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One-Pot Oxidation/Isomerization of *Z*-Allylic Alcohols with Oxygen as Stoichiometric Oxidant

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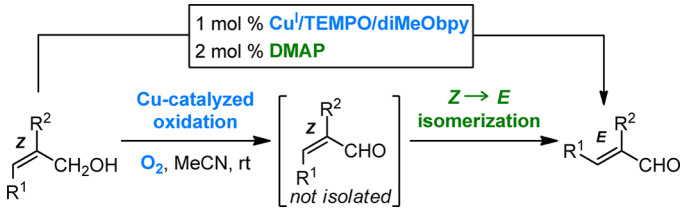
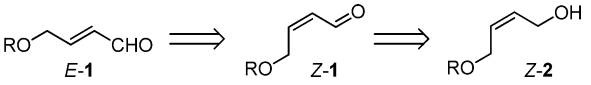
ABSTRACT



A method for generating (*E*)-α,β-unsaturated aldehydes from *Z*-allylic alcohols or *E*/*Z*-mixtures is described. The one-pot procedure involves a Cu-catalyzed oxidation followed by an organocatalytic *Z*/*E*-isomerization with *N*,*N*-dimethylaminopyridine (DMAP).

The finite availability of fossil resources urges chemists to rethink some fundamental elements of synthesis planning.[1] Strategies for designing more eco-efficient and cost-effective chemical transformations are overlapping with the agendas of "green chemistry" and "sustainable chemistry".[2] Thus, the avoidance of isolating and purifying intermediates and the joining of successive reaction steps into one-pot processes[3] are highly desirable. Many synthetic routes proceed via nonstorable aldehyde intermediates that are generated shortly before use. Telescoping the oxidation step with follow-up reactions obviates the requirement for isolating the aldehyde and provides cost savings in solvent usage and reaction vessel time. The main obstacle for merging reactions with an initial oxidation step[4] is overcoming the often harsh reaction conditions along with stoichiometric byproducts. While organocatalytic reactions with preceding MnO_2 oxidation have been reported,[5] it is desirable to reduce the amount of oxidant. Rueping et al. recently reported an oxidative iminium-activated cascade using tetra-*n*-propylammonium perruthenate (TPAP) as the catalyst and *N*-methylmorpholine-*N*-oxide (NMO) as the oxidant.[6] Further improvements could be achieved with O_2 (or aerobic oxygen) as well as H_2O_2. Both oxidants generate H_2O as the sole byproduct that is usually tolerated by the subsequent organocatalytic transformations.

Herein, we report our efforts in cascading an oxidation with an organocatalytic isomerization step that emerged from the preparation of a series differently protected *E*-4-hydroxybut-2-enal (*E*-**1**) derivatives for a total synthesis campaign. Published routes involve cross-metathesis of double protected *Z*-but-2-ene-1,4-diols with acrolein[7] or *E*-selective half-reduction of but-2-yne-1,4-diol with RedAl or $LiAlH_4$ followed by monoprotection.[8]



For economic reasons and safety concerns we decided against large-scale metal hydride reductions but opted for

(1) Sheldon, R. A. *Catal. Today* **2011**, *167*, 3.
(2) (a) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301. (b) Sheldon, R. A.; Arends, I.; Hanefeld, U. in *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007. (c) Sheldon, R. A. *Chem. Commun.* **2008**, 3352.
(3) (a) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605. (b) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492.
(4) Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851.
(5) For example, see: Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102.
(6) (a) Rueping, M.; Sundén, H.; Sugiono, E. *Chem.—Eur. J.* **2012**, *18*, 3649. (b) Rueping, M.; Dufour, J.; Maji, M. S. *Chem. Commun.* **2012**, *48*, 3406.
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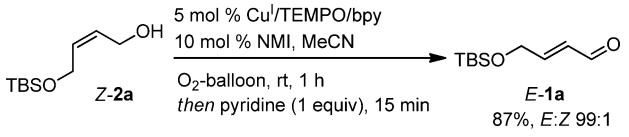
the oxidation of monoprotected *Z*-but-2-ene-1,4-diols[9] (*Z*-**2**) followed by an *Z*/*E*-isomerization. In the literature, oxidations of *Z*-**2** have been described with virtually any known oxidant.[10] Interestingly, only pyridine-based oxidations (PCC,[11] Parikh–Doering[12]) result in concomitant *Z*/*E*-isomerization. We speculated that pyridine is the responsible isomerization catalyst. Indeed, treatment of *Z*-**1** with pyridine (1 equiv)[13] results in a clean isomerization to afford *E*-**1** within 15 min. At this time, we took notice of an efficient aerobic Cu^{I}(bpy)-TEMPO oxidation of primary alcohols reported by Stahl.[14] His efficient protocol is based on pioneering work by Semmelhack,[15] Markó,[16] Sheldon,[17] and Koskinen.[18] As monoprotected *Z*-but-2-ene-1,4-diol was one of the most reactive substrates in Stahl's screening, we used his optimized conditions and added pyridine (1 equiv) after completion of the oxidation (Scheme 1). Aldehyde *E*-**1** was isolated in 87% yield. Although this one-pot procedure already solves the initial problem, we were not satisfied with the efficiency of the isomerization.

