Advanced Synthesis & Catalysis

Accepted Article

Title: Iridium catalyzed propenylation reactions for the synthesis of 4-pyridone derivatives

Authors: Xue-dan Bai, Jie Wang, and Ying He

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801177

Link to VoR: http://dx.doi.org/10.1002/adsc.201801177

10.1002/adsc.201801177

WILEY-VCH

Iridium-Catalyzed Propenylation Reactions for the Synthesis of 4-Pyridone Derivatives

Xue-dan Bai, Jie Wang, and Ying He*

Abstract: Herein we report an iridium-catalyzed propenylation reaction of allylic carbonates with 4-hydroxypyridine derivatives. The process efficiently provides 4-pyridone derivatives with high stereoselectivities under mild conditions. The products could constitute valuable building blocks for the synthesis of natural products and other bioactive molecules. Preliminary mechanistic studies indicated that a tandem allylic substitution/isomerization reaction occurs to afford the propenylation products.

Keywords: Iridium catalysis • propenylation reactions • 4-pyridone derivatives • allylic substitution • isomerization

4-Pyridones are versatile building blocks in organic synthesis and their derivatives constitute a large class of drugs, natural products, and other bioactive molecules (Figure 1).[1] Consequently, substantial effort has been devoted to the development of methods for the diversification and elaboration of this scaffold. As an inexpensive and commercially available starting material, 4-hydroxypyridine is an attractive precursor for the preparation of 4-pyridone derivatives, and it has been employed as a nucleophilic reagent in a number of synthetic methods.[2,3]

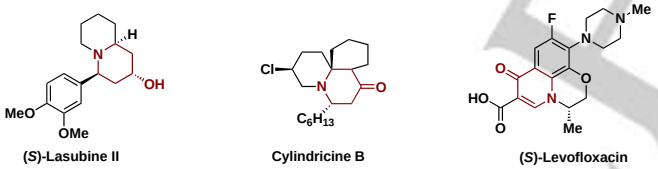
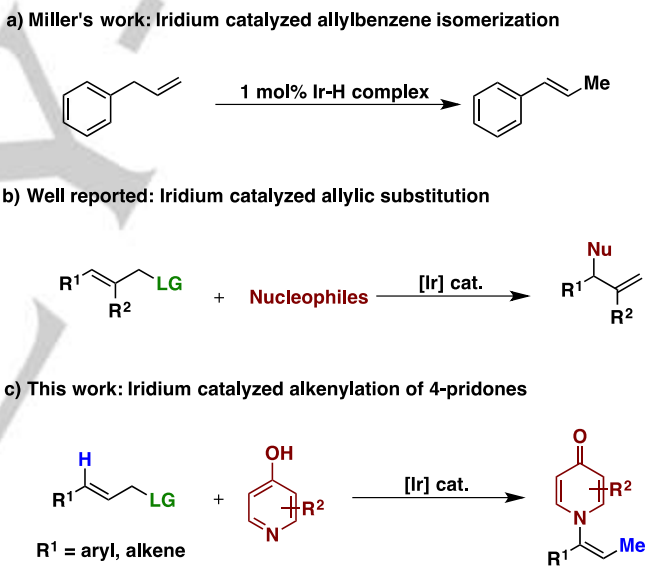


Figure 1. Selective bioactive molecules containing 4-pyridone motifs.

Alkenylation reactions have emerged as an area of considerable interest during the past few decades. In addition to the classic Heck reaction,[4] a number of other strategies have been reported including C-H activation, alkene rearrangement reactions, and coupling reactions for vinyl species.[5] While alkenylation chemistry provides a means for the direct formation of compounds containing C=C bonds. Transition metal complex catalyzed olefin isomerization offers another powerful technique for the preparation of olefins and their derivatives.[6,7] Very recently, the Miller group reported a new efficient strategy of the controlled isomerization of olefins using an iridium-pincer complex as the catalyst (Scheme 1, a).[8] On the other hand, iridium catalyzed allylic substitution for C-N formation is a well-established strategy for allylic amines and N-heterocycles (Scheme 1, b).[9, 10] Inspired by these reports, we wondered whether we could combine these two systems in one-pot, as a means of achieving the direct propenylation of nucleophiles. On the basis of its utility in the preparation of bioactive compounds, we selected 4-hydroxypyridine as the nucleophile and anticipated that our studies would lead to a synthesis of propenylated 4-pyridones (Scheme 1, c).



