Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

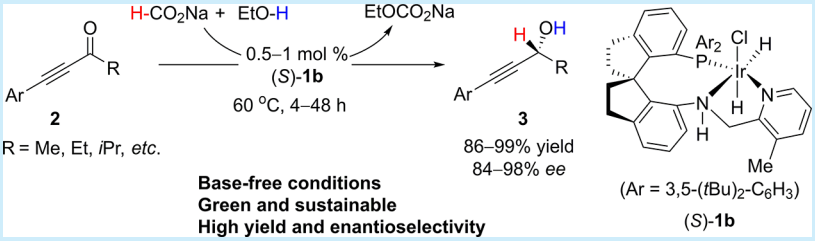
Iridium-Catalyzed Asymmetric Transfer Hydrogenation of Alkynyl Ketones Using Sodium Formate and Ethanol as Hydrogen Sources

Yang-Ming Zhang,[†] Ming-Lei Yuan,[†] Wei-Peng Liu,[†] Jian-Hua Xie,*[,†] and Qi-Lin Zhou[†,‡]

[†]State Key Laboratory and Institute of Elemento-organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Nankai University, Tianjin 300071, China

Supporting Information



ABSTRACT: A green and efficient iridium-catalyzed asymmetric transfer hydrogenation of alkynyl ketones to chiral propargylic alcohols has been developed. By using sodium formate and ethanol as hydrogen sources, a series of alkynyl ketones were hydrogenated by chiral spiro iridium catalyst (*S*)-**1b** to provide optically active chiral propargylic alcohols with up to 98% ee under base-free conditions. This protocol provides a practical and sustainable method for the preparation of optically active propargylic alcohols.

Optically active propargylic alcohols are useful and important chiral building blocks for the synthesis of various bioactive and structurally interesting compounds.[1] Catalytic asymmetric hydrogenation of alkynyl ketones is undoubtedly a direct and promising approach to chiral propargylic alcohols. However, due to the reason that many alkynyl ketones are labile to basic ketone hydrogenation conditions,[2] only limited catalytic systems documented were efficient for the hydrogenation of alkynyl ketones.[3] In contrast, the catalytic asymmetric transfer hydrogenation, which can be performed under mild reaction conditions, has been well-developed for the reduction of alkynyl ketones to chiral propargylic alcohols.[4] In 1997, Noyori reported the asymmetric transfer hydrogenation of alkynyl ketones by using chiral Ru-TsDPEN catalysts with *i*PrOH/KOH as a hydrogen donor.[5] Since then, the asymmetric transfer hydrogenation of alkynyl ketones to optically active chiral propargylic alcohols has received intensive attention[6] and has been successfully applied in the enantioselective synthesis of bioactive natural products.[7] However, most of the reported asymmetric transfer hydrogenations used Ru-TsDPEN or its analogs as catalysts and *i*PrOH/KOH or HCO_2H/NEt_3 as hydrogen donors. In this letter, we report an iridium-catalyzed asymmetric transfer hydrogenation of alkynyl ketones to chiral propargylic alcohols with sodium formate and ethanol as hydrogen sources under base-free conditions, producing chiral propargylic alcohols in high yield and enantioselectivity.

Recently, we found that the chiral iridium catalysts Ir-SpiroPAP (**1**) with a tridentate spiro pyridine-aminophosphine ligand developed in our group[8] were highly efficient for the asymmetric transfer hydrogenation of simple ketones.[9] With ethanol as a hydrogen donor[10] and *t*BuOK as a base, a series of alkyl aryl ketones were reduced to their corresponding chiral alcohols with good to excellent enantioselectivity. Considering that ethanol is a renewable resource and a feedstock for the chemical industry,[11] as well as an environmental- and human-friendly solvent, we were encouraged to evaluate this catalytic system for the reduction of alkynyl ketones. This evaluation led us to find that chiral spiro iridium catalysts **1** were also efficient for the asymmetric transfer hydrogenation of alkynyl ketones in the presence of both sodium formate and ethanol as hydrogen sources without the addition of any base (Scheme 1).

