Organic LETTERS

Letter

pubs.acs.org/OrgLett

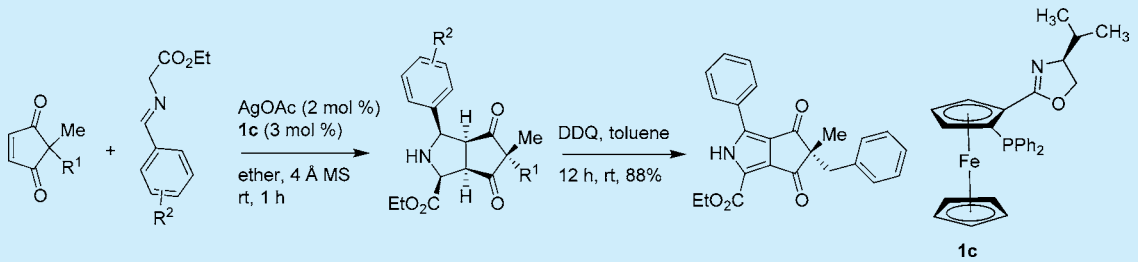
Silver(I)−Ferrophox Catalyzed Enantioselective Desymmetrization of Cyclopentenedione: Synthesis of Highly Substituted Bicyclic Pyrrolidines

Tapas Das,[†] Prasenjit Saha,[†] and Vinod K. Singh*[,†,‡]

[†]Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal-462066, India

[‡]Department of Chemistry, Indian Institute of Technology, Kanpur-208016, India

Supporting Information



ABSTRACT: A highly enantioselective desymmetrization of prochiral cyclopentene-1,3-dione via [3 + 2] cycloaddition of azomethine ylide using a silver(I)−ferrophox complex has been demonstrated. The method has been utilized in the synthesis of highly functionalized enantioenriched 5,5-fused bicyclic pyrrolidine derivatives under mild reaction conditions.

Catalytic enantioselective desymmetrization processes pose a major challenge to constructing highly functionalized synthetically viable motifs.[1,2] Some interesting examples include desymmetrization of prochiral cyclopentene-1,3-dione via alkylation to provide synthons for many biologically active compounds (Scheme 1). For instance, Corey et al. employed enantioselective reduction of cyclopentan-1,3-dione using oxazaborolidine[1a] and Mikami et al. reported a Cu(II)-phosphoramidite catalyzed 1,4 addition of dialkylzinc to cyclopentene-1,3-diones.[1b] Very recently, Mukherjee and co-workers reported conjugate addition of α-angelica lactone and formal C(sp^2)−H alkylation to cyclopentene-1,3-diones by using bifunctional organocatalysts.[1c,d] Although these strategies provide the corresponding products in a highly enantio-/diastereoselective manner, low reaction temperatures (usually −10 to −40 °C) with a prolonged reaction time was required to achieve high chiral induction in almost all the cases. Thus, development of an efficient desymmetrization protocol under mild reaction conditions to synthesize highly functionalized molecules is highly desired.

Our interest in the area comes from the significance of bicyclic pyrrolidine containing scaffolds (Figure 1) in several drugs.[3] Literature reports for building these molecules include asymmetric desymmetrization using chiral transition-metal catalysis.[4] Several chiral complexes containing transition metals such as Zn,[5] Ag,[6] Cu,[7] Au,[8] Ni[9] have been exploited in the asymmetric [3 + 2] 1,3-dipolar cycloadditions of azomethine ylides to construct functionalized bicyclic pyrrolidines. Some recent reports include carrying out such transformations using organocatalysts as well.[10]

