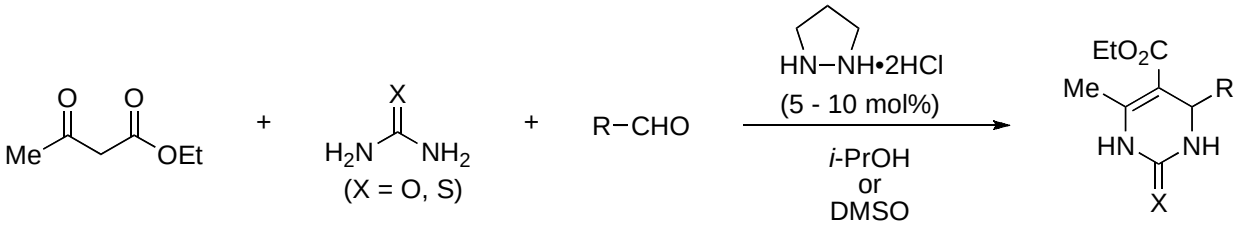
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Biginelli Reactions Catalyzed by Hydrazine Type Organocatalyst

Leave this area blank for abstract info.

Ichiro Suzuki,* Yukari Iwata and Kei Takeda



TETRAHEDRON
LETTERS

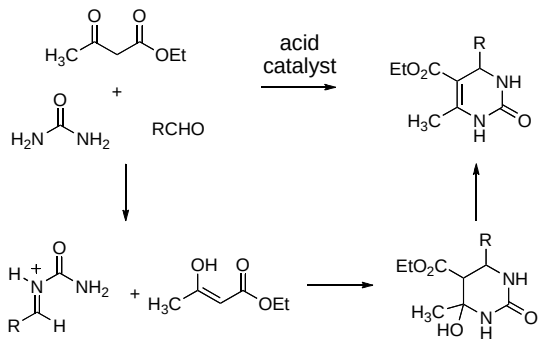
Biginelli Reactions Catalyzed by Hydrazine Type Organocatalyst

Ichiro Suzuki,* Yukari Iwata and Kei Takeda

Department of Synthetic Organic Chemistry, Graduate School of Biomedical Sciences, Hirosahima University, Kasumi 1-2-3, Minami-ku, Hiroshima, 734-8553, Japan

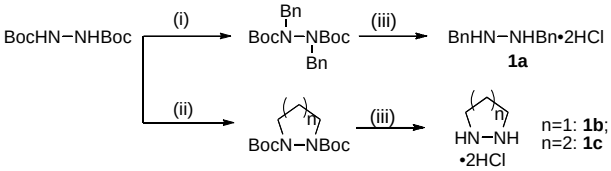
Abstract—Pyrazolidine dihydrochloride can be used in the acceleration of Biginelli reactions between urea, ethyl acetoacetate and various aldehydes to provide DHPMs in good to excellent yields.

Biginelli-type condensation reaction, which is one of the multicomponent reactions, is a very useful reaction for preparing 3,4-dihydropyrimidin-2(1*H*)-ones. Traditionally, Biginelli reactions were carried out under strongly acidic conditions with heating, and the yields were only low to moderate.[1]



Scheme 1. Biginelli reaction.

Recently, several 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) have been revealed to have interesting biological and pharmaceutical properties, including antiviral, antitumor, antibacterial, antiinflammatory and antihypertensive properties, and these compounds have emerged as integral backbones of several calcium channel blockers, antihypertensives, α_{1a}-adrenergic antagonists, and neuropeptide Y (NPY) antagonists.[2] Thus, in the past ten years, Biginelli reactions have attracted much attention, and many improved methods, including enantioselective versions, have been exploited. In these advanced methods, Lewis or Brønsted acid was mainly used as a catalyst under milder conditions with much better results compared to the results obtained by employing traditional conditions.[3] Recently, secondary amine-based organocatalysts that promote the reactions via enamine formation have been extensively studied;[4] however, for Biginelli reactions, only a few examples using (*S*)-proline or chiral secondary amines as organocatalysts have been reported.[5] In these examples, refluxing in EtOH and a neat condition were employed, but their efficiencies were not sufficiently high and only racemic products were obtained. In the course of our study to develop efficient nucleophilic chiral organocatalysts, we became interested in hydrazines because hydrazines are more nucleophilic due to the α-heteroatom effect[6a-6c] and their salts with acids are more acidic than related amines.[6d] Some hydrazids have been reported to catalyze Diels-Alder reactions and 1,3-dipolar cycloaddition reactions efficiently, but the number of examples is not so large.[7] In this communication, we report that pyrazolidine dihydrochloride **1b** is a more effective organocatalyst than the widely used modified pyrolidine derivatives for Biginelli reactions.