The asymmetric transfer hydrogenation of 4-phenylbut-3-yn-2-one (**2a**) was initially performed under our previous reaction conditions, that is (*S*)-**1b**/EtOH/*t*BuOK at 40 °C,[9] and no desired reduction product was obtained. Only the Michael addition byproduct, formed by the ethoxide addition to the C≡C bond of **2a**, was observed (Table 1, entry 1). The transfer hydrogenation of **2a** also did not occur under the conditions using HCO_2H/NEt_3 as a hydrogen donor (entries 2 and 3). To our delight when HCO_2Na (2 equiv) is applied as a hydrogen donor, the alkynyl ketone **2a** was reduced to propargylic alcohol (*R*)-**3a** in high enantioselectivity (97% ee, entry 4). The reaction became faster when the reaction temperature increased to 60 °C, and the reaction finished

Received: June 8, 2018

DOI: 10.1021/acs.orglett.8b01787
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Iridium Catalyzed Asymmetric Transfer Hydrogenation of Alkynyl Ketones

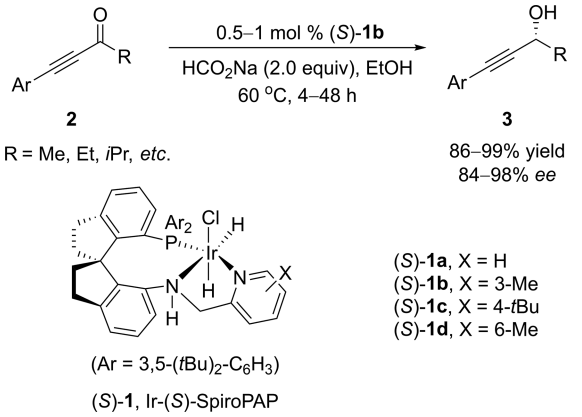


Table 1. Asymmetric Transfer Hydrogenation of 2a. Optimizing Reaction Conditions[a]

entry	(S)-1	hydrogen donor	solvent	temp (°C)	time (h)	conv (%)[b]	ee (%)[c]
1[d]	(S)-1b	EtOH/ tBuOK	EtOH	40	20	–	ND
2[e]	(S)-1b	HCO_2H/ NEt_3	CH_2Cl_2	40	20	–	ND
3[e]	(S)-1b	HCO_2H/ NEt_3	EtOH	40	20	–	ND
4	(S)-1b	HCO_2Na	EtOH	40	20	97	97
5	(S)-1b	HCO_2Na	EtOH	60	8	99	96
6	(S)-1b	HCO_2Na	EtOH	80	6	99	90
7[f]	(S)-1b	HCO_2Na	EtOH	60	20	78	89
8	(S)-1b	HCO_2Na	MeOH	60	8	40	75
9	(S)-1b	HCO_2Na	iPrOH	60	8	52	72
10	(S)-1b	HCO_2Li	EtOH	60	20	60	94
11	(S)-1b	HCO_2K	EtOH	60	7	99	96
12	(S)-1b	HCO_2Cs	EtOH	60	5	99	96
13[g]	(S)-1b	HCO_2Na	EtOH	60	12	94	95
14[h]	(S)-1b	HCO_2Na	EtOH	60	20	95	95
15	(S)-1a	HCO_2Na	EtOH	60	8	97	94
16	(S)-1c	HCO_2Na	EtOH	60	20	47	78
17	(S)-1d	HCO_2Na	EtOH	60	10	94	93
18[i]	(S)-1b	HCO_2Na	EtOH	60	20	95	95

