Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

COMMUNICATION

Cite this: DOI: 10.1039/x0xx00000x

Pd-catalyzed enantioselective intramolecular α-arylation of α-substituted cyclic ketones: Facile synthesis of functionalized chiral spirobicycles

Lulu Fan, Shinobu Takizawa,* Yoshiki Takeuchi, Kazuhiro Takenaka and Hiroaki Sasai*

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Catalytic synthesis of chiral spirocyclic ketones was accomplished *via* the Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones. The obtained spirocyclic ketone could be converted into a bifunctional organocatalyst.

The spirobicyclic framework is frequently found in natural products and biologically active compounds.[1] In the last two decades, chiral ligands and organocatalysts with a spiro skeleton have received considerable attention in asymmetric catalysis because of their unique structural properties and high asymmetric induction efficiency.[2,3] However, enantioselective synthesis of optically pure spirobicyclic compounds remains a formidable task because the chiral catalysts must control not only the enantiodiscrimination but also the formation of the quaternary carbon center.[4] Efficient synthesis of chiral spirobicycles with multiple functional groups is more challenging and attractive in organic asymmetric synthesis.[2,4g-k] Herein, we report the facile synthesis of chiral spirobicycles **2** through the Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones **1**. The combination of $Pd(OAc)_2$, (S,R_p)-Josiphos and K_2CO_3 in 1,2-dimethoxyethane (DME) at 90 °C was effective for the dynamic kinetic asymmetric transformation (DYKAT) in the α-arylation of ketones **1**. The functionalized spiro compound **2a** could be converted into the chiral acid–base organocatalyst.

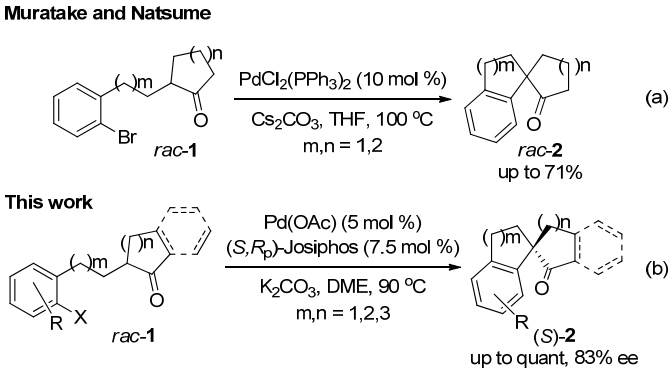
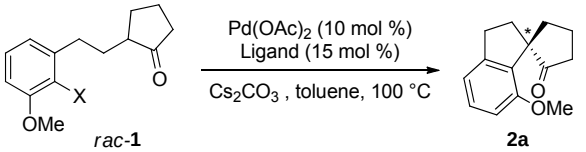


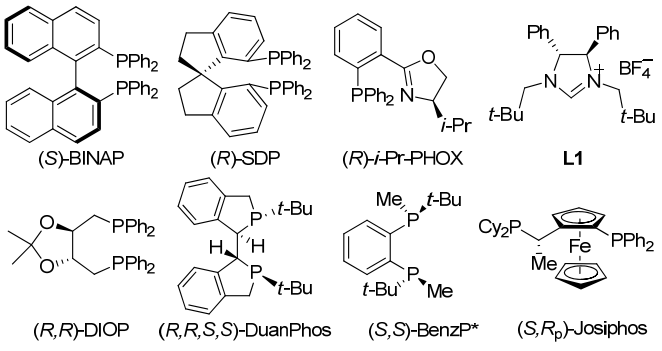
Fig. 1 Enantioselective Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones **1**.

Table 1 Screening of chiral ligands.[a]



Entry	**1** (X)	Ligand	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	**1a** (Br)	—	24	88	—
2	**1a**	(*S*)-BINAP	24	75	5 (*S*)
3	**1a**	(*R*)-SDP	24	59	18 (*R*)
4	**1a**	(*R*)-*i*-Pr-PHOX	48	66	11 (*R*)
5[e]	**1a**	**L1**	48	42	15 (*S*)
6	**1a**	(*R*,*R*)-DIOP	48	85	Rac
7	**1a**	(*R*,*R*,*S*,*S*)-DuanPhos	24	12	61 (*S*)
8	**1a**	(*S*,*S*)-BenzP*	48	77	46 (*R*)
9	**1a**	(S,R_p)-Josiphos	48	58	83 (*S*)
10	**1a′** (I)	(S,R_p)-Josiphos	96	39	53 (*S*)