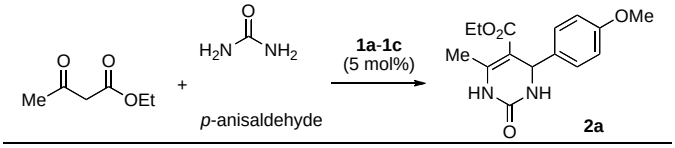


Scheme 2. *Reagents and conditions*: (i) NaH (2.4 equiv.), BnBr (2.2 equiv.) in DMF, 0 ˚C to rt, 75%. (ii) NaH (2.4 equiv.), $BrCH_2(CH_2)_nCH_2Br$ (1.2 equiv.), 0 ˚C to rt, 86% for n=1 and 80% for n=2. (iii) HCl (5 equiv.) in 1,4-dioxane, rt, 94% for **1a**, 90% for **1b** and 95% for **1c**.

* Corresponding author. Tel.: +081-082-257-5321; fax: +081-082-257-5184; e-mail: isuzuki@hiroshima-u.ac.jp.

First, we prepared hydrazines **1a-1c** as shown in Scheme 2 and screened them for their catalytic abilities in Biginelli reactions.[8] Hydrazine salts **1a-1c** were prepared as dihydrochlorides. We also tried to prepare 1,2-dibenzyhydrazine, pyrazolidine and 1,2-piperazine in acid-free forms; however, these acid-free hydrazines were unstable and suffered from air-oxidation under neutral to basic conditions.[9] The reactions were carried out using *p*-anisaldehyde, urea and ethyl acetoacetate in the presence of 5 mol% of catalysts **1a-1c**, 10 mol% of dibenzylamine hydrochloride, (*S*)-proline and HCl in methanol at room temperature. The results are summarized in Table 1.

Table 1. Hydrazine-catalyzed Biginelli reaction using *p*-anisaldehyde, ethyl acetoacetate and urea.[a]

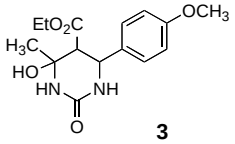


Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	Bn_2NH•HCl[b]	MeOH	24	< 5[c]
2	**1a**	MeOH	24	98
3	**1a**	MeOH	3.5	30[c]
4	**1b**	MeOH	3.5	98
5	**1c**	MeOH	3.5	< 5[c]
6	(*S*)-Proline[b]	none[d]	3.5	< 5[c]
7	(*S*)-Proline[b]	MeOH	3.5	0
8	HCl[b]	MeOH	3.5	18[c]

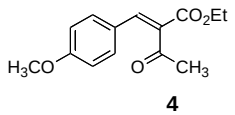
a) Reactions were carried out using aldehydes (1.0 mmol), ethyl acetoacetate (1.5 mmol) and urea (1.5 mmol) in MeOH (1 mL) with 5-10 mol% of catalysts at rt. b) 10 mol% of catalysts were loaded. c) *p*-anisaldehyde was recovered and any other byproducts were not formed. d) Solvent-free conditions were employed; see ref. 5a.