[a]Reaction conditions: 0.2 mmol of **2a** (0.04 M), 0.4 mmol of HCO_2Na, 1 mol % catalyst, EtOH (5.0 mL). [b]Determined by ^1H NMR. NR means no reaction. [c]Determined by HPLC using chiral column. The configuration is (*R*). ND means not determined. [d]Adding 0.02 mmol of *t*BuOK. [e]0.4 mmol of HCO_2H, HCO_2H/NEt_3 = 2/5 (v/v). [f]0.2 mmol of HCO_2Na. [g][**2a**] = 0.08 M. [h][**2a**] = 0.1 M. [i]0.5 mol % catalyst (S/C = 200).

within 8 h (entry 5). However, further increasing the reaction temperature to 80 °C resulted in lower enantioselectivity (90% ee, entry 6). Reducing the amount of HCO_2Na to 1 equiv lowered both the conversion and enantioselectivity of the reaction (entry 7). Solvent experiments showed that EtOH was the best solvent. The reactions in MeOH and *i*PrOH gave low conversion and low enantioselectivity (entries 8 and 9). Other alkali metal formates can also be used as hydrogen sources although the HCO_2Li gave a lower reaction rate and conversion (entries 10–12). Increasing the concentration of the substrate resulted in comparable enantioselectivity, but longer reaction times were required to complete the reaction (entries 13 and 14). The catalysts (*S*)-**1** containing different substituted groups on the pyridine ring were also tested. The catalysts having no substituent or having a methyl group exhibited high activity and high enantioselectivity; however, the catalyst (*S*)-**1c** containing a 4-*t*Bu group gave low conversion and enantioselectivity (entries 5 and 15–17). The reaction can also be performed by using 0.5 mol % of catalyst (*S*)-**1b** (entry 18).

Under the optimal reaction conditions, a range of aryl alkynyl ketones **2** were evaluated, and the results are summarized in Table 2. The electronic property of the R group in the substrates had no effect on the yield and enantioselectivity of the reaction, although the substrate **2d**, which has an electron-withdrawing group (R = CF_3), gave a faster reaction rate (entries 1, 2, and 4). However, when the R group is a bulky isopropyl (**2c**), the reaction became sluggish, and both the yield and enantioselectivity decreased (entry 3). The ester group in the substrates **2e** and **2f** was tolerated under the reaction conditions (entries 5 and 6). The substituent at the *para*- or *meta*-position of the phenyl ring of the aryl alkynyl group of ketones **2** had little impact on the yield and enantioselectivity of the reaction (entries 7–12). For steric reasons the substitution at the *ortho*-position lowered the enantioselectivity of the reaction (entries 13 and 14). Generally, an electron-withdrawing substitution at the arylalkynyl group of the ketones **2** accelerated the reaction rate (entries 9, 10, 12, and 14).

Table 2. Asymmetric Transfer Hydrogenation of Alkynyl Ketones 2 with (*S*)-1b[a]

entry	Ar	R	time (h)	3	yield (%)[b]	ee (%)[c]
1	C_6H_5	Me	8	**3a**	99	96 (*R*)
2	C_6H_5	Et	11	**3b**	99	96 (*R*)
3	C_6H_5	*i*Pr	40	**3c**	90	84 (*R*)
4	C_6H_5	CF_3	4	**3d**	99	98 (*S*)
5	C_6H_5	$(CH_2)_2CO_2Et$	4	**3e**	86	96
6	C_6H_5	$(CH_2)_3CO_2Et$	12	**3f**	93	95
7	4-MeC_6H_4	Me	24	**3g**	95	95 (*R*)
8	4-$MeOC_6H_4$	Me	30	**3h**	99	96 (*R*)
9	4-ClC_6H_4	Me	7	**3i**	92	96 (*R*)
10	4-BrC_6H_4	Me	7	**3j**	96	97
11	3-MeC_6H_4	Me	10	**3k**	98	97
12	3-ClC_6H_4	Me	8	**3l**	99	96
13	2-$MeOC_6H_4$	Me	48	**3m**	95	86
14	2-ClC_6H_4	Me	10	**3n**	96	91

[a]Reaction conditions were the same as those listed in Table 1, entry 5. [b]Isolated yield. [c]Determined by HPLC using a chiral column.

