

Pendant Alkoxy Groups on N Aryl Substitutions Drive the Efficiency of Imidazolylidene Catalysts for Homoenolate Annulation from Enal and Aldehyde

著者	Kyan Ryuji, Sato Kohei, Mase Nobuyuki, Narumi Tetsuo
journal or publication title	Angewandte Chemie International Edition
volume	59
number	43
page range	19031-19036
year	2020-08-20
出版者	Wiley
権利	This is the accepted version of the following article: Angew. Chem. Int. Ed. 2020, 59, 19031, which has been published in final form at [https://doi.org/10.1002/anie.202008631]. This article may be used for non-commercial purposes in accordance with the Wiley Self-Archiving Policy [https://authorservices.wiley.com/author-resources/Journal-Authors/licensing/self-archiving.html].
URL	http://hdl.handle.net/10297/00027740

doi: 10.1002/anie.202008631

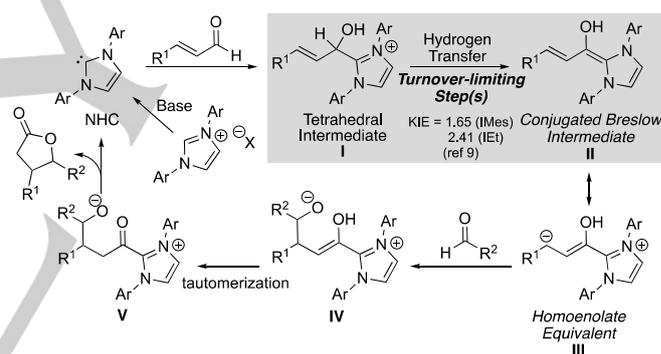
Pendant Alkoxy Groups on N-Aryl Substitutions Drive the Efficiency of Imidazolylidene Catalysts for Homoenolate Annulation from Enal and Aldehyde

Ryuji Kyan^[a], Kohei Sato^[b,c], Nobuyuki Mase^[a,b,c,d] and Tetsuo Narumi*^[a,b,c,d]

Abstract: Hydrogen-transfer in the tetrahedral intermediate generated from an imidazolylidene catalyst and α,β -unsaturated aldehyde forms a conjugated Breslow intermediate. This is a critical step affecting the efficiency of the NHC-catalyzed γ -butyrolactone formation *via* homoenolate addition to aryl aldehydes. A novel type of imidazolylidene catalyst with pendant alkoxy groups on the *ortho*-N-aryl groups is described. Catalyst of this sort facilitates the formation of the conjugated Breslow intermediate. Studies of the rate constants for homoenolate annulation affording γ -butyrolactones, reveal that introduction of the oxygen atoms in the appropriate position of the N-aryl substituents can increase the efficiency of imidazolylidene catalysts. Structural and mechanistic studies revealed that pendant alkoxy groups can be located close to the proton of the tetrahedral intermediate, thereby facilitating the proton transfer.

Conjugated Breslow intermediates, generated by the reaction of α,β -unsaturated aldehydes with N-heterocyclic carbenes (NHCs), are reactive species that enable conversion of simple carbonyl compounds to structurally complex molecules.¹ In particular, the umpolung activation of α,β -unsaturated aldehydes generates a homoenolate species with both a nucleophilic site at the γ -carbon and an electrophilic site at the carbonyl carbon. This species allows unique bond formations that differ from the classical examples. Glorius and Bode independently reported the first NHC-catalyzed homoenolate reaction for γ -butyrolactone formation using imidazolium-derived NHCs (imidazolylienes).² Mechanistically, reaction of the imidazolylienes with α,β -unsaturated aldehydes generates the tetrahedral intermediate (I), which can be converted by hydrogen transfer to the conjugated Breslow intermediate (II) (Scheme 1). Subsequently, nucleophilic attack by the

homoenolate equivalent (III) to the aryl aldehyde results in the formation of an adduct (IV). This is followed by tautomerization and cyclization to form a γ -butyrolactones. Using NHC-catalyzed generation of homoenolate equivalents,³ a series of synthetic methodologies producing multi-substituted heterocycles and carbocycles including γ -lactams,⁴ cyclopentenes,⁵ δ -lactones,⁶ bicyclic β -lactones⁷ or benzenes⁷ have been developed. However, the further exploration of this rich chemistry is currently hampered by the paucity of methods for increasing the homoenolate reactivity of NHCs⁸ and by poor examples of the mechanistic and the kinetic studies of homoenolate reactions catalyzed by NHC, particularly imidazolylienes⁹ and imidazolinylienes.¹⁰



Scheme 1. NHC-catalyzed γ -butyrolactone formation via homoenolate addition.

