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First Iridium-Catalyzed Highly Enantioselective Hydrogenation of β-Nitroacrylates

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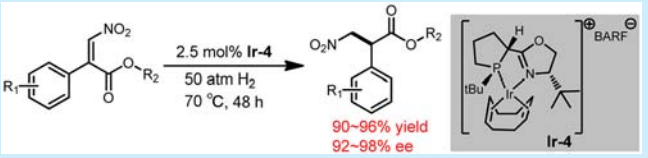
Supporting Information

ABSTRACT: The first highly chemo- and enantioselective hydrogenation of β-nitroacrylates was accomplished with an iridium catalyst (**Ir-4**) with yields and enantioselectivities of up to 96% and 98% ee, respectively. The resulting α-chiral β-nitro propionates are attractive building blocks for the synthesis of chiral β^2-amino acids, which are the core scaffolds of bioactive natural products, pharmaceuticals, and β-peptides.



Increasing attention has been devoted to the efficient construction of β-amino acids because of their wide occurrence in pharmacologically and biologically interesting molecules[1] such as the well-known β-lactam drugs and paclitaxel. β^2-Amino acids are particularly attractive among different β-amino acids and are embedded in many bioactive natural products and pharmaceuticals (Figure 1). For example,

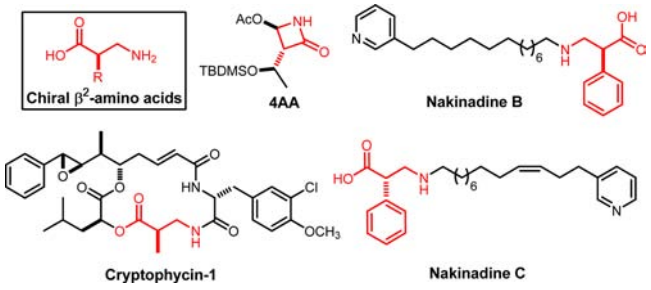


Figure 1. Drugs and bioactive natural products.

cryptophycin-1 was reported by Merck for the treatment of AIDS and cancers and can also be used as a fungicide;[2] β^2-amino acids derived β-lactam 4AA are the core unit of the eminent antibiotic drug carbapenem;[3] and pyridine alkaloids nakinadines B and C have been demonstrated to show cytotoxicity.[1,4] More importantly, the pioneering works by Seebach and Gellmann demonstrated that β^2 -amino acid residues are essential for the formation of most interesting and specific β-peptide secondary structures, which are necessary for versatile functionalities.[5,6]

Versatile and efficient synthesis of chiral β^2-amino acids will be of great interest, while only limited progress was achieved compared with the β^3-amino acid counterparts. Asymmetric hydrogenation of protected or functionalized prochiral amino-substrates is documented by Zheng, Chan, and Qiu, including β-phthalimide acrylates[7] and α-amino- methyl acrylates.[8,9] Organo-catalytic enantioselective aminomethylation of aldehydes (Mannich reaction) is another elegant tactic to this end.[10] We envision that asymmetric reduction of the prochiral β-nitroacrylates will be an alternative approach but not limited to the valuable β^2-amino acids since the resulting β-nitroesters can also serve as a masked functionality to many interesting molecules through simple transformation[11] (Figure 2).

Figure 2. Multifunctionalities of chiral β^2-nitro acids.

Compared with the asymmetric reduction of the simple β,β-disubstituted nitroalkenes, the similar transformation of β-nitroacrylates was relatively underdeveloped. The List group developed the first highly organocatalytic enantioselective-transfer hydrogenation of β-nitroacrylates with Jacobsen-type thiourea catalyst and commercially available Hantzsch ester.[12] Subsequently, a similar transformation was reported by Paradies.[13] Asymmetric bioreductions by *Saccharomyces carlsbergensis* old yellow enzyme[14] and enoate reductase[15] were disclosed by Stewart and Wu, respectively. These approaches suffer from high catalyst loading, a complex reaction system, or tedious workup. Development of a new methodology of asymmetric reduction of β-nitroacrylates to furnish the chiral β^2-amino acids is of high significance. Considering the atom economy and environmental compatibility, we envisage that direct asymmetric hydrogenation will be a compelling approach. Herein, we

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document our efforts in the enantioselective hydrogenation of β-nitroacrylates catalyzed by transition metals (Figure 3).