The asymmetric transfer hydrogenation of alkynyl ketone **2d** with HCO_2Cs[12] was tracked by *in situ* IR spectroscopy. We found that the HCO_2Cs was converted to cesium ethyl carbonate ($EtOCO_2Cs$) after providing hydrogen (Figure 1). In the reaction of **2d** (1704 cm^{-1}) with 1.2 equiv of HCO_2Cs (1602 cm^{-1}) catalyzed by (*S*)-**1b** (2 mol %) at 60 °C, the peaks at 1704 and 1602 cm^{-1} decreased rapidly at the first stage and a new peak at 1640 cm^{-1}, which belongs to $EtOCO_2Cs$, increased. After reaction for 3 h, the peaks at 1704 and 1602 cm^{-1} disappeared, and the peak at 1640 cm^{-1} was a single major peak in the spectrum. In addition, no obvious peak at 1743 cm^{-1}, which belongs to ethyl acetate,[13] was observed in the reaction. These results indicate that the

DOI: 10.1021/acs.orglett.8b01787
Org. Lett. XXXX, XXX, XXX–XXX

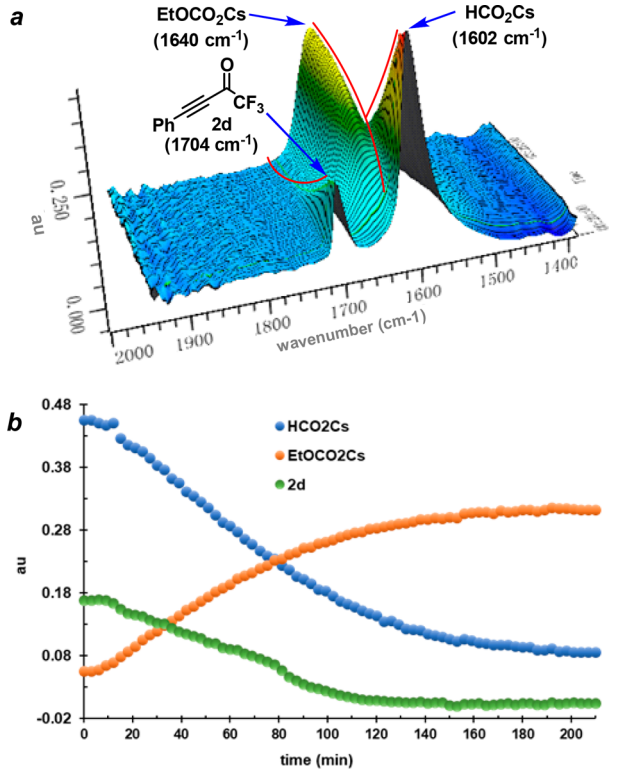
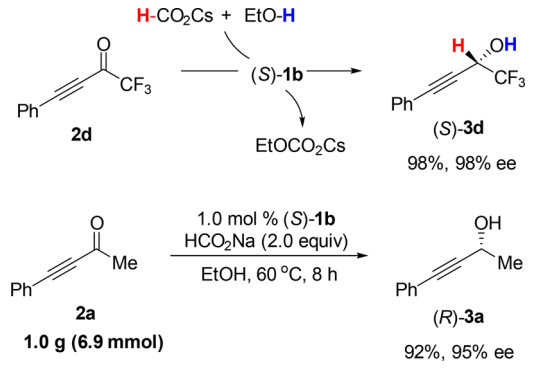


Figure 1. Plots of asymmetric transfer hydrogenation of **2d** (monitored by a ReactIR spectrometer).

formate salt and EtOH served as the hydride and proton sources, respectively, in the reaction (Scheme 2).