When dihydrochloride **1a** was used as a catalyst, the reaction occurred and DHPM **2a** was obtained quantitatively after 24 hr, whereas dibenzylamine hydrochloride did not show any remarkable catalytic activity (entries 1 and 2). These results encouraged us to test the catalytic activities of other hydrazine dihydrochlorides **1b** and **1c**, and we found pyrazolidine dihydrochloride **1b** showed superior catalytic activity to that of **1a** and **1c**. The reaction proceeded very smoothly in the presence of 5 mol% of catalyst **1b** to provide DHPM **2a** quantitatively in 3.5 hr, whereas catalyst **1c** showed only a low level of catalytic activity (entries 4 and 5). Although we cannot clearly explain this difference in catalytic activity at present, we do not think that there is a simple interpretation for this difference. In general, basicity and nucleophilicity of typical amines can be estimated roughly based on electronic effects of substituents and steric congestion around a nitrogen atom. On the other hand, in hydrazines, lone-pair – lone-pair repulsion leads to an electronic preference for a nearly 90° dihedral angle between the lone-pair orbital axes, and the pyramidality at nitrogen changes with ring size and with NN twist angle.[10]

Due to these electronic and structural features, it is difficult to approximate reactivity of catalysts **1a-1c** in a manner similar to the method used for typical amines. Yadav et al. reported that (*S*)-proline could catalyze Biginelli reactions under solvent-free conditions at rt;[5a] however, we could not reproduce their results and only a trace amount of DHPM **2a** was obtained with recovery of *p*-anisaldehyde and ethyl acetoacetate at rt (entry 6). On the other hand, when (*S*)-proline-catalyzed reaction was carried out in MeOH, cyclic product **3**[5b] and adduct **4** (E/Z mixture) were obtained in 7% and 5% yields, respectively, with no DHPM **2a**.[11]



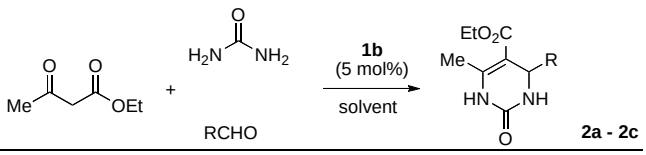
3



4

In the case of using HCl, which is a typical catalyst for Biginelli reaction, DHPM **2a** was obtained in only 18% yield at room temperature (entry 8). In Biginelli reaction, a Brønsted acid is essential to facilitate *N*-acyliminium ion formation, which is a rate-determining step. Catalyst **1b** can also work as a Brønsted acid catalyst, but its acidity should be lower than that of HCl. Despite the lower acidity, catalyst **1b** showed a considerably higher level of catalytic activity than did HCl. These results suggest that catalyst **1b** worked not only as an acid catalyst but also as a nucleophilic catalyst to form a reactive enehydrazine intermediate from ethyl acetoacetate. While (*S*)-proline also affected the reaction in a manner similar to catalyst **1b**, (*S*)-proline catalyzed the reactions less efficiently than did catalyst **1b**, because the nucleophilicity of catalyst **1b** is enhanced by the α-heteroatom effect. Next we screened the reaction solvents for their efficiency by using three aldehydes, *p*-anisaldehyde, *p*-nitrobenzaldehyde and hexanal. The results are shown in Table 2.

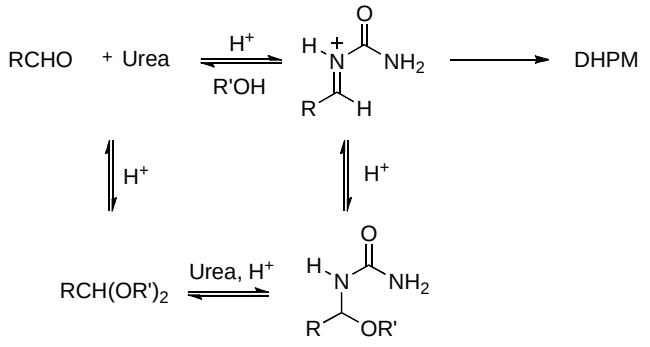
Table 2. Solvent-effects on hydrazine•2HCl-catalyzed Biginelli reactions.[a]