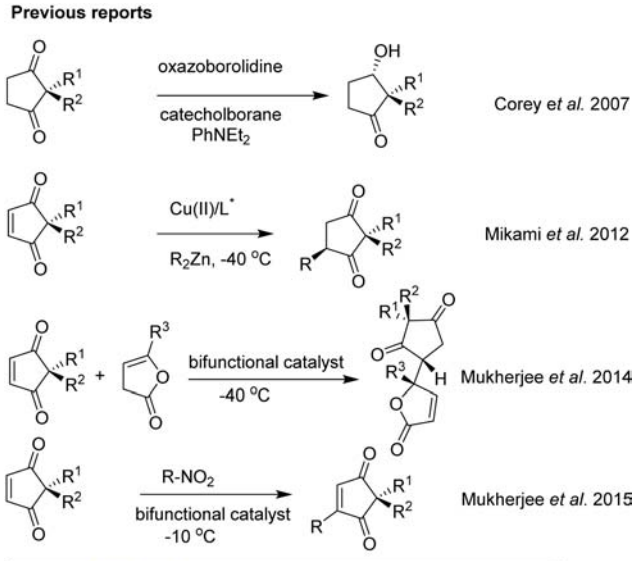
Herein, we propose a chiral Ag(I)−ferrophox catalyzed enantioselective desymmetrization[11] of prochiral cyclopentene-1,3-dione via a [3 + 2] cycloaddition reaction with azomethine ylides to construct highly substituted 5,5-fused bicyclic-pyrrolidines at room temperature under mild reaction conditions.

Initially, prochiral cyclopentene-1,3-dione **2a** as a dipolarophile and azomethine ylide **3a** as a 1,3-dipole were chosen as model substrates for the enantioselective desymmetrization reaction. In the presence of DBU, the reaction between **2a** and **3a** in toluene at room temperature failed to give the desired cyclized product. However, the combination of AgOAc (10 mol %) and DBU (20 mol %) resulted in the desired cycloadducts in 55% yield. As our aim was to investigate the desymmetrization of cyclopentenedione **2a** in a stereoselective manner, we turned our attention to chiral phosphine based ligand systems. The desymmetrization of cyclopentenedione **2a** was carried out in the presence of AgOAc (10 mol %) and *R*-BINAP (11 mol %) in toluene. To our delight, the desymmetrized product was formed as a mixture of diastereoisomers (65:35) where the major one **4a** was isolated in 30% yield and good enantiomeric excess (85%) (Table 1, entry 1). Encouraged by the preliminary results, various mono- and bis-phosphine based chiral ligands **1a−1g** were studied to improve the diastereo- and enantioselectivity of desired desymmetrized cycloadduct **4a**. Sterically, more hindered bis-phosphine ligand (*R*)-DTBM-SEGPHOS did not show any considerable effect in outcome of

Received: September 9, 2015
Published: October 6, 2015

DOI: 10.1021/acs.orglett.5b02582
Org. Lett. 2015, 17, 5088−5091

Scheme 1. Synthesis of Chiral Cyclopentanes *via* Desymmetrization Approach



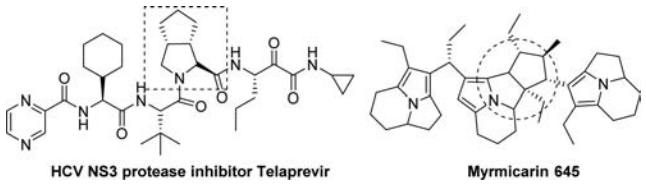
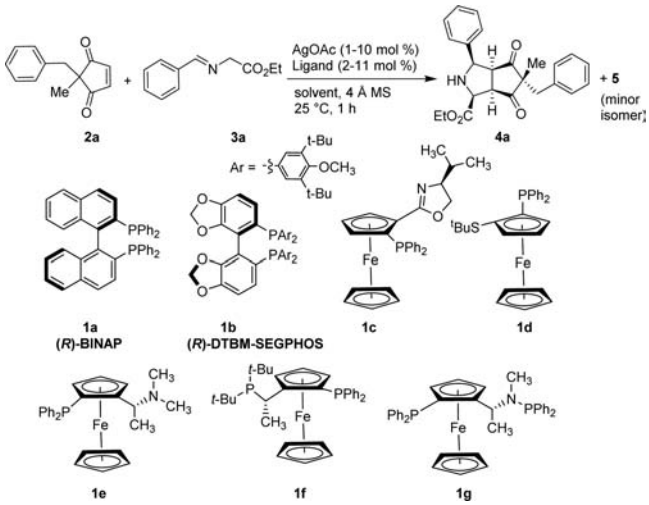


Figure 1. Selected drugs containing bicyclic-pyrrolidine.