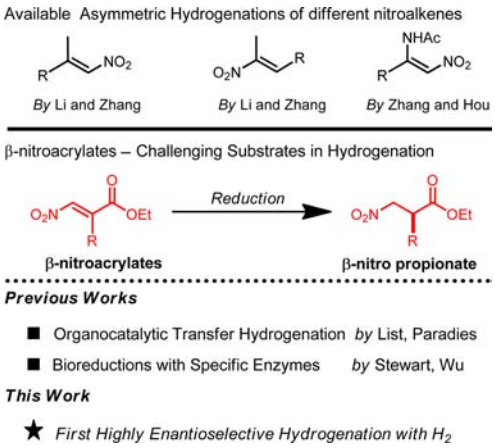
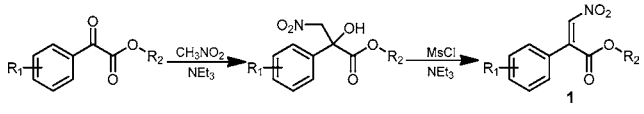


Figure 3. First enantioselective hydrogenation of β-nitroacrylates.

The inspiration of asymmetric hydrogenation to β^2-amino acids was triggered not only by the current limited progress in asymmetric reduction of β-nitroacrylates but also by our continuing efforts in the asymmetric hydrogenation of nitroalkenes. In our previous works, we developed the first highly enantioselective rhodium-catalyzed hydrogenation of β, β-disubstituted nitroalkenes[16] and α,β-disubstituted nitroalkenes[17] and a modified practical hydrogenation assisted by basic additives.[18] A novel bifunctional catalyst was also designed, synthesized, and applied for the rhodium-catalyzed hydrogenation.[19] β-Amino nitroalkenes were hydrogenated enantioselectively by Rh/TangPhos;[20] subsequently, an elegant iridium catalytic system was developed for this process.[21] Encouraged by these exciting results, we switched our attention to the asymmetric hydrogenation of β-nitroacrylates and envisioned that any progress in this topic will be of both fundamental and practical importance.

The β-nitroacrylates required in this proposal were prepared typically starting from α-ketoesters, which are commercially available or can be synthesized efficiently from Grignard reagents and oxalate.[12,14] A series of β-nitroacrylates were synthesized with *Z*-isomers predominantly through Henry reaction of α-ketoesters followed by NEt_3-assisted dehydration of mesylates (Scheme 1).

Scheme 1. Synthesis of β-Nitroacrylates



Our study started by exploring the asymmetric hydrogenation of **1a** as the model substrate. The previously established catalytic systems[16−19] were initially tested since they have been proven to be efficient for enantioselective hydrogenation of different nitroalkenes. Unfortunately, neither of them gave satisfying enantioselectivity and conversion for **1a**. In an effort to overcome the "untouched problem", the evaluation of a large and diverse set of catalysts was carried out (Figure 4), including rhodium catalysts, ruthenium catalysts, and iridium catalysts; representative results are shown in Table 1.

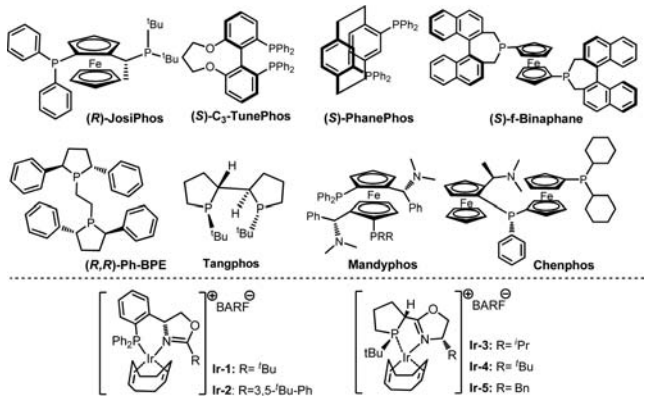


Figure 4. Representative chiral ligands and catalysts.