Solvent	R, Yield / % (reaction time)		
	p-$MeOC_6H_4$ (**2a**)	*p*-$NO_2C_6H_4$ (**2b**)	*n*-C_5H_{11} (**2c**)
MeOH	98 (4 h)	49 (24 h)[b]	decomp (1 h)
EtOH	93 (4h)	51 (24 h)[b]	decomp (1 h)
i-PrOH	78 (4 h)[b], 95 (24 h)	68 (24 h)[b]	79 (24 h)[c]
CH_3CN	86 (4 h)[b], 92 (24 h)	51 (24 h)[b]	41 (24 h)[c]
DMSO	61 (4 h)[b], 94 (24 h)	67 (24 h)[b]	62 (24 h)[c]
THF	79 (4 h)[b], 89 (24 h)	61 (24 h)[b]	45 (18 h)[c]

a) Reactions were carried out using aldehydes (1.0 mmol), ethyl acetoacetate (1.5 mmol) and urea (1.5 mmol) with 5mol% of catalyst **1b** at rt. b) An aldehyde was recovered. c) Decomposed products were accompanied.

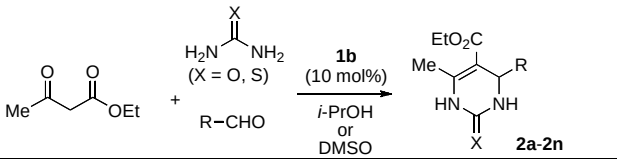
For *p*-anisaldehyde, the reactions proceeded to give excellent yields in MeOH, EtOH, *i*-PrOH, CH_3CN, DMSO and THF; however we encountered some difficulties when *p*-nitrobenzaldehyde and hexanal were employed. When *p*-nitrobenzaldehyde was used, the reaction was very slow and provided DHPM **2b** in only 49% yield with recovery of *p*-nitrobenzaldehyde even after 24 hr in MeOH. For other solvents, *i*-PrOH and DMSO gave somewhat better results than did EtOH, CH_3CN and THF. On the other hand, in the reactions of hexanal, only decomposed products were formed with no DHPM **2c** in MeOH and EtOH, though hexanal disappeared within 1 hr. Although we could not specify the decomposition pathway, an enehydrazine formation from hexanal and catalyst **1b** may be involved in the decomposition pathway.[12] Among the solvents tested, *i*-PrOH gave a better result, providing DHPM **2c** in 79% yield, than the results obtained using CH_3CN, THF and DMSO. For an *N*-acyliminium ion formation step in alcoholic solvents, an acetal and an α-alkoxy-*N*-acylamine can also be formed, and they are in equilibrium as shown in Scheme 3. *p*-Anisaldehyde is considered to form a relatively stable *N*-acyliminium ion by resonance stabilization, and consequently Biginelli reaction could proceed smoothly. On the other hand, an *N*-acyliminium ions from *p*-nitrobenzaldehyde and hexanal are unstable due to the lack of resonance stabilization and are prone to suffer from nucleophilic attack by the solvent to give unreactive α-alkoxy-*N*-acylamines. When *i*-PrOH was used as a solvent, its steric hindrance should suppress the formation of the acetal and/or the α-alkoxy-*N*-acylamine, leading to improvement in the *N*-acyliminium ion formation step. While less nucleophilic solvents, such as CH_3CN, THF and DMSO, are also more appropriate, in CH_3CN and THF, urea is hardly soluble, and catalyst **1b** could work less efficiently as an acid catalyst in DMSO, resulting in slower reaction rates than that in *i*-PrOH.



Scheme 3. Equilibrium of an *N*-acyliminium ion in R'OH.

Based on the results of solvent screening, we then examined Biginelli reactions using various aldehydes in *i*-PrOH (for some cases in DMSO), and the results are summarized in Table 3. Considering the relatively slow reaction rate in *i*-PrOH, we used 10 mol% of catalyst **1b**.

