tang, L.; Zhang, W. *Adv. Synth. Catal.* **2016**, *358*, 2510.

(12) Verniest, G.; De Kimpe, N. *Synlett* **2003**, 2013.

(13) Gavardinas, K.; Jadhav, P. K.; Stack, D. R.; Clemens, I. R. Substituted N-Arylpyrrolidines as Selective Androgen Receptor Modulators. WO2006124447, Nov 23, 2006.

DOI: 10.1021/acs.orglett.7b00171
Org. Lett. XXXX, XXX, XXX−XXX