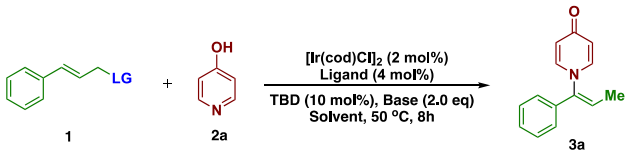
Scheme 1. Iridium catalyzed isomerization, allylic substitution, and propenylation reactions.

We began our studies by examining the reaction of cinnamyl carbonate (**1a**) and 4-hydroxypyridine (**2a**). The iridacycle catalyst was generated in situ by the treatment of $[Ir(cod)Cl]_2$ and Feringa phosphoramidites **L1** with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[11] Using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as a base, we were pleased to find that the reaction proceeded smoothly to afford the desired propenylation product rather than allylic substitution product in 94% yield and ≥30:1 selectivity for the (*Z*)-isomer (Table 1, entry 1). Different phosphoramidite ligands were also studied. However, the yield of the product decreased dramatically when other phosphoramidite ligands were used (Table 1, entries 2-4). No desired product was obtained when using PPh_3 or $P(OPh)_3$ as the ligand (Table 1, entries 5 and 6). The use of other cinnamyl electrophiles such as –Cl, –OBoc, –

[a] Xue-dan Bai, Jie Wang, Prof. Dr. Ying He
School of Chemical Engineering, Nanjing University of Science & Technology, Nanjing, 210094, China
E-mail: yhe@njust.edu.cn

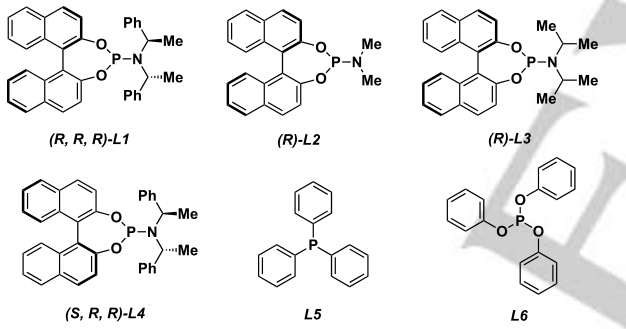
OBz, –OP(OEt)$_2$ and –OH led to diminished yield (Table 1, entries 7-11), as did the use of Et_3N as the base (Table 1, entry 13). Changing to toluene as the solvent result in a comparable yield of 93% with high stereoselectivity (Table 1, entry 12).

Table 1. Optimization of reaction conditions.[a]



1 2a 3a

Entry	Ligand	Leaving group (LG)	Base	Solvent	Yield (%)[b]
1	*(R, R, R)-L1*	OCOOMe	DBU	THF	94
2	*(R)-L2*	OCOOMe	DBU	THF	<5
3	*(R)-L3*	OCOOMe	DBU	THF	57
4	*(S, R, R)-L4*	OCOOMe	DBU	THF	<10
5	*L5*	OCOOMe	DBU	THF	-
6	*L6*	OCOOMe	DBU	THF	-
7	*(R, R, R)-L1*	OBoc	DBU	THF	43
8	*(R, R, R)-L1*	OH	DBU	THF	-
9	*(R, R, R)-L1*	$OPO(OEt)_2$	DBU	THF	<10
10	*(R, R, R)-L1*	OBz	DBU	THF	47
11	*(R, R, R)-L1*	Cl	DBU	THF	76
12	*(R, R, R)-L1*	OCOOMe	DBU	Toluene	93
13	*(R, R, R)-L1*	OCOOMe	Et_3N	THF	16