Table 3. Biginelli reactions using **1b** as a catalyst in *i*-PrOH and DMSO.[a]



Entry	R	X	Time (h)	Product	Yield (%)
1	*p*-$MeOC_6H_4$	O	8	**2a**	97
2	*p*-$NO_2C_6H_4$	O	18	**2b**	90, 23[b]
3	*n*-C_5H_{11}	O	2	**2c**	decomp[c]
4	cyclohexyl	O	8	**2d**	93
5	*tert*-butyl	O	8	**2e**	95
6	*p*-ClC_6H_4	O	4	**2f**	92
7	*p*-BrC_6H_4	O	4	**2g**	95
8	*m*-$MeOC_6H_4$	O	3	**2h**	93
9	*o*-$MeOC_6H_4$	O	5	**2i**	97
10	*m*-$NO_2C_6H_4$	O	10	**2j**	0, 88[d]
11	*o*- $NO_2C_6H_4$	O	24	**2k**	< 46, 91[d]
12	C_6H_5CH=CH	O	24	**2l**	70, decomp[d]
13	2-furyl	O	24	**2m**	62, decomp[d]
14	*p*-$MeOC_6H_4$	S	48	**2n**	91

a) Reactions were carried out using an aldehyde (1.0 mmol), ethyl acetoacetate (1.5 mmol), urea (1.5 mmol) and **1b** (10 mol%) in *i*-PrOH or DMSO (1 mL) at rt. b) The reaction was carried out at reflux for 24 hr. c) Hexanal was consumed completely in 2 hr. d) The reactions were carried out in DMSO at rt for 24 hr.

p-Anisaldehyde and *p*-nitrobenzaldehyde afforded DHPM **2a** and **2b** in 97% and 90% yields, respectively (entries 1 and 2). For *p*-nitrobenzaldehyde, we also employed reflux conditions; however, the yield was lowered to 23%, probably due to decomposition of catalyst **1b** (entry 2).[13] When the reaction of hexanal was carried out in the presence of 10 mol% of catalyst **1b**, interestingly, only decomposed products were obtained with no DHPM **2c** as in the reactions carried out in EtOH or MeOH, though DHPM **2c** was obtained in 79% yield in the presence of 5 mol% of catalyst **1b** in *i*-PrOH (entry 3 in Table 3 and Table 2). In the reaction of hexanal, the amount of catalyst **1b** seemed to be important and to affect the reaction course. On the other hand, cyclohexanecarbaldehyde and pivalaldehyde afforded DHPM **2d** and **2e** in 93% and 95% yields, respectively (entries 4 and 5). For cyclohexanecarbaldehyde, its steric hindrance would prevent enehydrazine and/or acetal formation to facilitate the reactions. Other aromatic aldehydes also gave DHPM **2f**–**2i** in excellent yields (entries 6-9). Unexpectedly, *m*-nitrobenzaldehyde did not react to give DHPM **2j**, and diisopropyl acetal of *m*-nitrobenzaldehyde was formed in 39% yield. For *m*-nitrobenzaldehyde, DMSO was better solvents to provide DHPM **2j** in 88% yield (entry 10). Although we cannot clearly explain this solvent effect, low solubility of an intermediary *N*-acyliminium ion and related *N*-acyl species to *i*-PrOH may affect the reaction efficiency. *o*-Nitrobenzaldehyde gave DHPM **2k** in 46% yields along

with considerable amounts of inseparable impurities, and in this case also DMSO was an optimal solvent to give DHPM **2k** in 91% yield (entry 11). Biginelli reactions using cinnamaldehyde and acid-sensitive furfural were also catalyzed by catalyst **1b**, providing DHPMs **2l** and **2m** in 70% and 62% yields, respectively (entries 12 and 13). We examined the same reactions in DMSO, but only decomposed products were obtained. It is noteworthy that relatively low-reactive thiourea could be used as a component of Biginelli reactions and **2n** was obtained in 91% yield, whereas prolonged reaction time (48 hr) was needed (entry 14).

In conclusion, we demonstrated that pyrazolidine dihydrochloride **1b** worked as a better catalyst for the Biginelli reaction than do secondary amines to provide DHPMs in good to excellent yields under mild conditions. Development of new hydrazine-type organocatalysts for enantioselective Biginelli reactions is now underway.