Scheme 2. Asymmetric Transfer Hydrogenation of 2d with HCO_2Cs in EtOH and in Gram Scale



The asymmetric transfer hydrogenation can be performed on gram scale without significant loss of enantioselectivity. With catalyst (*S*)-**1b** (1 mol %), the substrate **2a** (1.0 g) was hydrogenated to (*R*)-**2a** in 92% isolated yield and 95% ee (Scheme 2). Interestingly, most of the produced white solid sodium ethyl carbonate (SEC, $EtOCO_2Na$), which has promising potential for applications as a raw material in related fields, such as the formation of solid fuels, disinfectant agents, and alcoholic beverages,[14] in the reaction can be removed by filtration. After recovering the EtOH solvent through distillation, the product (*R*)-**3a** can be obtained by distillation under reduced pressure (70 °C, 0.008 Torr). It is worth mentioning that, although only a 72% yield and 95% ee were observed after reaction for 24 h, the recovered catalyst which was obtained from the extraction of the final residue with hexane still has catalytic activity for asymmetric hydrogenation of alkynyl ketone **2a** under the same reaction conditions (see Supporting Information). This result indicates that the catalyst (*S*)-**1b** was stable and robust under the reaction conditions and easily recycled. The low turnover numbers (*e.g.*, 190, Table 1, entry 18) of the hydrogenation of **2a** is likely due to the fact that the propargylic alcohol product inhibits the activity of the catalyst (*S*)-**1b**.

In conclusion, we have developed a green and efficient iridium-catalyzed asymmetric transfer hydrogenation of alkynyl ketones to chiral propargyl alcohols. With sodium formate and ethanol as hydrogen sources under base-free conditions, a variety of alkynyl ketones were hydrogenated by chiral spiro iridium catalyst (*S*)-**1b** to provide chiral propargyl alcohols in high yield and enantioselectivity. This protocol provides a practical and sustainable method for the preparation of optically active propargyl alcohols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01787.

Experimental procedures and the characterizations of the substrates and products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jhxie@nankai.edu.cn.

ORCID

Jian-Hua Xie: 0000-0003-3907-2530

Qi-Lin Zhou: 0000-0002-4700-3765

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21325207, 21532003, and 21421062) and the "111" project (B06005) of the Ministry of Education of China for financial support.

■ REFERENCES

(1) (a) Ma, S.-M.; He, Q.-W. *Chin. J. Org. Chem.* **2002**, *22*, 375. (b) Lu, G.; Li, Y.-M.; Li, X.-S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736. (c) Yadav, J. S.; Chandrasekhar, S. In *Drug Discovery and Development*; Chorghade, M. S., Ed.; John Wiley & Sons: Hoboken, NJ, 2007; Vol. 2, pp 141−160. (d) Stang, P. J., Diederich, F., Eds. *Modern Acetylene Chemistry*; Wiley-VCH: Weinheim, 2008. (e) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (f) Wang, Q.; Pu, L. *Synlett* **2013**, *24*, 1340.

(2) (a) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(3) Arai, N.; Satoh, H.; Utsumi, N.; Murata, K.; Tsutsumi, K.; Ohkuma, T. *Org. Lett.* **2013**, *15*, 3030.

(4) Blacker, A. J. In *Handbook of Homogenous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; pp 1215−1244.

(5) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

DOI: 10.1021/acs.orglett.8b01787
Org. Lett. XXXX, XXX, XXX−XXX

(6) (a) Bogliotti, N.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2005**, *46*, 6915. (b) Druais, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2012**, *14*, 516. (c) Fang, Z.; Wills, M. *J. Org. Chem.* **2013**, *78*, 8594. (d) Murphy, S. K.; Dong, V. M. *J. Am. Chem. Soc.* **2013**, *135*, 5553. (e) Fang, Z.; Wills, M. *Org. Lett.* **2014**, *16*, 374. (f) Kumaraswamy, G.; Narayanarao, V.; Shanigaram, P.; Balakishan, G. *Tetrahedron* **2015**, *71*, 8960. (g) Shatskiy, A.; Kivijärvi, T.; Lundberg, H.; Tinnis, F.; Adolfsson, H. *ChemCatChem* **2015**, *7*, 3818. (h) Vyas, V. K.; Knighton, R. C.; Bhanage, B. M.; Wills, M. *Org. Lett.* **2018**, *20*, 975. (i) Zheng, L.-S.; Férard, C.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Commun.* **2018**, *54*, 283.