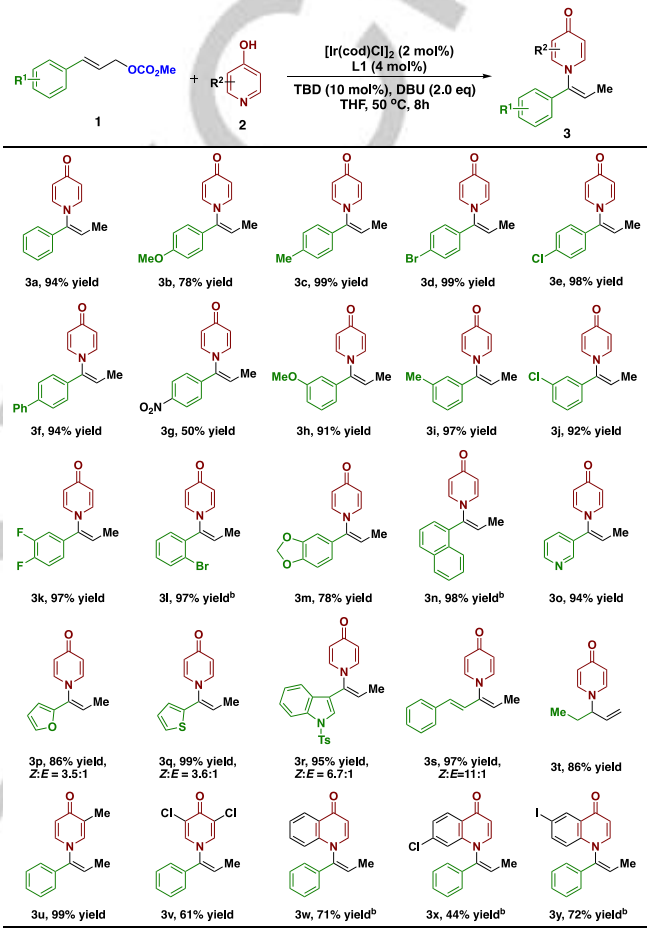
(R, R, R)-L1 *(R)-L2* *(R)-L3*

(S, R, R)-L4 *L5* *L6*

[a] Standard conditions : **1** (0.1 mmol), **2a** (0.2 mmol), $[Ir(cod)Cl]_2$ (2 mol%), **Ligand 1** (4 mol%), TBD (10 mol%), DBU (0.2 mmol), THF (1.0 ml), 50°C for 8h, argon atmosphere. [b] Isolated yields; LG = leaving group.

With the optimized conditions in hand, we next explored substrate scope for the reaction. Various substituted group in the *para*-positions of arenes were well tolerated under optimized conditions. High to excellent yields were obtained using most electron-neutral, electron-donating and electron-withdrawing cinnamyl methyl carbonates as substrates (Table 2, compounds **3a**-**3f**). However, only a moderate yield of 50% was obtained when strong electron-deficient *p*-nitrocinnamyl carbonate **1g** was used (Table 2, compound **3g**). A range of *ortho*-, *meta*- and *para*-substituted, electron-poor, and electron-rich analogues gave high yield of propenylation products utilizing 4-hydroxypyridine as a nucleophile (Table 2, compounds **3h**-**3l**). The reaction was also amenable to electron-poor and electron-rich heterocycles, and high yields were obtained, albeit with moderate stereoselectivities in the case of electron-rich heterocycles (Table 2, compounds **3o**-**3r**). Finally, we note that the reaction was not limited to cinnamyl methyl carbonates; a vinylogous substrate also furnished the desired product in high yield (Table 2, compound **3s**). However, when using methyl pent-2-en-1-yl carbonate as the substrate, propenylation product was not observed; and allylic product **3t** was obtained with 86% yield instead (Table 2, compound **3t**).