References

1. (a) Biginelli, P. *Ber*. **1891**, *24*, 2962; (b) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879; (c) Kappe, C. O.; Stadler, A. in *Org. Reaction,* Paquette, L. A., Ed.; Wiley-interscience: New York, 2004, vol. 63, pp 1, and references cited herein.
2. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.
3. (a) Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*, 7343; (b) Suzuki, I.; Suzumura, Y.; Takeda, K. *Tetrahedron Lett.* **2006**, *47*, 7861; (c) Huang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386; (d) Su, W.; Li, J.; Zheng Z.; Shen, Y. *Tetrahedron Lett*. **2005**, *46*, 6037; (e) Sun, Q.; Wang, Y.; Ge, Z.; Cheng, T.; Li, R. *Synthesis*, **2004**, 1047; (f) Muñoz-Muñiz, O.; Juaristi, E. *Arkivoc* **2003**, *xi*, 16; (g) Maiti, G.; Kundu, P.; Guin, C. *Tetrahedron Lett.* **2003**, *44*, 2757; (h) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587; (i) Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305; (j) Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett.* **2002**, *43*, 2657; (k) Lu, J.; Bai, Y. *Synthesis*, **2002**, 466; (l) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett*, **2001**, 863; (m) Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. *Tetrahedron Lett.* **2001**, *42*, 7873; (n) Lu, J.; Ma, H. *Synlett*, **2000**, 63; (o) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864; (p) Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075; (q) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270; (r) Hu, E. H.; Sidler, D. R.; Dolling, U. –H. *J. Org. Chem.* **1998**, *63*, 3454;
4. (a) List, B. *Chem. Commun.* **2006**, 819; (b) List, B. *Acc. Chem. Res*. **2004**, *37*, 548; (c) Notz, W.; Tanaka, F.; Barbas, III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580.
5. (a) Mabry, J.; Ganem, B. *Tetrahedron Lett.* **2006**, *47*, 55. (b) Yadav, J. S.; Kumar, S. P.; Kondaji, G.; Rao, R. S.; Nagaiah, K. *Chem. Lett.* **2004**, *33*, 1168.
6. (a) Grekov, A. P.; Veselov, V. Y. *Russ. Chem. Rev.* **1978**, *16*, 87; (b) Fina, N. J.; Edwards, J. O. *Int. J. Chem. Kinet.* **1973**, *5*, 1; (c) Fleming, I. in *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: Chichester, 1976. (d) Hinman, R. L. *J. Org. Chem.* **1958**, *23*, 1587.
7. (a) Lemay, M.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 4663; (b) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141; (c) Cavill, J. L.; Peters, J. –U.; Tomkinson, N. C. O. *Chem. Commun.* **2003**, 728.
8. **1a**-**1c** are known compounds; see ref. for **1b** and **1c**: Ahn, J. –H.; Shin, M. -S.; Jun, M. -A.; Jung, S. -H.; Kang, S. -K.; Kim, K. -R.; Rhee, S. -D.; Kang, N. -S.; Kim, S. -Y.; Sohn, S. -K.; Kim, S. -G.; Jin, M. -S.; Lee, J. -O.; Cheon, H. -G.; Kim, S. -S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2622.
9. Engel, P. S.; Wu, W. –X. *J. Am. Chem. Soc.* **1989**, *111*, 1830.
10. (a) Song, J. –W.; Li, H. –J.; Choi, Y. –S.; Yoon, C. –J. *J. Phys. Chem. A* **2006**, 110, 2065. (b) Nelsen, S. F.; Rumack, D. T.; Sieck, L. Y.; Meot-Ner (Mautner), M. *J. Am. Chem. Soc.* **1988**, *110*, 6303. (c) Nelsen, S. F.; Peacock, V.; Weisman, G. R. *J. Am. Chem. Soc.* **1976**, *98*, 5269.
11. We attempted to isolate **3**; however, compound **3** was partially dehydrated to give DHPM **2a** during purification using a SiO_2 column chromatography.
12. When hexanal was treated with 5 mol% of catalyst **1b** in methanol at rt, hexanal disappeared within 1 hr, and considerable amount of inseparable decomposed products were formed along with hexanal dimethylacetal.
13. When a solution of catalyst **1b** in *i*-PrOH was refluxed, the solution immediately became yellow and decomposition of catalyst **1b** was observed on TLC.