Scheme 1. One-Pot Oxidation–Isomerization of *Z*-**2a** Using Stahl's Conditions and a Stoichiometric Amount of Pyridine



A plausible mechanism involves a reversible 1,4-addition of pyridine and is related to the Morita–Baylis–Hillman (MBH) and the Rauhut–Currier (RC) reactions. Therefore, we tested a series of successful MBH and RC catalysts that would be expected to survive the oxidation conditions. Interestingly, Stahl uses *N*-methylimidazole (NMI), an aromatic amine base additive that could act as the isomerization catalyst. Figure 1 depicts the catalytic activity of pyridine, NMI, and other nitrogen-based catalysts (0.25 M *Z*-**2b** in MeCN-d_3, R = Ac, 1 mol % catalyst). Pyridine was the slowest of all tested amines and led to just 4% conversion in the observed time window (185 min).

NMI was significantly faster (11% conversion) but still not a useful catalyst. In 1985, Keck[19] reported *N*,*N*-dimethylaminopyridine (DMAP)[20] as the catalyst for the isomerization of α,β-unsaturated thioesters, and Evans[21] used a similar isomerization in the total synthesis of lepicidine. Apart from these two examples, there has been no systematic investigation of pyridine/DMAP-catalyzed isomerizations. In our test reaction, DMAP was a very active catalyst resulting in complete conversion. Using Mayr's nucleophilicity parameter *N* as a guide,[22] we tested more nucleophilic analogs of DMAP (*N* = 15 in MeCN). The recently reported Bn-Super-DMAP[23] (*N* = 18)

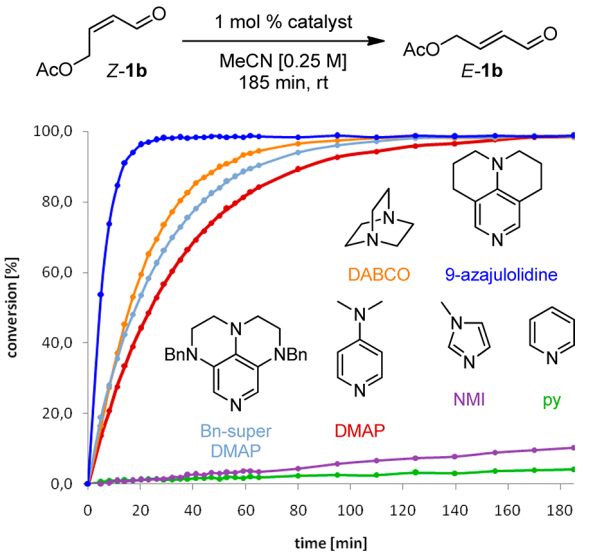


Figure 1. Conversion of *Z*-**1b** vs time plots of the *Z*/*E*-isomerization with different aromatic amines as catalyst.

(8) (a) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Payl, F. *J. Org. Chem.* **2000**, *65*, 7959. (b) Crimmins, M. T.; DeBaillie, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 4936.

(9) *E*-But-2-ene-1,4-diol is significantly more expensive.

(10) (a) Swern: Uenishi, J.; Motoyama, M.; Kimura, Y.; Yonemitsu, O. *Heterocycles* **1998**, *47*, 439. (b) PCC: Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708. (c) PDC: Crilley, M. M. L.; Golding, B. T.; Pierpoint, C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2061. (d) TPAP/NMO: Zhang, P.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12550.

(11) Ramachandran, P. V.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2005**, *70*, 2329.

(12) Boone, M. A.; McDonald, F. E.; Lichter, J.; Lutz, S.; Cao, R.; Hardcastle, K. I. *Org. Lett.* **2009**, *11*, 851.