Table 1. Catalyst Screening and Optimization of Reaction Conditions[a]



entry	ligand	solvent	yield (%)[b]	dr[c]	*ee* (%)[d]
1	**1a**	toluene	30	65:35	85
2	**1b**	toluene	35	70:30	90
3	**1c**	toluene	50	80:20	95
4	**1d**	toluene	45	66:34	91
5	**1e**	toluene	52	75:25	77
6	**1f**	toluene	38	66:34	91
7	**1g**	toluene	43	75:25	81
8	**1c**	Et_2O	65	80:20	96
9[e]	**1c**	Et_2O	72	80:20	94
10[f]	**1c**	Et_2O	72	83:17	98

[a]Reactions were carried out using 0.3 mmol of **2a** (1 equiv) and 0.39 mmol of **3a** (1.3 equiv) in the presence of 10 mol % AgOAc and 11 mol % ligand **1c**. [b]Isolated yield of major diastereomer. [c]Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Enantiomeric excess (*ee*) was determined by chiral HPLC analysis. [e]5 mol % AgOAc and 6 mol % **1c** were used. [f]2 mol % AgOAc and 3 mol % **1c** were used.

the reaction (Table 1, entry 2). Interestingly, use of the ferrophos ligands improved the yield and enantioselectivity of the desired cycloadduct **4a**. Evaluation of various ferrophos ligands **1c**−**1g** indicated that monophosphine ligand **1c** containing an oxazoline ring was found to be superior, providing the desired product **4a** in 50% yield, 80:20 diastereoselectivity, and excellent enantioselectivity (95%) (Table 1, entry 3). It is possible that the oxazoline ring in the ligand plays a vital role for coordination in the metal−ligand complex which might be responsible for improved stereoinduction.[13] For further improvement of this catalytic system, other silver salts such as $AgBF_4$ and AgOTf were also examined in combination with ligand **1c**. However, in these cases, no product formation was observed (see Supporting Information (SI), Table S1, entries 1, 2). Replacement of the silver metal salt by copper(I) was of no avail (Table S1, entry 3). Next, we optimized the reaction conditions by extensive solvent screening utilizing the model substrates in the presence of AgOAc (10 mol %) and ligand **1c** (11 mol %) at room temperature. Virtually, no reaction was observed in chlorinated solvent such as DCM and polar solvent such as MeOH (Table S1, entries 4 and 6). However, nonpolar solvents such as dioxane and ether considerably improved the results. Among all the screened solvents, ether was the best in terms of yield (65%) and diastereo-/enantioselectivity (96%) (Table 1, entry 8).

We further optimized the reaction conditions by reducing the catalyst loading and varying the reaction temperature. The product **4a** was obtained with improved yield (72%), diastereoselectivity (83:17), and enantioselectivity (98%) when the catalyst loading was reduced to 2 mol % from 5 mol % (Table 1, entry 10). Although further reduction of the catalyst loading (i.e., 1 mol %) furnished the desired product **4a**, the stereoselectivity was not satisfactory (Table S1, entry 8). By lowering the reaction temperature from room temperature to −20 °C, a significant drop in the diastereoselectivity was observed (Table S1, entries 9−12). From the above-mentioned results, it was concluded that the best optimized conditions for this desymmetrization protocol include 2 mol % AgOAc, 3 mol % ligand **1c** in ether at room temperature (Table 1, entry 10).

Having identified effective conditions, we evaluated the scope of the dipolarophile for enantioselective desymmetrization. At first, various azomethine ylides **3a**−**3j** derived from electron-poor and -rich aromatic aldehydes were investigated (Figure 2). Electron-donating and -withdrawing groups were well tolerated, and the corresponding bicyclic-pyrrolidine derivatives were obtained in moderate to good yields (58−76%), diastereoselectivities (75:25−83:17), and excellent enantioselectivities