(7) For selected papers, see: (a) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666. (b) Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Org. Lett.* **2009**, *11*, 935. (c) Xing, Y.; O'Doherty, G. A. *Org. Lett.* **2009**, *11*, 1107. (d) Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Tetrahedron* **2010**, *66*, 6358. (e) Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8025. (f) Brandt, D.; Dittoo, A.; Bellosta, V.; Cossy, J. *Org. Lett.* **2015**, *17*, 816. (g) Takahashi, K.; Arai, Y.; Honda, T. *Tetrahedron Lett.* **2017**, *58*, 4048. (h) Siva Nagi Reddy, K. S. N.; Sabitha, G. *Tetrahedron Lett.* **2017**, *58*, 1198. (i) Wang, T.; Duan, X.; Zhao, H.; Zhai, S.; Tao, C.; Wang, H.; Li, Y.; Cheng, B.; Zhai, H. *Org. Lett.* **2017**, *19*, 1650.

(8) For reviews, see: (a) Xie, J.-H.; Zhou, Q.-L. *Huaxue Xuebao* **2014**, *72*, 778. (b) Yang, X.-H.; Xie, J.-H.; Zhou, Q.-L. *Org. Chem. Front.* **2014**, *1*, 190. For selected papers, see: (c) Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7329. (d) Xie, J.-H.; Liu, X.-Y.; Yang, X.-H.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 201. (e) Yang, X.-H.; Wang, K.; Zhu, S.-F.; Xie, J.-H.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2014**, *136*, 17426.

(9) Liu, W.-P.; Yuan, M.-L.; Yang, X.-H.; Li, K.; Xie, J.-H.; Zhou, Q.-L. *Chem. Commun.* **2015**, *51*, 6123.

(10) For papers for transfer hydrogenation with ethanol as a hydrogen donor, see: (a) Zweifel, T.; Naubron, J.-V.; Büttner, T.; Ott, T.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3245. (b) Zweifel, T.; Scheschkewitz, D.; Ott, T.; Vogt, M.; Grützmacher, H. *Eur. J. Inorg. Chem.* **2009**, *2009*, 5561. (c) Lundberg, H.; Adolfsson, H. *Tetrahedron Lett.* **2011**, *52*, 2754.

(11) (a) Rass-Hansen, J.; Falsig, H.; Jørgensen, B. J. *J. Chem. Technol. Biotechnol.* **2007**, *82*, 329. (b) Gray, K. A.; Zhao, L.; Emptage, M. *Curr. Opin. Chem. Biol.* **2006**, *10*, 141.

(12) HCO_2Cs has better solubility than HCO_2Na in EtOH, and a slightly excessive amount of HCO_2Cs (*e.g.*, 1.2 equiv) could make the asymmetric transfer hydrogenation of alkynyl ketone **2d** complete in a reasonably short time.

(13) In the asymmetric transfer hydrogenation of simple ketones with ethanol as a hydrogen donor and chiral spiro iridium complex (*S*)-**1a** as the catalyst, the ethanol was converted to ethyl acetate (IR, 1743 cm^{-1}). See ref 9.

(14) Han, S.-J.; Wee, J.-H. *Ind. Eng. Chem. Res.* **2016**, *55*, 12111.

DOI: 10.1021/acs.orglett.8b01787
Org. Lett. XXXX, XXX, XXX−XXX