Table 2. Substrate scope.[a]

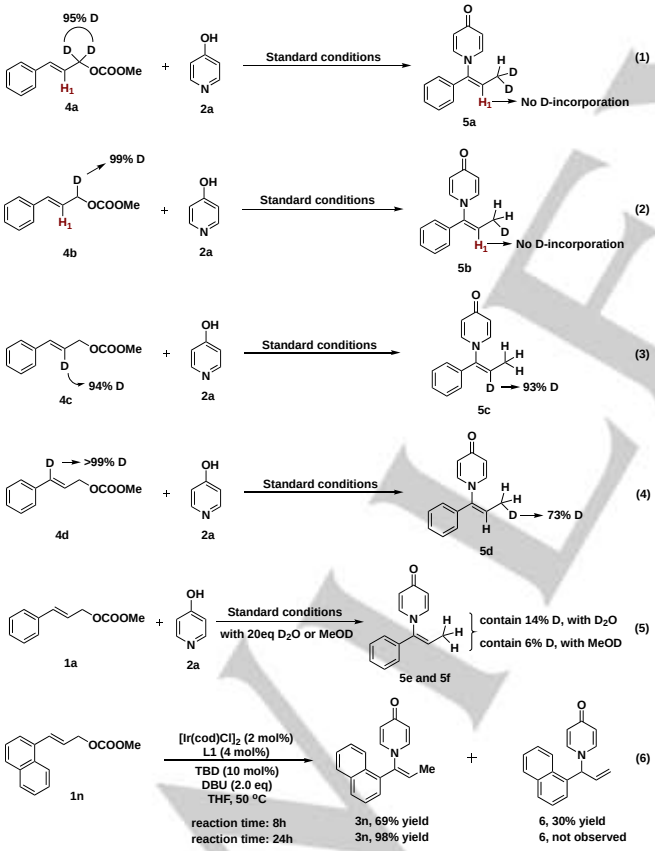


[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $[Ir(cod)Cl]_2$ (2 mol%), **L1** (4 mol%), TBD (10 mol%), DBU (0.2 mmol), THF (1.0 ml), 50°C for 8h, argon atmosphere, isolated yields; *Z*/*E* ratio was calculated by ^{1}H-NMR, **3b** was selected as an example for the NOE experiment, see SI for details; [b] The reaction was reacted for 24 h at 50 °C.

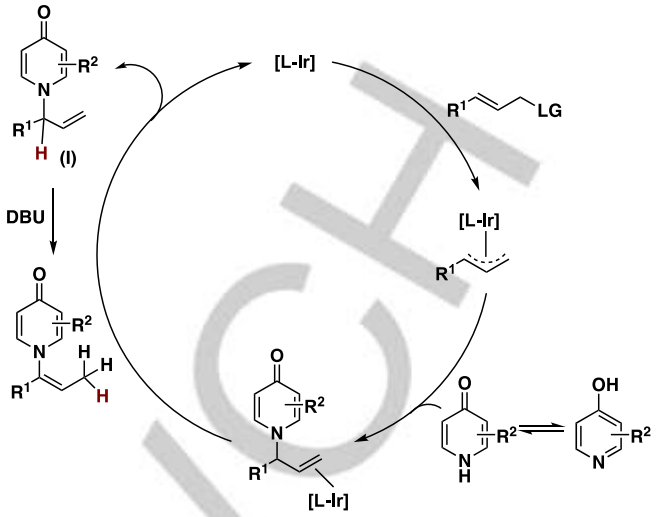
With respect to the 4-pyridone partner, 3-methyl substituted and 3,5-dichloro-substituted 4-hydroxypridines reacted smoothly under reaction conditions, forming the desired pyridone products in quantitative and 61% yield, respectively (Table 2, compounds **3u** and **3v**).[12] Additionally, the quinolone bearing several functional groups, including an iodo substituent, could also prepared in moderate to good yields (Table 2, compounds **3w**-**3y**).