DOI: 10.1021/acs.orglett.5b02582
Org. Lett. 2015, 17, 5088−5091

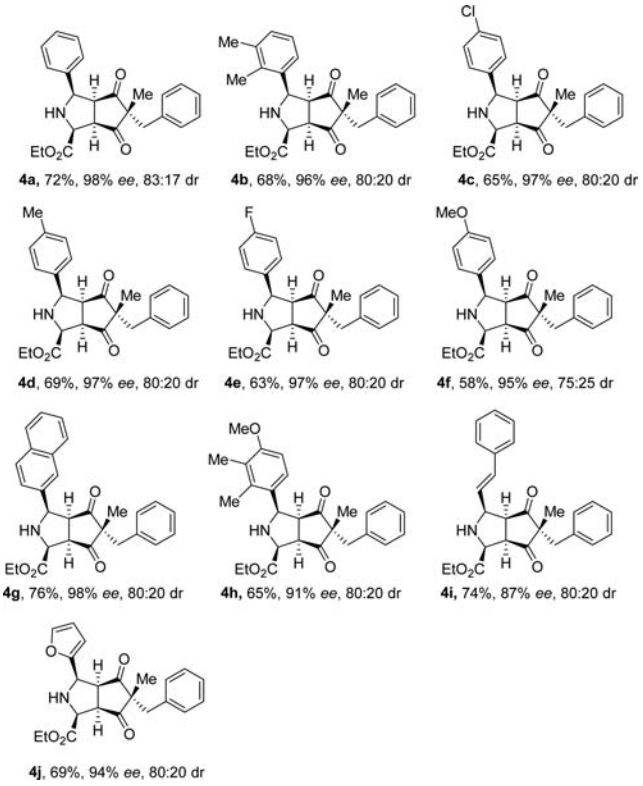


Figure 2. Scope of different azomethine ylide in desymmetrization reaction.

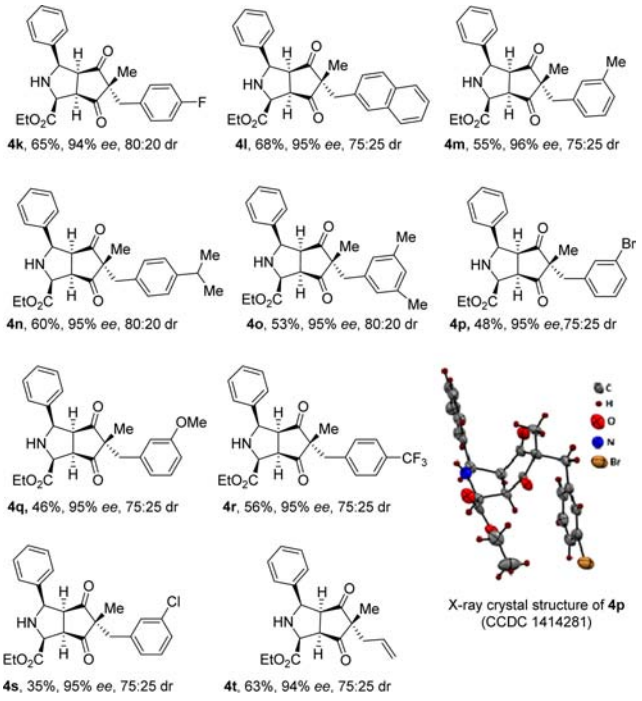


Figure 3. Scope of various cyclopentenedione in desymmetrization reaction (CCDC 1414281 for **4p**).[12]

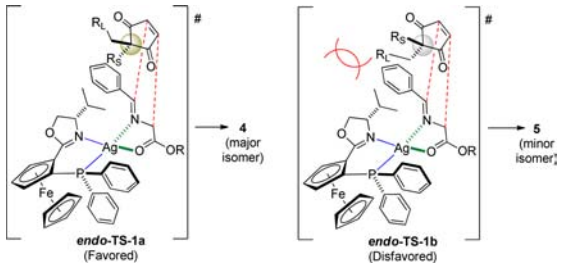


Figure 4. Proposed transition state.

(87–98%). The azomethine ylides having sterically bulky trisubstituted aromatic ring **3h** and naphthyl moiety **3g** (see SI) smoothly produced the corresponding cycloadduct **4h** and **4g** in good yields (65% and 76% respectively) and excellent *ee* (91% and 98% respectively). The azomethine ylides containing cinnamyl and heteroaromatic ring **3i** and **3j** underwent a desymmetrization reaction to provide the corresponding bicyclic-pyrrolidines **4i** and **4j** in good yields (74% and 69%) and good to excellent enantioselectivity viz. 87% and 94% respectively.