The N-aryl groups of NHCs play a critical role in determining the nature of NHC catalysts including the acidity of the precatalysts,¹¹ the reaction preference,¹² and the kinetic profiles.¹³ As part of our interest in the development of effective NHC catalysts for the homoenolate-mediated reactions, we recently reported the substituent effects of the N-aryl groups of imidazolylienes on their catalyst activity for homoenolate annulation in the presence of excess base affording γ -butyrolactones (Figure 1a).⁹ In that study, the 2,6-diethylphenyl group was identified as a suitable N-aryl group and the imidazolylidene with 2,6-diethylphenyl groups showed higher catalyst activity than the frequently used IMes in the reaction. Moreover, our mechanistic studies revealed that the effect of the 2,6-diethylphenyl groups could affect the hydrogen-transfer step which limits the turnover.

[a] R. Kyan, Prof. Dr. N. Mase, Dr. T. Narumi
Graduate School of Science and Technology, Shizuoka University
3-5-1 Johoku, Hamamatsu 432-8561 Shizuoka (Japan)
E-mail: narumi.tetsuo@shizuoka.ac.jp

[b] Dr. K. Sato, Prof. Dr. N. Mase, Dr. T. Narumi
Department of Applied Chemistry and Biochemical Engineering,
Faculty of Engineering, Shizuoka University (Japan)

[c] Dr. K. Sato, Prof. Dr. N. Mase, Dr. T. Narumi
Course of Applied Chemistry and Biochemical Engineering,
Department of Engineering, Graduate School of Integrated Science
and Technology, Shizuoka University (Japan)

[d] Prof. Dr. N. Mase, Dr. T. Narumi
Research Institute of Green Science and Technology, Shizuoka
University (Japan)

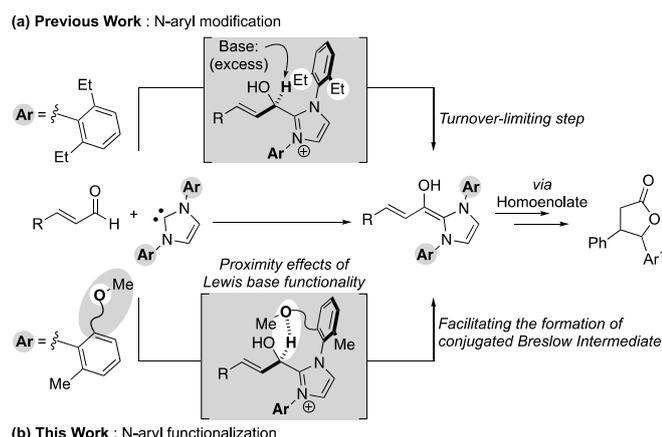
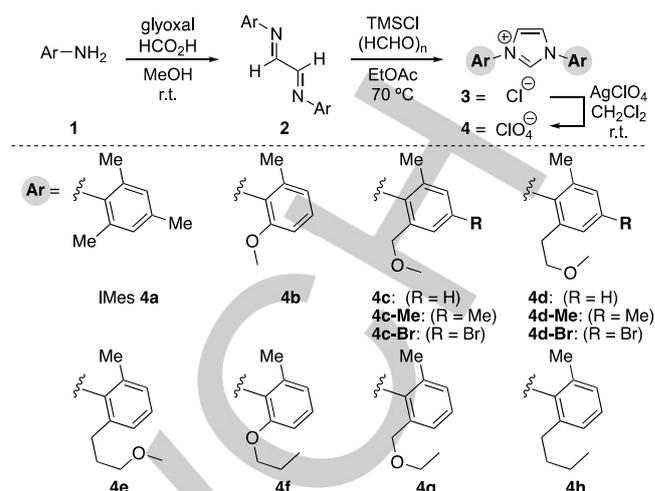


Figure 1. Imidazolydene catalysts for homoenate annulation.

Based our observations concerning the potentials of N-aryl groups as NHC catalysts, we considered the possibility of the functionalization of N-aryl substituents that could promote the formation of the conjugated Breslow intermediates (Figure 1b). This led us to the catalyst design utilizing the proximity effects by Lewis bases functionality that have been reported to increase the rate of nucleophilic addition of NHC into the aryl aldehyde substrates^{13c} and also to accelerate the proton transfer in the tetrahedral intermediates.^{13a}

In this study, we describe the proximity effects on tetrahedral intermediates in imidazolydene catalysis with pendant alkoxy groups. These studies reveal that introduction of the oxygen atoms on the *ortho*-substituents of N-aryl groups of the imidazolydene catalysts leads to enhancement of the efficiency of the imidazolydene catalysts in γ -butyrolactone formation. In particular, the imidazolydene catalysts bearing 2-methoxyethyl-6-methylphenyl groups show higher homoenate reactivity than IMes. Mechanistic studies disclosed that the introduced oxygen functionalities can facilitate the hydrogen-transfer of the tetrahedral intermediate in turnover-limiting steps, resulting in acceleration of the generation of the conjugated Breslow intermediate.