(13) It is possible to use substoichiometric amounts of pyridine at the cost of extended reaction times.

(14) (a) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901. (b) Hoover, J. M.; Steves, J. E.; Stahl, S. S. *Nat. Protoc.* **2012**, *7*, 1162. (c) For an alternative organocatalytic oxidation, see: Shibuya, M.; Osada, Y.; Sasano, Y.; Tomizawa, M.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 6497.

(15) (a) Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374. (b) Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A. *Tetrahedron Lett.* **1986**, *27*, 1119.

(16) (a) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044. (b) Markó, I. E.; Gautier, A.; Chellé-Regnaut, I.; Giles, P. R.; Tsukazaki, M.; Urch, C. J.; Brown, S. M. *J. Org. Chem.* **1998**, *63*, 7576. (c) Markó, I. E.; Gautier, A.; Mutonkole, J.-L.; Dumeunier, R.; Ates, A.; Urch, C. J.; Brown, S. M. *J. Organomet. Chem.* **2001**, *624*, 344. (d) Markó, I. E.; Gautier, A.; Dumeunier, R.; Doda, K.; Philippart, F.; Brown, S. M.; Urch, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1588.

(17) (a) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 1591. (b) Dijksman, A.; Marino-González, A.; Mirata i Payeras, A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826. (c) Sheldon, R. A.; Arends, I. W. C. E.; Ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774. (d) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232. (e) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414. (f) Gamez, P.; Arends, I. W. C. E.; Sheldon, R. A.; Reedijk, J. *Adv. Synth. Catal.* **2004**, *346*, 805.

(18) Kumpulainen, E. T. T.; Koskinen, A. M. P. *Chem.—Eur. J.* **2009**, *15*, 10901.

(19) Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709.

(20) Steglich, W.; Höfle, G. *Tetrahedron Lett.* **1970**, *54*, 4727.

(21) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

(22) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(23) (a) De Rycke, N.; Berionni, G.; Couty, F.; Mayr, H.; Goumont, R.; David, O. R. P. *Org. Lett.* **2011**, *13*, 530. (b) For a review, see: De Rycke, N.; Couty, F.; David, O. R. P. *Chem.—Eur. J.* **2011**, *17*, 12852.

showed a remarkable increase in the reaction rates, and the well-established MBH-catalyst DABCO (N = 19) was even faster. The most effective candidate of our screening was 9-azajulolidine,[24] an exceptional acylation catalyst[25] that was recently used in aza-MBH reactions.[26]

Despite the good correlation between reaction rates and nucleophilicity parameters, we are not convinced that the addition of the catalyst is the rate-limiting step. Studies of Houk and Krenske[27] on 1,4-additions of thiols to vinylketones suggest that *Z*-alkenones react faster than the corresponding *E*-diastereomers. If the principle of the microscopic reversibility is applicable, the elimination to the thermodynamically more stable *E*-isomer should be rate-limiting, thereby making the nucleofugic properties of the catalyst the dominating factor. In summary, DMAP is a good and affordable catalyst possessing sufficient activity. If a lower catalyst loading is desired or less reactive substrates are used, 9-azajulolidine is an excellent choice.

After investigating the second step of the combined oxidation–isomerization, we tried to optimize the one-pot procedure (Table 1). Employing an oxygen balloon allowed a lower catalyst loading to be used, which minimized inferences in the subsequent transformation as being more important than the use of air as oxidant. At this point, we wondered whether DMAP could act as an aromatic base in the oxidation step. Replacing NMI by DMAP not only was possible but also resulted in an accelerated oxidation (entries 1 and 2). Together with changing the ligand to the more electron-rich diMeObpy,[17f] it was now possible to carry out the one-pot oxidation–isomerization with 1 mol % Cu^{I}/TEMPO/diMeObpy and 2 mol % DMAP. Gratifyingly, the positive effects of DMAP and diMeObpy appear to be synergistic (entries 1–4). The oxidation has been used in a preparative[28] setting up to 0.1 mol scale. Alternative protecting groups did not affect the rate of the oxidation step but showed a marked influence on the isomerization rate (entries 5–8).