Next, the scope of enantioselective desymmetrization was further explored on a variety of cyclopentenediones **2k–2t** (see SI) having different substitutions at the aromatic ring. Both electron-donating and -withdrawing substituents are well tolerated under the reaction conditions, and desymmetrized cycloadducts **4k–4s** (Figure 3) were obtained in moderate to good yields (35–68%) and excellent enantioselectivities (94–96%). However, it was observed that the *meta* substituent on the aromatic ring of cyclopentenediones (Figure 3) has a deleterious effect in comparison to the *para* substituent. This might be due to the steric hindrance of the meta substituent on the aromatic ring with the phenyl ring of the azomethine ylide. The allyl substituent at the quaternary stereocenter in cyclopentenedione **2t** produced the corresponding bicyclic-pyrrolidine **4t** in moderate yield (63%) with excellent enantioselectivity (94%) via a [3 + 2] cycloaddition reaction without affecting the allyl group.

Based on the stereochemical outcome of the product, the enantioselectivity could be rationalized by the proposed transition state *endo*-TS-**1a** and -**1b** (Figure 4).[13] The reaction might be proceeding by coordination of azomethine ylide to the Ag(I) in a distorted tetrahedral fashion. The isopropyl group on the oxazoline ring and phenyl ring on phosphorus hinders the approach of the dipolarophile from the *Si* C═N face of azomethine ylide, thus favoring one of the *endo* stereoisomers (**4**) as a major product arising from *endo*-TS-**1a** (Figure 4). Whereas *endo*-TS-**1b** would lead to the formation of a minor diastereomer (**5**) probably due to the steric repulsion arising from the bulky R_L group.[14]

In order to evaluate the scalability of the [3 + 2] cycloaddition reaction, the desymmetrization of cyclopentenedione **2a** was conducted on the 1 g scale. The catalyst loading could be lowered to 1 mol %, and the corresponding bicyclic-pyrrolidine cycloadduct **4a** was isolated in 65% yield and 95% *ee* as the major diastereomer (80:20 dr). This experiment demonstrates the operational simplicity of the desymmetrization protocol and the associated potential for use in the large scale synthesis of enantio-/diastereopure bicyclic-pyrrolidine derivatives.

The potential usefulness of this catalytic enantioselective desymmetrization was also demonstrated by converting the bicyclic-pyrrolidine cycloadduct **4a** to enantiopure bicyclic-pyrrole **6** by oxidation with DDQ in toluene at room temperature.[15] Bicyclic-pyrrole **6** was obtained in excellent yield (82%) without loss of any enantioselectivity (94%) (Scheme 2).

DOI: 10.1021/acs.orglett.5b02582
Org. Lett. 2015, 17, 5088–5091

Scheme 2. Synthesis of Pyrrole from Pyrrolidine

4a (1g), 95% *ee* **6**, 94% *ee*

In conclusion, we have developed an efficient, operationally simple protocol for the synthesis of 5,5-fused bicyclopyrrolidine by desymmetrization of prochiral cyclopentenedione via [3 + 2] cycloaddition of azomethine ylide catalyzed by a silver(I)−ferrophox complex. A variety of bicyclic-pyrrolidine derivatives were synthesized in good yields (up to 76%) and excellent enantioselectivities (up to 98%) under mild reaction conditions. The synthetic potential of this desymmetrization approach has also been shown by the synthesis of bicyclic-pyrrole in a highly enantio-/diastereoselective manner. Mechanistic investigation and further applications of this chemistry are actively ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02582.

Experimental procedures, characterization data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra and HPLC chromatogram for all new compounds (PDF)
X-ray crystal structure data for compound **4p** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vinodks@iitk.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

V.K.S. thanks the DST for a research grant through a J. C. Bose Fellowship. T.D. and P.S. thank IISER Bhopal for their fellowship. We thank Dr. Vishnumaya Bisai, IISER Bhopal, for proof-reading this manuscript. We thank Dr. Alakesh Bisai, IISER Bhopal, for fruitful suggestions. We thank Mr. Lalit Mohan Jha, IISER Bhopal, for single crystal XRD analysis.