In an effort to gain more insight into the reaction mechanism, deuterium labeling and control experiments were carried out. As shown in eq 1 and eq 2, no D/H scrambling of the H_1 position was observed in propenylation products **5a** and **5b**. In addition, 93% deuterium atom incorporation has been found in H_1 of **5c** (eq 3), which corresponds to nearly quantitative

retention of deuterium at the H_1 position in the transformation from **4c** to **5c**. However, using substrate **4d** labeled with deuterium next to the aryl ring led to the product **5d** with 73% D incorporation at the methyl group, indicating the incomplete D-migration in the course of the transformation (eq 4). The lower than expected 99% D might be due to trace water in the reaction medium. When the same reaction was performed with 20 eq D_2O or MeOD added, the products **5e** and **5f** with 14% and 6% deuterium incorporation in the methyl group were obtained, respectively (eq 5). We also observed that the use of bulky substrate **1n** resulted in desired product **3n** in 69% yield, along with allylic substituted product **6** in 30% isolated yield under the standard conditions. Longer reaction time was required to obtain the desired propenylation product **3n** in 98% yield (eq 6).[13] When allylic product **6** and DBU was heated in THF overnight, product of **3n** was obtained. This result suggest that the isomerization of intermediate (**I**) was attributed the base DBU (See SI for details). Based on these results, we proposed that the reaction proceeded *via* two steps: allylic substitution, followed by isomerization. The allylic products (**I**) would be first formed under the classic allylic substitution conditions, and then the isomerization of terminal alkene (**I**) would result in the desired product. (Scheme 3).[7j, 14]

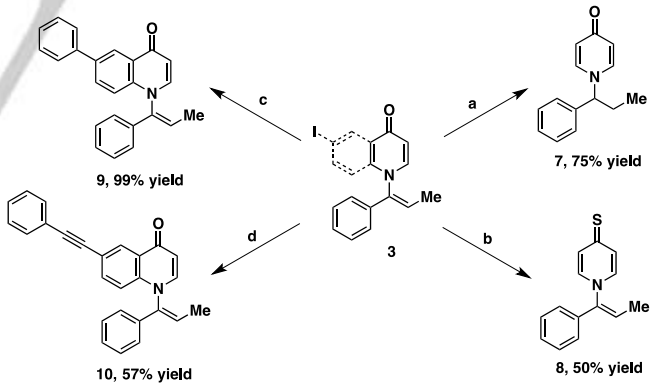


Scheme 2. Deuterium labeling and control experiments.



Scheme 3. Proposed Mechanism.

To explore the functionalization of the alkene moiety and the pyridone scaffold, synthetic elaborations were performed on the pyridone products (Scheme 4). The reduction of **3a** furnished the product 1-(1-phenylpropyl)pyridin-4(1H)-one in 75% isolated yield. Treatment of **3a** with Lawesson reagent afforded the pyridine-4-thione derivative in moderate yield.[15] Compound **9** and **10** could be prepared through a Suzuki coupling and Sonogashira coupling, affording the product in 99% and 57% yield, respectively, leaving the double bond intact for further transformations.



Scheme 4. Synthetic transformations. (a) Pd/C, H_2, MeOH, rt; (b) Lawesson reagent, toluene, reflux; (c) $PhB(OH)_2$, $(dppf)PdCl_2$, CsF, DME, 80°C; (d) Phenylacetylene, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, 50°C.

In summary, we have disclosed a mild and efficient method of Iridium-catalyzed propenylation reactions of pyridin-4(1H)-one analogues. The reaction afforded the 4-pyridone derivatives in excellent to high yields with high stereoselectivities. Furthermore, the preliminary mechanism was proposed to proceed through two catalytic cycles: allylic substitution and isomerization. We

expect this transformation to have broad implications, as it suggests a new general strategy for alkenylation reactions.