With optimized conditions for the oxidation of *Z*-**2** in hand, we investigated the scope of this one-pot process for other allylic alcohols. Our method is well-suited for substrates where the *E*-isomer is less available or, more importantly, where the allylic alcohol is an *E*/*Z*-mixture. In such a case, the *E*/*Z*-ratio can be driven into the thermodynamic equilibrium without the need for chromatographic separation of the allylic alcohol. As shown in

(24) Held, I.; Xu, S.; Zipse, H. *Synthesis* **2007**, 1185 and references therein.
(25) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4826.
(26) Lindner, C.; Tandon, R.; Liu, Y.; Maryasin, B.; Zipse, H. *Org. Biomol. Chem.* **2012**, *10*, 3210.
(27) Krenske, E. H.; Petter, R. C.; Zhu, Z.; Houk, K. N. *J. Org. Chem.* **2011**, *76*, 5074.
(28)

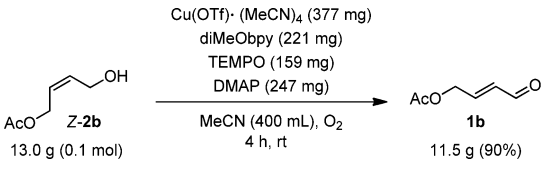
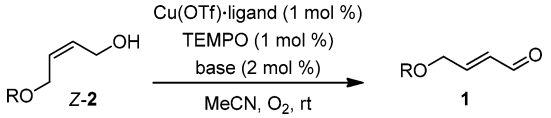


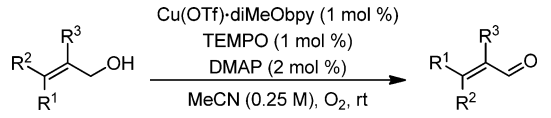
Table 1. One-Pot Oxidation–Isomerization of Monoprotected *Z*-But-2-ene-1,4-diols (*Z*-**2**)

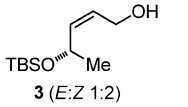
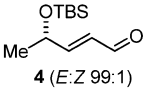
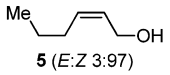
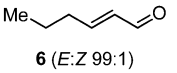
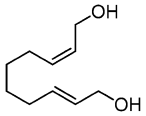
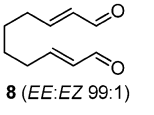
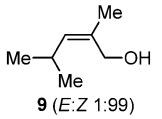
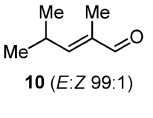
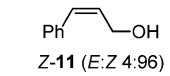
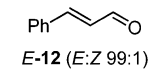
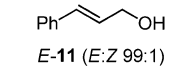
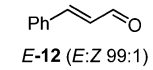
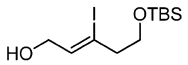
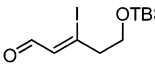


entry	**2**, R	t [h]	ligand	base	E/Z[a]	[%][b]
1[c]	**2b**, Ac	1.5	bpy	NMI	7:93	20
2[c]	**2b**, Ac	1.5	bpy	DMAP	99:1	58
3[c]	**2b**, Ac	1.5	diMeObpy	NMI	15:85	78
4[c]	**2b**, Ac	1.5	diMeObpy	DMAP	99:1	89
5[d]	**2a**, TBS	1.25	diMeObpy	DMAP	99:1	86
6[d]	**2c**, Bn	3.5	diMeObpy	DMAP	99:1	96
7[d]	**2d**, PMB	5	diMeObpy	DMAP	99:1	86
8[c]	**2e**, THP	2.5	diMeObpy	DMAP	99:1	95

[a] Determined by NMR spectroscopy. [b] Isolated yield. [c] 1 mmol scale. [d] 10 mmol scale.

Table 2. Substrate Scope for Oxidation of Allylic Alcohols



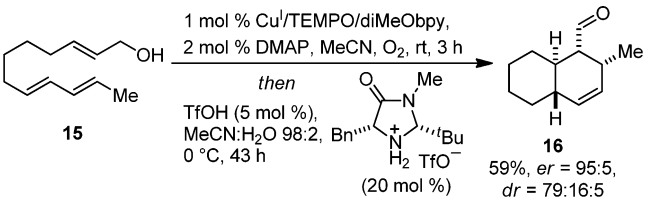
entry	alcohol	aldehyde	t [h]	[%][a]
1[d]	 **3** (*E*:*Z* 1:2)	 **4** (*E*:*Z* 99:1)	11	91
2[d]			5[b]	89
3[e]	 **5** (*E*:*Z* 3:97)	 **6** (*E*:*Z* 99:1)	15.5[b]	66
4[d]	 **7** (*EE*:*EZ* 1:99)	 **8** (*EE*:*EZ* 99:1)	7.5	91
5[e]	 **9** (*E*:*Z* 1:99)	 **10** (*E*:*Z* 99:1)	69[c]	67
6	 *Z*-**11** (*E*:*Z* 4:96)	 *E*-**12** (*E*:*Z* 99:1)	28[f]	85
7	 *E*-**11** (*E*:*Z* 99:1)	 *E*-**12** (*E*:*Z* 99:1)	2[f]	86
8[d]	 **13** (*E*:*Z* 1:99)	 **14** (*E*:*Z* 1:99)	1.25	89