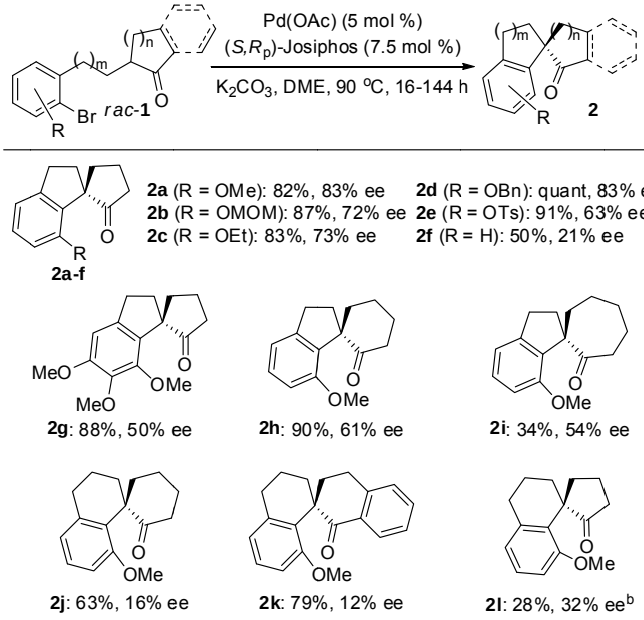
[a]Reaction conditions: **1**/$Pd(OAc)_2$/chiral ligand = 1/0.01/0.15, Cs_2CO_3 (2 eq), toluene (0.2 M). [b]^{1}H-NMR yield using CH_2Br_2 as an internal standard. [c]Determined by HPLC (Chiralpak IA). [d]$PdCl_2(PPh_3)_2$ (10 mol %) was used. [e]NaO*t*-Bu (3 eq) and **L1** (22 mol %) were used.



Transition metal-catalyzed α-arylation of carbonyl groups is a powerful synthetic method for constructing α-arylated compounds; however, asymmetric α-arylation of carbonyl units is still ongoing.[5]

In 1997, Muratake and Natsume reported racemic synthesis of spirobicycles **2** *via* Pd-catalyzed intramolecular α-arylation of cyclic ketones **1** (Fig. 1a).[6] As a continuation of our study of spiro-type catalysts,[7] we became interested in a DYKAT for spirocyclic ketones **2** (Fig. 1b) and their applications to new spiro-type organocatalysts. Initially, we selected **1a** (X = Br) as our model substrate (Table 1) because the OMe group on the aromatic ring could be readily transformed to a Brønsted acid region. Although the steric hindrance caused by multiple substituents on the aromatic ring may prevent the formation of the spiro skeleton, desired racemic **2a** was formed in 88% yield under the reported conditions[6] (Table 1, entry 1). Next we focused on searching for an appropriate chiral ligand to construct **2a** with high optical purity. The use of BINAP, SDP, *i*-Pr-PHOX, or *N*-heterocyclic carbene ligand **L1** provided desired spiro[4.4]nonanone **2a** in moderate-to-good yields (42–75%) with low enantioselectivities (up to 18% ee) (entries 2–5). The reaction with (*R*,*R*)-DIOP afforded **2a** in 85% yield as a racemic mixture (entry 6). The ee values of **2a** increased when P-chiral ligands such as DuanPhos (61% ee, entry 7) and BenzP* (46% ee, entry 8) were used. Among the chiral ligands tested,[8] only the Josiphos ligand, which contains a ferrocene unit, produced good enantioselectivity (83% ee, entry 9). Substrate **1a′** (X = I) failed to provide high enantioselectivity of spiro[4.4]nonanone **2a** (entry 10). The optimal result for **2a** (82% yield, 83% ee) was obtained when the reaction of **1a** was performed in DME at 90 °C in the presence of K_2CO_3 as a base (Scheme 1).[8]

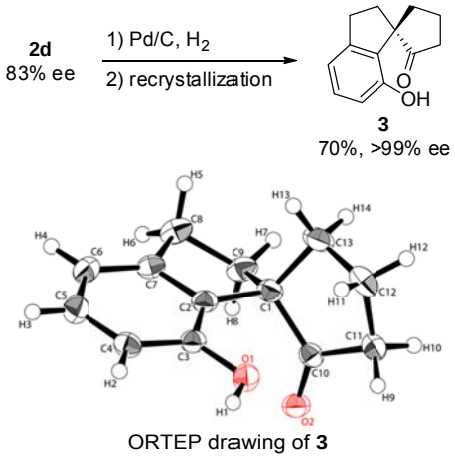
Scheme 1 Substrate scope of Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones **1**.[a]