The asymmetric hydrogenation of **1a** was initially carried out with 5% catalyst under 50 atm of H_2 atmosphere in DCM. Since rhodium catalysts with chiral ferrocene ligands furnished efficient reactivity and enantioselectivity in our previous studies, the $rh(cod)_2BF_4$/JosiPhos catalytic system was originally tested; however, it only gave 5.3% ee (Table 1, entry 1). Parameter screening demonstrated that temperature is crucial for the reactivity (Table 1, entry 1 vs 6) and the nonpolar toluene is beneficial for the conversion (Table 1, entries 6−10), while the erosion of enantioselectivity was emitted (Table 1, entry 10). A parallel execution of combination of the subspecies of ferrocene ligands with rhodium salts did not reveal any satisfactory improvement in the enantioselectivities (Table 1, entries 11−13).

Other chiral bidentate ligands were also evaluated with disappointing outputs, including planar chiral ligand, atropisomeric biaryl ligand, and rigid P-chiral ligand (Table 1, entries 2−5). Ruthenium catalysts were evaluated and seemed to be inert for this chiral transformation (Table 1, entries 14−16). Based on the chiral toolbox developed by our group[22] and the elegant performance of iridium catalysts in transfer hydrogenation of nitroalkenes,[23] we turned our attention to the iridium−PN ligands catalyst for the hydrogenation of **1a**. Versatile conformationally rigid phosphino-oxazolines were tested under standard conditions. To our delight, the phospholane−oxazoline ligands (Table 1, entries 19−21) furnished good to excellent enantioselectivities (82−94% ee), which are already very high for this type of asymmetric hydrogenation. In order to counterbalance the reaction efficiency and enantioselectivity (the ee value) appropriately for identifying a potentially useful catalytic system, enantioselectivity was highlighted as a more important parameter to optimize in comparison with the conversion. A mathematical function of conversion and square of the enantioselectivity was established. Such a mathematical formula together with careful scanning of different solvents and mixed solvents indicated **Ir-4** in DCM as a promising system (Table 1, note e).

In light of the limited efficacy with **Ir-3** as catalyst for hydrogenation of **1a**, a large, diverse set of additives was evaluated (see the Supporting Information for details). These additives are typically used in iridium-catalyzed hydrogenation (iodine, chiral, and nonchiral acids and bases) or specifically added in the asymmetric reduction of nitroalkenes (CH_3NO_2 and KF). Unfortunately, no synergistic effect was detected; both acidic and basic additives can deactivate the catalyst execrably.

Fine tuning and detailed optimization of the reaction parameters showed that the thermal effect is more remarkable,

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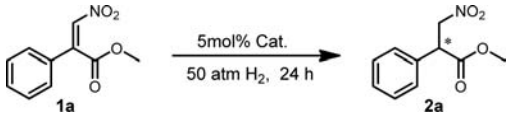
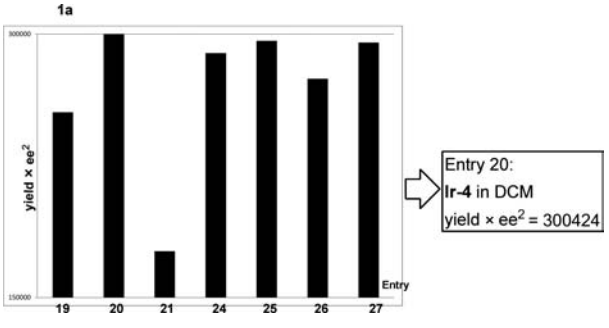
Table 1. Selected Catalytic Systems for Hydrogenation of 1a