Experimental Section

General procedure for the synthesis of 3. The reaction was carried out in a glovebox under an argon atmosphere. $[Ir(cod)Cl]_2$ (1.4 mg, 0.002 mmol), **L1** (2.5 mg, 0.004 mmol), and TBD (1.4 mg, 0.01 mmol) were added to a 2 dram scintillation vial (vial A) equipped with a magnetic stirring bar. Vial A was then charged with THF (0.5 mL) and stirred at 50 °C for 30 min. To another 2 dram scintillation vial (vial B) was added propenyl carbonate (0.1 mmol), 4-hydroxypyridine analogues (0.2 mmol), DBU (0.2 mmol) and THF (0.5 mL). The pre-formed catalyst solution (vial A) was then transferred to vial B. Then vial B was sealed and stirred at 50 °C for a certain time. Upon completion of the reaction, vial B was removed from the glovebox and uncapped. Saturated NH_4Cl aqueous solution was added and the mixture was extracted with DCM (10 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography over silica gel to afford the desired product.

Acknowledgements

We gratefully acknowledge the Natural Science Foundation of Jiangsu Province (BK20180447) and the Fundamental Research Funds for the Central Universities (30918011313) for financial support. We thank Dr. Lei Wang for assistance with the NOE experiment. We also thank Prof. Hongmiao Wu from Nanjing University of Technology for helpful discussions. We specially thank Prof. Yi-ming Wang from University of Pittsburgh for language polishing of the manuscript.

References

[1] a) J. Y. Nagasawa, J. Song, H. Chen, H. Kim, J. Blazel, S. Ouk, B. Groschel, V. Borges, V. Ong, L. Yeh, J. Girardet, J. Vernier, A. Ranes, A. Pinkerton, Bioorg. Med. *Chem. Lett.* **2011**, *21*, 760. b) T. Mesganaw, J. A. Ellman, *Org. Process Res. Dev.* **2014**, *18*, 1097. c) G. Lapointe, K. Schenk, P. Renaud, *Org. Lett.* **2011**, *13*, 4774. d) G. Pandey, V. Janakiram, *Chem. -Eur. J.* **2015**, *21,* 13120. e) M. Sato, H. Kawakami, T. Motomura, H. Aramaki, T. Matsuda, M. Yamashita, Y. Ito, Y. Matsuzaki, K. Yamataka, S. Ikeda, H. Shinkai, *J. Med. Chem.* **2009**, *52*, 4869. f) M. Feng, L. Does, A. Bantjes, *J. Med. Chem.* **1993**, *36*, 2822.

[2] a) W. Shao, Y. Wang, Z.-P. Yang, X, Zhang, S.-L. You, *Chem. -Asian J.* **2018**, *13*,1103. b) J. P. Schmidt, C. Li, B. Breit, *Chem. -Eur. J.* **2017**, *23*, 6531. c) M. Breugst, H. Mayr, *J. Am. Chem. Soc.* **2010**, *132*, 15380. d) C. Aubert, P. Betschmann, M. J. Eichberg, V. Gandon, T. J. Heckrodt, J. Lehmann, M. Malacria, B. Masjost, E. Paredes, K. P. C. Vollhardt, G. D. Whitener, *Chem. -Eur. J.* **2007**, *13*, 7443.

[3] a) H. E. Ho, M. J. James, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* **2018**, *20*, 1439. b) M. J. James, N. D. Grant, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* **2016**, *18*, 6256. c) J. Diesel, A. M. Finogenova, N. Cramer, *J. Am. Chem. Soc.* **2018**, *140*, 4489. d) R. L. Sahani, R.-S. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*,12736.

[4] For selective recent reviews on Heck reactions, see: a) F.-X. Felpin, L. Nassar-Hardy, F. Le Callonnec, E. Fouquet, *Tetrahedron* **2011**, *67*, 2815. b) D. McCartney, P. J. Guiry, *Chem. Soc. Rev.* **2011**, *40*, 5122. c) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170. d) I. P. Belestskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.

[5] For selective reviews on alkenylation reactions, see: a) V. P. Boyarskiy, D. S.Ryabukhin, N. A. Bokach, A. V. Vasilyev, *Chem. Rev.* **2016**, *116*, 5894. b) X. Shang, Z.-Q Liu, *Chem. Soc. Rev.* **2013**, *42*, 3253. c) Y. Yamamoto, *Chem. Soc. Rev.* **2014**, *43*, 1575. d) S. Tang, K. Liu, C. Liu, A. Lei, *Chem. Soc. Rev.* **2015**, *44*, 1070. e) B. M. Trost, J. T. Masters, *Chem. Soc. Rev.* **2016**, *45*, 2212.