[a]Reaction conditions: **1**/Pd(OAc)$_2$/chiral ligand = 1/0.05/0.075, K_2CO_3 (2 eq), DME (0.2 M), 90 °C. Yields of isolated **2**. The ee of **2** was determined by HPLC (Chiralpak IA for **2a**, **2c**–**2l** Chiralpak OD-3 for **2b**). [b]DuanPhos was used insted of the Josiphos.[9]

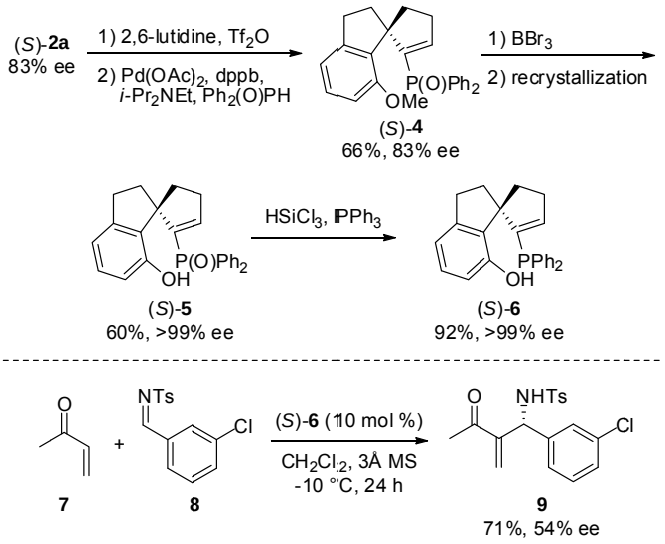
The substrate scope is shown in Scheme 1. During our investigation of the substituent effect on the aromatic ring in racemic **1a**–**1g**, we found that the benzyl group (**1d**: R = OBn) led to the best outcome; spiro[4.4]nonanone **2d** was obtained in quantitative yield with 83% ee. Substrates **1f**, which contained no alkoxy groups, gave spiro[4.4]nonanones **2f** with lower enantioselectivity (21% ee); thus alkoxy substituents on the aromatic ring play an important role in the enantiodiscrimination that produces the chiral spiro[4.4]nonanone skeleton. The present transformation constructed of spiro[4.5], [4.6], and [5.5]alkanones **2h**–**2l** in up to 61% ee. The absolute configuration of spirocyclic ketone **2d** was assigned as *S* by X-ray analysis of deprotected product **3** (Scheme 2).[10]

Scheme 2 Determination of absolute configuration of the spirocyclic ketone.



To demonstrate the potential utility of the spiro compounds, **2a** was transformed to chiral spiro-type organocatalyst **6**. As shown in Scheme 3, **2a** (83% ee) underwent triflation and phosphonation to give **4** with 66% yields in two steps. After demethylation of **4**, recrystallization of **5** (83% ee) produced optically pure **5** in 60% yield. Finally, reduction of phosphine oxide **5** afforded desired acid–base organocatalyst **6** in 92% yield. To evaluate the catalytic activity of our spiro-type organocatalyst, we used (*S*)-**6** for the enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction, which is an atom-economical C–C bond-forming reaction.[11] Preliminary results showed that spiro-type organocatalyst **6** promoted the aza-MBH reaction of **7** with **8** to afford adduct **9** in 71 % yield with 54% ee.

Scheme 3 Preparation of acid–base organocatalyst **6** and its application to the aza-MBH reaction.



Conclusions

We have developed the catalytic and enantioselective synthesis of spirocyclic ketones **2** through the Pd-catalyzed intramolecular α-arylation of α-substituted cyclic ketones **1**. Investigation into the reaction mechanism as well as the development of new spiro-type ligands and organocatalysts from **2** is currently underway.

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research on Innovative Areas -Advanced Molecular Transformations by Organocatalysis- from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan, the CREST project of the Japan Science and Technology Corporation (JST), and JST Advance Catalytic Transformation Program for Carbon Utilization (ACT-C). We acknowledge the technical staff of the Comprehensive Analysis Center of ISIR, Osaka University (Japan).