entry	conditions (cat.; solv; temp)[a]	conv[b] (%)	ee[c] (%)
1	Rh/(*R*)-JosiPhos	90	5.3
2	Rh/(*R*, *R*)-Ph-BPE	<5	NA
3	Rh/(*S*)-C_3-Tunephos	<5	NA
4	Rh/Tangphos	36	0.4
5	Rh/(*S*)-Phanephos	15	8.2
6	Rh/(*R*)-JosiPhos; DCM; rt	<5	NA
7	Rh/(*R*)-JosiPhos; EA; rt	32	5.6
8	Rh/(*R*)-JosiPhos; MeOH; rt	<5	NA
9	Rh/(*R*)-JosiPhos; THF; rt	30	1.5
10	Rh/(*R*)-JosiPhos; tol; rt	74	2.3
11	Rh/Mandyphos; tol; rt	>95	1.5
12	Rh/Chenphos; tol; rt	>95	5.2
13	Rh/(*S*)-f-Binaphane; tol; rt	>95	4.2
14[d]	Ru/(*S*)-C_3-tunephos	10	3
15[d]	Ru/Duanphos	6	20
16[d]	Ru/MeO-Biphep	9	20
17	Ir-1	5	11
18	Ir-2	7	8
19	Ir-3	38	82 (−) (*S*)
20	Ir-4	34	94 (−) (*S*)
21	Ir-5	25	84 (−) (*S*)
22	Ir-4; MeOH	16	13 (−) (*S*)
23	Ir-4; EA	17	50 (−) (*S*)
24	Ir-4; toluene	43	82 (−) (*S*)
25	Ir-4; THF	41	87 (−) (*S*)
26	Ir-4; DCM/tol = 1:1	44	79 (−) (*S*)
27	Ir-4; DCM/THF = 1:1	42	91 (−) (*S*)

[a]Unless otherwise mentioned, all reactions were carried out with a catalyst/substrate molar ratio of 1:20 under 50 atm of H_2 in DCM at 50 °C (solvent = DCM; temperature = 50 °C). Metal precursors: Rh = $Rh(cod)_2BF_4$, Ru = $[RuCl_2(p\text{-cymene})]_2$. [b]Conversion was determined by ^{1}HNMR of the crude product of hydrogenation. [c]The ee was determined by HPLC on a chiral phase; the configuration was assigned by comparison with the reported data. [d]$[RuCl_2(p\text{-cymene})]_2$/ligand/substrate = 1:2:40. Key: NA, not available; DCM, dichloromethane, EA, ethyl acetate, THF, tetrahydrofuran, Tol, toluene; rt = room temperature (25 °C).



and elevation in the reaction temperature will accelerate the desired catalytic cycle and lead to a decrease in catalyst loading without an obvious reduction in the enantioselectivity (Table 2). More importantly, a higher temperature possibly decelerate the formation of the hydride-bridged Ir trimer, which will result in catalyst deactivation.[24] Systematic optimization furnished **2a** in 95% yield with up to 93% ee through iridium-catalyzed enantioselective hydrogenation (Table 2, entry 6).

Table 2. Optimization for Hydrogenation of 1a with Ir-4

entry	cat.[a] (%)	conditions	conv[b] (%)	ee[c] (%)
1	5	70 °C; 80 atm; 24 h	> 95	92
2	2.5	70 °C; 80 atm; 24 h	55	93
3	1.25	70 °C; 80 atm; 24 h	21	93
4	2.5	60 °C; 80 atm; 24 h	32	94
5	2.5	70 °C; 50 atm; 24 h	54	93
6	2.5	70 °C; 50 atm; 48 h	95	93

[a]Unless otherwise mentioned, all reactions were carried out with **Ir-4** as catalyst, *X*% = molar ratio. [b]Conversion was determined by ^{1}H NMR of the crude product of hydrogenation. [c]Enantiomeric excess was determined by HPLC on a chiral phase.

With the optimized reaction conditions, the scope of this iridium-catalyzed enantioselective hydrogenation was explored with an array of *β*-nitroacrylates (Figure 5). To our delight, all types of substrates **1a**−**k** underwent hydrogenation to furnish the chiral *β*-nitroesters in good to excellent enantioselectivities (92−98% ee).