[6] For selective reviews on olefin isomerization, see: a) M. Hassam, A. Taher, G. E. Arnott, I. R. Green, W. A. L. van Otterlo, *Chem. Rev.* **2015**, *115*, 5462. b) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27. c) S. Krompiec, M. Krompiec, R. Penczek, H. Ignasiak, *Coord. Chem. Rev.* **2008**, *252*, 1819. d) E. Larionov, H. Li, C. Mazet, *Chem. Commun*, **2014**, *50*, 9816.

[7] For selective recent publications on olefin isomerization, see: a) C. Chen, T. R. Dugan, W. W. Brennesse, D. J. Weix, P. L. Holland, *J. Am. Chem. Soc.* **2014**, *136*, 945. b) J. R. Clark, J. R. Griffiths, S. T. Diver, *J. Am. Chem. Soc.* **2013**, *135*, 3327. c) B. M. Trost, J. J. Cregg, N. Quach, *J. Am. Chem. Soc.* **2017**, *139*, 5133. d) S. W. M. Crossley, F. Barabé, R. A. Shenvi, *J. Am. Chem. Soc.* **2014**, *136*, 16788. e) C. R. Larsen, D. B. Grotjahn, *J. Am. Chem. Soc.* **2012**, *134*, 10357. f) M. Pérez, L. J. Hounjet, C. B. Caputo, R. Dobrovetsky, D. W. Stephan, *J. Am. Chem. Soc.* **2013**, *135,* 18308. g) F. M. Chadwick, A. I. McKay, A. J. Martinez-Martinez, N. H. Rees, T. Krämer, S. A. Macgregor, A. S. Weller, *Chem. Sci.* **2017**, *8*, 6014. h) A. Schmidt, A. R. Nödling, G. Hill, *Angew. Chem. Int. Ed.* **2015**, *54*, 801. i) V. M. Lombardo, C. D. Thomas, K. A. Scheidt. *Angew. Chem. Int. Ed.* **2013**, *52*, 12910. j) Q.-L. Xu, L.-X. Dai, S.-L. You, *Org. Lett.* **2010**, *12*, 800.

[8] M. R. Kita, A. J. M. Miller, *Angew. Chem. Int. Ed.* **2017**, *56*, 5498.

[9] For selected reviews on iridium-catalyzed allylic amination, see: a) J. F. Teichert, B. L. Feringa, *Angew. Chem. Int. Ed.* **2010**, *49*, 2486. b) R. Takeuchi, *Synlett* **2002**, *2002*, 1954. c) R. Takeuchi, S. Kezuka, *Synthesis* **2006**, *2006*, 3349. d) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675. e) J. F. Hartwig, L. M. Stanley, *Acc. Chem. Res.* **2010**, *43*, 1461. f) J. F. Hartwig, M. J. Pouy, *Top. Organomet. Chem.* **2011**, *34*, 169. g) W.-B. Liu, J.-B. Xia, S.-L. You, *Top. Organomet. Chem.* **2011**, *38*, 155. h) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662. i) J. Qu, G. Helmchen, *Acc. Chem. Res.* **2017**, *50*, 2539.