Notes and references

The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki-shi, Osaka 567-0047, Japan. E-mail: taki@sanken.osaka-u.ac.jp; Fax: +81-6-6879-8469; Tel: +81-6-6879-8466

1 For recent reviews on natural products and biologically active compounds bearing spiro skeletons, see: (*a*) D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas, III, *ACS Catal.*, 2014, **4**, 743; (*b*) S. Dadiboyena, *Eur. J. Med. Chem.*, 2013, **63**, 347; (*c*) M. C. McLeod, M. A. Brimble, D. C. K. Rathwell, Z. E. Wilson and T.-Y. Yuen, *Pure Appl. Chem.*, 2012, **84**, 1379; (*d*) J. C. Green, G. L. I. V. Burnett and T. R. R. Pettus, *Pure Appl. Chem.*, 2012, **84**, 1621; (*e*) A. Bartoli, F. Rodier, L. Commeiras, J.-L. Parrain and G. Chouraqui, *Nat. Prod. Rep.*, 2011, **28**, 763; (*f*) Y.-S. Cai, Y.-W. Guo and K. Krohn, *Nat. Prod. Rep.*, 2010, **27**, 1840; (*g*) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003; (*h*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748.

2. For selected reviews and papers on chiral ligands and catalysts bearing a spiro skeleton, see: (*a*) G. B. Bajracharya, M. A. Arai, P. S. Koranne, T. Suzuki, S. Takizawa and H. Sasai, *Bull. Chem. Soc. Jpn.*, 2009, **82**, 285; (*b*) K. Ding, Z. Han and Z. Wang, *Chem. - Asian J.*, 2009, **4**, 32; (*c*) J.-H. Xie and Q.-L. Zhou, *Acc. Chem. Res.*, 2008, **41**, 581; (*d*) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656; (*e*) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (*f*) Z. Freixa, M. S. Beentjes, G. D. Batema, C. B. Dieleman, G. P. F. van Strijdonck, J. N. H. Reek, P. C. J. Kamer, J. Fraanje, K. Goubitz and P. W. N. M. van Leeuwen, *Angew. Chem., Int. Ed.*, 2003, **42**, 1284.

3. For recent reports in enantioselective catalysis using spiro-type ligands and catalysts, see: (*a*) C. Wu, and J. Zhou, *J. Am. Chem. Soc.*, 2014, **136**, 650; (*b*) X. Wang, P. Guo, Z. Han, X. Wang, Z. Wang and K. Ding, *J. Am. Chem. Soc.*, 2014, **136**, 405; (*c*) X.-L. Xie, S.-F. Zhu, J.-X. Guo, Y. Cai and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2014, **53**, 2978; (*d*) X. Li, D. Chen, H. Gu and X. Lin, *Chem. Commun*., 2014, **50**, 7538; (*e*) Uraguchi, R. Tsutsumi, T. Ooi, *Tetrahedron*, 2014, **70**, 1691; (*f*) S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, H. Sasai, *Asian J. Org. Chem.*, 2014, **3**, 412; (*g*) Z.-Y. Cao, X. Wang, C. Tan, X.-L. Zhao, J. Zhou and K. Ding, *J. Am. Chem. Soc.*, 2013, **135**, 8197; (*h*) Q.-Q. Cheng, S.-F. Zhu, Y.-Z. Zhang, X.-L. Xie and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2013, **135**, 14094; (*i*) J. Hu, Y. Lu, Y. Li and J. Zhou, *Chem. Commun*., 2013, **49**, 9425; (*j*) K.-L. Huang, C. Guo, L.-J. Cheng, L.-G. Xie, Q.-L. Zhou, X.-H. Xu and S.-F. Zhu, *Adv. Synth. Catal.*, 2013, **355**, 2833; (*k*) X. Li, Y. Zhao, H. Qu, Z. Mao and X. Lin, *Chem. Commun.*, 2013, **49**, 1401; (*l*) S. Song, S.-F. Zhu, Y. Li and Q.-L. Zhou, *Org. Lett.*, 2013, **15**, 3722; (*m*) S. Song, S.-F. Zhu, Y.-B. Yu and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2013, **52**, 1556; (*n*) X.-G. Song, S.-F. Zhu, X.-L. Xie and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2013, **52**, 2555; (*o*) V. Sridharan, L. Fan, S. Takizawa, T. Suzuki and H. Sasai, *Org. Biomol. Chem.*, 2013, **11**, 5936; (*p*) P.-C. Yan, X.-Y. Zhang, X.-W. Hu, B. Zhang, X.-D. Zhang, M. Zhao, D.-Q. Che, Y.-Q. Li and Q.-L. Zhou, *Tetrahedron Lett.*, 2013, **54**, 1449; (*q*) P.-C. Yan, G.-L. Zhu, J.-H. Xie, X.-D. Zhang, Q.-L. Zhou, Y.-Q. Li, W.-H. Shen and D.-Q. Che, *Org. Process Res. Dev.*, 2013, **17**, 307; (*r*) B. Zhang, S.-F. Zhu and Q.-L. Zhou, *Tetrahedron Lett.*, 2013, **54**, 2665.