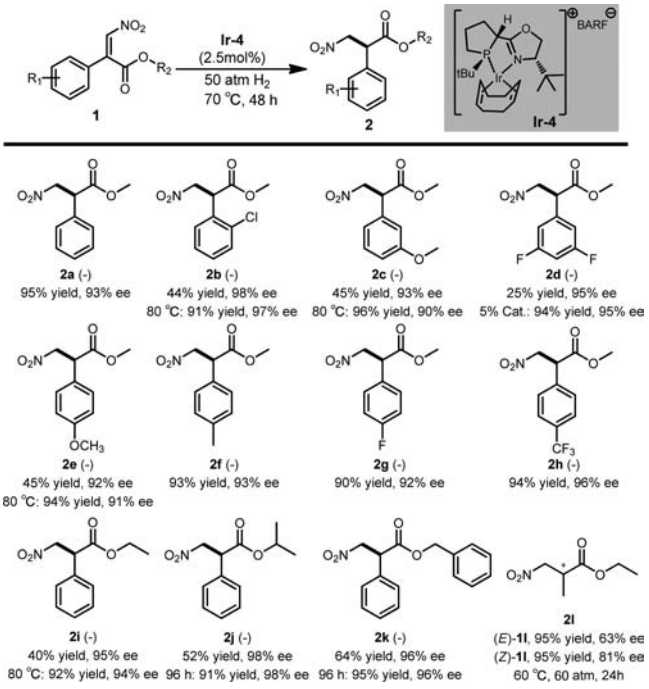


Figure 5. *β*-Nitroacrylates scope in **Ir-4**-catalyzed hydrogenation.

Remarkably, the *β*-nitroacrylate **1b**, with an *o*-chloro substituent on the benzene ring, can be hydrogenated with an enantioselectivity of up to 98% ee, albeit with modest yield, which can be improved either by temperature elevation or higher catalyst loading. Though excellent enantioselectivities were detected when the nitroacrylates **1c** (93% ee) and **1d** (95% ee) were submitted, the reaction efficiency seems to be suppressed by the introduction of substituents to the *meta*-position of benzene ring, regardless of whether it was electrondonating or electron-withdrawing. Surprisingly, the MeO substituent appears to be unamiable and acts as an "ugly factor"; a sharp decrease in the reaction efficiency was observed in the hydrogenation of 3-methoxyphenyl-substituted and 4-methoxyphenyl-substituted nitroacrylates (Figure 5, 1c and 1e), but a high level of enantioselectivity was retained.

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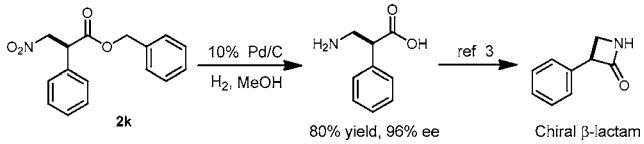
In addition, the other nitroacrylates, with either electron-donating or electron-withdrawing groups at the *para* position of the benzene ring, were well tolerated. Compound **1h** was hydrogenated with excellent stereocontrol in nearly quantitative yields (94% yield and 96% ee). The alkyl-substituted *β*-nitroacrylates (*E*)-**1l** and (*Z*)-**1l** were also tested and hydrogenated smoothly with useful enantioselectivity (Figure 5, 1l).

The effect of different ester groups was also taken into consideration, and the ester group can be varied significantly as probed with *α*-phenyl substituted *β*-nitroacrylates (**1a**, **1i**–**k**), while prolongation is necessary for full conversion. The enantioselectivity increased slightly with size and bulkiness of the ester moiety and followed the trend CH_3 < Et < Bn < iPr. Gratifyingly, nitroacrylate **1j** was successfully hydrogenated in high yield with almost complete stereocontrol; this is the highest enantioselectivity achieved among different reduction tactics of nitroacrylates.

The synthetic potential of this method was demonstrated by the direct preparation of free chiral β^2-amino acid (3-amino-2-phenylpropanoic acid) under simple hydrogenation conditions in the presence of Pd/C, without concomitant loss of enantiomeric purity. It can be transformed further to *β*-lactam in high yield according to the previous report (Scheme 2).