■ REFERENCES

(1) (a) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346. (b) Aikawa, K.; Okamoto, T.; Mikami, K. *J. Am. Chem. Soc.* **2012**, *134*, 10329. (c) Manna, M. S.; Mukherjee, S. *Chem. Sci.* **2014**, *5*, 1627. (d) Manna, M. S.; Mukherjee, S. *J. Am. Chem. Soc.* **2015**, *137*, 130.

(2) Harwood, L. M.; Vickers, R. J. Azomethine Ylides. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons, Inc.: New York, 2002; Vol. *59*, pp 169−252.

(3) (a) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. *1*, pp 653−732. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(4) (a) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2840. (b) Muller, S.; Webber, M. J.; List, B. *J. Am. Chem. Soc.* **2011**, *133*, 18534. (c) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8167. (d) Ren, L.; Lei, T.; Gong, L.-Z. *Chem. Commun.* **2011**, *47*, 11683. (e) Zhou, L.; Liu, X.; Ji, J.; Zhang, Y.; Hu, X.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2012**, *134*, 17023. (f) Hayashi, M.; Shiomi, N.; Funahashi, Y.; Nakamura, S. *J. Am. Chem. Soc.* **2012**, *134*, 19366. (g) Aikawa, K.; Okamoto, T.; Mikami, K. *J. Am. Chem. Soc.* **2012**, *134*, 10329. (h) Takizawa, S.; Nguyen, T.M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5423.

(5) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236.

(6) (a) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400. (b) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (c) Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 5055. (d) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750. (e) Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025. (f) Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6055. (g) Nájera, C.; de Gracia Retamosa, M.; Martín-Rodríguez, M.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2009**, *2009*, 5622. (h) Liang, G.; Tong, M.-C.; Wang, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 3101. (i) Oura, I.; Shimizu, K.; Ogata, K.; Fukuzawa, S.-I. *Org. Lett.* **2010**, *12*, 1752.

(7) (a) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795. (c) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (d) Oki, H.; Fukuzawa, S.-I. *Org. Lett.* **2008**, *10*, 1747. (e) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084. (f) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 340. (g) Filippone, S.; Maroto, E. E.; Martín-Domenech, A.; Suarez, M.; Martín, N. *Nat. Chem.* **2009**, *1*, 578. (h) Kim, H. Y.; Shih, H.-Y.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7420. (i) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schurmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735. (j) Teng, H.-L.; Huang, H.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2011**, *47*, 5494.

(8) (a) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638. (b) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Wu, F.-L. *Tetrahedron: Asymmetry* **2010**, *21*, 1184.

(9) (a) Shi, J.-W.; Zhao, M.-X.; Lei, Z.-Y.; Shi, M. *J. Org. Chem.* **2008**, *73*, 305. (b) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7895. (c) Awata, A.; Arai, T. *Chem. - Eur. J.* **2012**, *18*, 8278.

(10) (a) Chen, X.- H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (b) Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 4050. (c) Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 1275. (d) Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 4680. (e) Lin, S.; Deiana, L.; Zhao, G.-L.; Sun, J.; Cordova, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7624.

(11) Liu, K.; Teng, H.-L.; Yao, L.; Tao, H.-Y.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 2250.

(12) CCDC 1414281 for **4p**; see Supporting Information for details

(13) Dai, L.; Xu, D.; Tang, L.-W.; Zhou, Z.-M. *ChemCatChem* **2015**, *7*, 1078.

(14) Stereochemistry of minor isomer has been studied from NOE experiments. For details, see the Supporting Information.

(15) (a) Arrieta, A.; Otaegui, D.; Zubia, A.; Cossío, F. P.; Diaz-Ortiz, A.; de la Hoz, A.; Herrero, M. A.; Prieto, P.; Foces-Foces, C.; Pizarro, J. L.; Arriortua, M. I. *J. Org. Chem.* **2007**, *72*, 4313. (b) Robles-Machín, R.; López-Pérez, A.; González-Esguevillas, M.; Adrio, J.; Carretero, J. C. *Chem. - Eur. J.* **2010**, *16*, 9864.

DOI: 10.1021/acs.orglett.5b02582
Org. Lett. 2015, 17, 5088−5091