[a] Isolated yield. [b] 9-Azajulolidine was used instead of DMAP. [c] After completion of the oxidation, 9-azajulolidine (5 mol %) was added and the reaction mixture was heated to 95 °C. [d] 1 mmol scale. [e] 10 mmol scale. The products were purified by distillation. [f] c = 0.5 M.

Table 2, allylic alcohol **3**[29] was obtained as a 2:1 *Z*/*E* isomeric mixture by a Wittig olefination/Dibal-H reduction sequence from TBS-protected lactaldehyde. The oxidation–isomerization of **3** to aldehyde **4** reveals that an alkyl substitution in the 4-position slows down the rate of the isomerization (entry 1). Replacing DMAP with 9-azajulolidine (entry 2) led to a significant acceleration of the reaction. Similarly, removal of the 4-silyloxy group resulted in a lower isomerization rate and necessitated the use of 9-azajulolidine (entry 3). In the bidirectional elongation of a dialdehyde, an olefination with an *E*/*Z*-selectivity of 95:5 accumulates to an *EE*/*EZ*-ratio of 90:10, rendering a separation of the minor isomer necessary. Taking advantage of our stereoconvergent oxidation, even starting from an *EE*/*EZ*-ratio of 1:99 of the bisallylic alcohol **7** (entry 4) results in a 99:1 *EE*/*EZ*-ratio of the dialdehyde **8**, an important building block in the synthesis of pheromones.[30] The isomerization of 2-Me-substituted α,β-unsaturated aldehydes such as **9**[31] proved to be very challenging (entry 5). Upon completion of the oxidation, only heating to reflux resulted in a complete isomerization to give aldehyde **10**. The oxidation of allylic alcohols *Z*-**11** and *E*-**11** under standard conditions showed comparable oxidation rates with a slow *Z*/*E*-isomerization (cf. entries 6 and 7). The low catalyst loading of 1 mol % (Cu^I/ligand/TEMPO) makes our protocol attractive even without accompanying isomerization. The oxidation of the allylic alcohol **13** is one step in our total synthesis of ripostatin B.[32] The desired aldehyde **14** could be obtained cleanly in 89% yield (entry 8).

At this point, we explored whether other organocatalytic reactions of α,β-unsaturated aldehydes than the DMAP-catalyzed isomerization could be coupled with the catalytic oxidation in a one-pot fashion. As a model reaction, we selected an organocatalytic intramolecular Diels–Alder reaction[33] first described by Koskinen[34] and MacMillan[35] that has been used in our group in total syntheses of UCS1025A[36] and amaminol B.[37] Scheme 2 shows the Diels–Alder step in the synthesis of the key decalin subunit **16** of UCS1025A from trienol **15**. To test the compatibility of the Diels–Alder reaction with the oxidation conditions,[38] we carried out both steps separately (with isolation of the aldehyde) and as a one-pot procedure. In both cases, very similar yields and selectivities were observed. On this basis, we are optimistic that other organocatalytic processes could be successfully coupled with Cu-catalyzed oxidations.

Scheme 2. One-Pot Oxidation/Diels–Alder Reaction



We have developed a stereoconvergent one-pot oxidation–isomerization of allylic alcohols with oxygen as the oxidant and DMAP as the organocatalyst. Our optimized conditions, with or without isomerization, constitute an efficient protocol (1 mol % Cu^I/TEMPO/diMeObpy and 2 mol % DMAP) that should allow for telescoping with other organocatalytic transformations[39] and further displace traditional superstoichiometric oxidants such as MnO_2.

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Supporting Information Available. Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(39) After submission of our manuscript, an aerobic oxidation-initiated organocatalytic multistep transformation of allylic alcohols was reported using 10 mol% Cu^I/TEMPO as a catalyst: Ho, X.-H.; Oh, H.-J.; Jang, H.-Y. *Eur. J. Org. Chem.* **2012**DOI: 10.1002/ejoc.201200863.

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