4. For recent reviews and papers on enantioselective synthesis of spiro compounds, see: (*a*) R. Quach, D. F. Chorleya and M. A. Brimble, *Org. Biomol. Chem*., 2014, **12**, 7423; (*b*) C. Guo, M. Schedler, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 10232; (*c*) Z. Zhou, X. Feng, X. Yin and Y.-C. Chen, *Org. Lett.*, 2014, **16**, 2370; (*d*) Y. Huang, C. Zheng, Z. Chai and G. Zhao, *Adv. Synth. Catal.*, 2014, **356**, 579; (*e*) A. K. Franz, N. V. Hanhan and N. R. Ball-Jones, *ACS Catal.*, 2013, **3**, 540; (*f*) L. Hong and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1023; (*g*) P. Zhang, Z. Han, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2013, **52**, 11054; (*h*) X. Jia, Z. Wang, C. Xia and K. Ding, *Catal. Sci. Technol.*, 2013, **3**, 1901; (*i*) X. Wang, P. Guo, X. Wang, Z. Wang and K. Ding, *Adv. Synth. Catal.*, 2013, **355**, 2900; (*j*) X. Wang, Z. Han, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2012, **51**, 936; (*k*) X. Wang, F. Meng, Y. Wang, Z. Han, Y.-J. Chen, L. Liu, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2012, **51**, 9276; (*l*) R. Rios, *Chem. Soc. Rev.*, 2012, **41**, 1060 and references therein.

5. (*a*) P. Novak and R. Martin, *Curr. Org. Chem.*, 2011, **15**, 3233; (*b*) C. C. C. Johansson and T. J. Colacot, *Angew. Chem., Int. Ed.*, 2010, **49**, 676; (*c*) A. C. B. Burtoloso, *Synlett*, 2009, 320; (*d*) L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, 2009.

6. H. Muratake and M. Natsume, *Tetrahedron Lett.*, 1997, **38**, 7581.

7. (*a*) K. Takenaka, S. C. Mohanta and H. Sasai, *Angew. Chem., Int. Ed.*, 2014, **53**, 4675; (*b*) K. Takenaka, Y. D. Dhage and H. Sasai, *Chem. Commun*., 2013, **49**, 11224; (*c*) R. K. Gabr, T. Hatakeyama, K. Takenaka, S. Takizawa, Y. Okada, M. Nakamura and H. Sasai, *Chem. Eur. J.*, 2013, **19**, 9518; (*d*) Y. Yoshida, S. Takizawa and H. Sasai, *Tetrahedron: Asymmetry*, 2012, **23**, 843; (*e*) C. Ramalingan, K. Takenaka and H. Sasai, *Tetrahedron*, 2011, **67**, 2889; (*f*) K. Takenaka, M. Akita, Y. Tanigaki, S. Takizawa and H. Sasai, *Org. Lett.*, 2011, **13**, 3506; (*g*) K. Takenaka, S. Hashimoto, S. Takizawa and H. Sasai, *Adv. Synth. Catal.*, 2011, **353**, 1067; (*h*) S. Takizawa, K. Kiriyama, K. Ieki and H. Sasai, *Chem. Commun.*, 2011, **47**, 9227 and references therein.

8. Screening of other reaction conditions, see ESI.

9. The reaction of **1l** using the Pd-Josiphos gave **2l** in 59% yield with 3% ee.

10. Crystallographic data (*S*)-**3** for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1023103. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk/data_request/cif).

11. For recent reviews on asymmetric MBH reaction, see: (*a*) Y. Wei and M. Shi, *Chem. Rev.*, 2013, **113**, 6659; (*b*) D. Basavaiah and G. Veeraraghavaiah, *Chem. Soc. Rev.*, 2012, **41**, 68; (*c*) S.-X. Wang, X. Han, F. Zhong, Y. Wang and Y. Lu, *Synlett*, 2011, 2766; (*d*) J. Mansilla and J. M. Saa, *Molecules*, 2010, **15**, 709; (*e*) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447; (*f*) Y. Wei and M. Shi, *Acc. Chem. Res.*, 2010, **43**, 1005.