[10] For selected papers on iridium-catalyzed allylic amination, see: a) R. Takeuchi, N. Ue, K. Tanabe, K. Yamashita, N. Shiga, *J. Am. Chem. Soc.* **2001**, *123*, 9525. b) K.-Y. Ye, H. He, W.-B. Liu, L.-X. Dai, G. Helmchen, S.-L. You, *J. Am. Chem. Soc.* **2011**, *133*, 19006. c) P. Tosatti, J. Horn, A. J. Campbell, D. House, A. Nelson, S. P. Marsden, *Adv. Synth. Cat.* **2010**, *352*, 3153. d) A. Leitner, S. Shekhar, M. J. Pouy, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 15506. e) A. Leitner, C. Shu, J. F. Hartwig, *Org. Lett.* **2005**, *7*,1093. f) T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164. g) D. J. Weix, D. Marković, M. Ueda, J. F. Hartwig, *Org. Lett.* **2009**, *11*, 2944. h) X. Zhang, Z.-P. Yang, L. Huang, S.-L. You, *Angew. Chem. Int. Ed.* **2015**, *51*, 1873. i) J. F. Teichert, M. Fañanás-Mastral, B. L. Feringa, *Angew. Chem. Int. Ed.* **2011**, *50*, 688. j) M. Lafrance, M. Roggen, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 3470. k) A. T. Meza, T. Wurm, L. Smith, S. W. Kim, J. R. Zbieg, C. E. Stivala, M. J. Krische, *J. Am. Chem. Soc.* **2018**, *140*, 1275. l) S. W. Kim, T. Wurm, G. A. Brito, W.-O.Jung, J. R. Zbieg, C. E. Stivala, M. J. Krische, *J. Am. Chem. Soc.* **2018**, *140*, 9087. m) L. M. Stanley, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 8971.

[11] a) C. Welter, O. Koch, G. Lipowsky, G. Helmchen, *Chem. Commun.* **2004**, 896. b) W.-B. Liu, C. Zheng, C.-X. Zhuo, L.-X. Dai, S.-L. You, *J. Am. Chem. Soc.* **2012**, *134*, 4812. c) C. Shu, A. Leitner, J. F. Hartwig, *Angew. Chem., Int. Ed.* **2004**, *43*, 4797. d) W.-B. Liu, C. M. Reeves, S. C. Virgil, B. M. Stoltz, *J. Am. Chem. Soc.* **2013**, *135*, 10626. e) W.-B.

Liu, N. Okamoto, E. J. Alexy, A. Y. Hong, K. Tran, B. M. Stoltz, *J. Am. Chem. Soc.* **2016**, *138*, 5234.

[12] For more bulky substrate 2-methylpyridin-4(1H)-one, less than 5% yield of the desired product was obtained. The allylic substitution product was obtained in 50% yield when using 2,6-dimethylpyridin-4(1H)-one as a substrate. See SI for the details.

[13] Compound **3n** was obtained in quantitative yield when **6** was subjected to the propenylation reaction system under the optimized conditions. See SI for the details.

[14] For selected publications on DBU catalyzed isomerization of alkenes, see: a) S. Martinez-Erro, A. Sanz-Marco, A. B. Gómez, A. Vázquez-Romero, M. S. G. Ahlquist, B. Martín-Matute, *J. Am. Chem. Soc.* **2016**, *138*, 13408. b) J. A. Dabrowski, F. Haeffner, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2013**, *52*, 7694.

[15] The linear product 1-cinnamylpyridine-4(1*H*)-thione was obtained when utilizing pyridine-4-thiol as a substrate. See SI for the details.

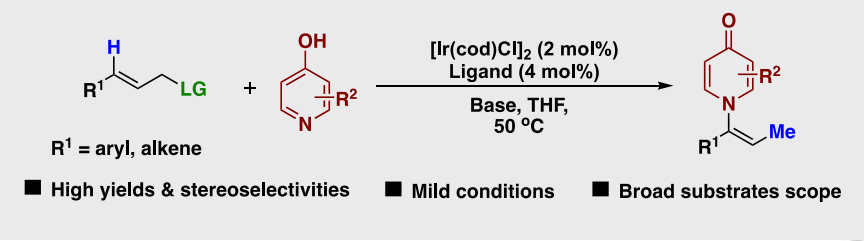
10.1002/adsc.201801177

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout : Alkenylation by iridium catalysis

COMMUNICATION



*Xue-dan Bai, Jie Wang, Ying He**

Page No. – Page No.

Iridium catalyzed propenylation reactions for the synthesis of 4-pyridone derivatives