Scheme 2. Derivative Synthesis of 2k



In conclusion, the first highly enantioselective hydrogenation of *β*-nitroacrylates with H_2 was accomplished by the catalyst of the iridium/P,N ligand (**Ir-4**). The resultant methodology serves as an efficient alternative for the asymmetric reduction of *β*-nitroacrylates and complements the readily available bioreductions and organocatalytic transfer hydrogenation, showing a potentially direct approach to the very useful stereogenic *β*-nitroester synthons for chemical synthesis and pharmaceutical science. Most importantly, the highest enantioselectivity was achieved, which is otherwise not so easily accomplished by the available reduction methodologies. Further investigations are ongoing in order to illustrate the Ir-catalyzed hydrogenation mechanism of *β*-nitroacrylates for ultimately establishing an efficient catalytic system with a significant improvement in both substrates scope and reactivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01758.

Experimental procedures and analytic data (NMR, HPLC traces) (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Prof. Wenjun Wu of Northwest A&F University on the occasion of his 70th birthday.

■ REFERENCES

(1) Kudo, F.; Miyanaga, A.; Eguchi, T. *Nat. Prod. Rep.* **2014**, *31*, 1056–1073.
(2) Chaganty, S.; Golakoti, T.; Heltzel, C.; Moore, R. E.; Yoshida, W. Y. *J. Nat. Prod.* **2004**, *67*, 1403–1406.
(3) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.
(4) Nishi, T.; Kubota, T.; Fromont, J.; Sasaki, T.; Kobayashi, J. *Tetrahedron* **2008**, *64*, 3127–3132.
(5) Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206–243.
(6) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *β*-Peptides: From Structure to Function. *Chem. Rev.* **2001**, *101*, 3219–3232.
(7) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359–3362.
(8) Guo, Y.; Shao, G.; Li, L.; Wu, W.; Li, R.; Li, J.; Song, J.; Qiu, L.; Prashad, M.; Kwong, F. Y. *Adv. Synth. Catal.* **2010**, *352*, 1539–1553.
(9) Qiu, L.; Prashad, M.; Hu, B.; Prasad, K.; Repic, O.; Blacklock, T. J.; Kwong, F. Y.; Kok, S. H. L.; Lee, H. W.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 16787–16792.
(10) Chi, Y.; English, E. P.; Pomerantz, W. C.; Horne, W. S.; Joyce, L. A.; Alexander, L. R.; Fleming, W. S.; Hopkins, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6050–6055.
(11) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
(12) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862–13863.
(13) Schneider, J. F.; Lauber, M. B.; Muhr, V.; Kratzer, D.; Paradies, J. *Org. Biomol. Chem.* **2011**, *9*, 4323–4327.
(14) Swiderska, M. A.; Stewart, J. D. *Org. Lett.* **2006**, *8*, 6131–6133.
(15) Liu, Y. J.; Pei, X. Q.; Lin, H.; Gai, P.; Liu, Y.-C.; Wu, Z.-L. *Appl. Microbiol. Biotechnol.* **2012**, *95*, 635–645.
(16) Li, S.; Huang, K.; Cao, B.; Zhang, J.; Wu, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 8573–8576.
(17) Li, S.; Huang, K.; Zhang, X. *Chem. Commun.* **2014**, *50*, 8878–8881.
(18) Li, S.; Huang, K.; Zhang, J.; Wu, W.; Zhang, X. *Chem. - Eur. J.* **2013**, *19*, 10840–10844.
(19) Zhao, Q.; Li, S.; Huang, K.; Wang, R.; Zhang, X. *Org. Lett.* **2013**, *15*, 4014–4017.
(20) Zhou, M.; Dong, D.; Zhu, B.; Geng, H.; Wang, Y.; Zhang, X. *Org. Lett.* **2013**, *15*, 5524–5527.
(21) Yan, Q.; Liu, M.; Kong, D.; Zi, G.; Hou, G. *Chem. Commun.* **2014**, *50*, 12870–12872.
(22) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278–1290.
(23) Soltani, O.; Ariger, M. A.; Carreira, E. M. *Org. Lett.* **2009**, *11*, 4196–4198.
(24) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513–516.

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