For the development of novel imidazolydene catalysts with pendant alkoxy groups, we synthesized a series of imidazolium salts (Scheme 2) in 5–45% yield in 3 steps. Briefly, the corresponding anilines (**1**) reacted with 40% glyoxal under acidic conditions to give diimines (**2**). Subsequently, the diimines (**2**) were converted to imidazolium chlorides (**3**).¹⁴ The pure imidazolium salts were obtained after the anion exchange of the chloride (**3**) to form the perchlorate (**4**).¹⁵



Scheme 2. Synthesis of imidazolium salts **4a–4h**.

To examine this catalyst design, we evaluated the catalytic activities of precatalysts **4b–4e** with pendant alkoxy groups on N-aryl *ortho*-substituents (Figure 2). As a standard condition, the reaction of cinnamaldehyde (**5**, 1.0 equiv) with *para*-bromobenzaldehyde (**6**, 2.0 equiv) was carried out in the presence of 10 mol% of the imidazolium salt and 10 mol% of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) in THF-*d*₆ (0.5 M) at 25 °C in an NMR tube, and the conversion was monitored by ¹H NMR spectroscopy. In this reaction systems, the conjugated Breslow intermediate is always present in catalytic amounts, so the electrophile, benzaldehyde is essentially in large excess. Thus, standard kinetic analysis of the conversion of cinnamaldehyde (**5**) to γ -butyrolactone (**7**) exhibits a pseudo-first-order dependence as a function of cinnamaldehyde concentration versus time over half-lives. The observed rate constant of the reaction with IMes · HClO₄ (**4a**) was $2.95 \times 10^{-2} \text{ min}^{-1}$.⁹ The catalytic activity of the precatalyst (**4b**) with 2-methoxy-6-methylphenyl groups was $k_{4b} = 0.41 \times 10^{-2} \text{ min}^{-1}$, much lower than that of **4a**. In contrast, the activity of precatalyst (**4c**) with 2-methoxymethyl-6-methylphenyl ($k_{4c} = 2.67 \times 10^{-2} \text{ min}^{-1}$) groups was comparable to that of **4a** ($k_{4c}/k_{4a} = 0.91$). The activity of the precatalyst (**4d**) with 2-methoxyethyl-6-methylphenyl groups was higher than that of **4a** ($k_{4d} = 4.12 \times 10^{-2} \text{ min}^{-1}$; $k_{4d}/k_{4a} = 1.40$). We also examined the precatalyst (**4e**), whose 2-(3-methoxypropyl)-6-methylphenyl groups contain longer alkyl linkers. The activity of precatalyst (**4e**) was lower than that of **4a** ($k_{4e} = 2.24 \times 10^{-2} \text{ min}^{-1}$; $k_{4e}/k_{4a} = 0.76$).¹⁶

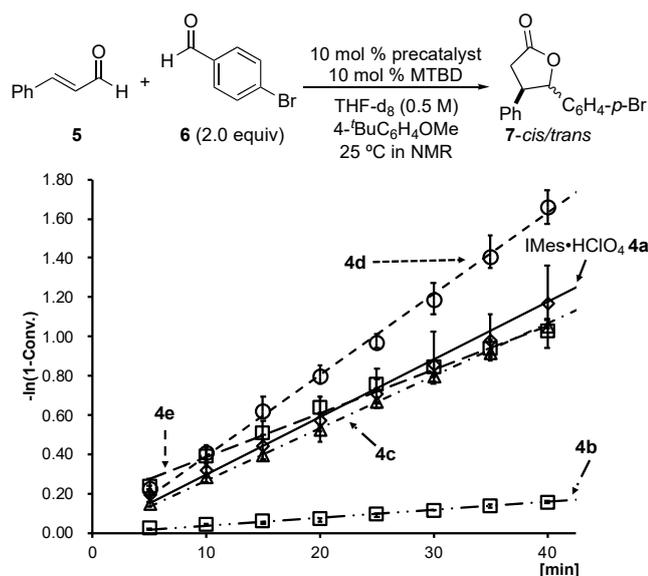


Figure 2. Kinetic profiles of γ -butyrolactone formation with precatalysts **4a–4e**.

To gain further information about the effect of the pendant alkoxy groups, we investigated the position of the oxygen atom without changing the length of the *ortho*-substituent using the precatalysts **4d**, **4f** and **4g**. This modification revealed that both the length of the *ortho*-substituents and the position of the oxygen atoms both contribute to the activity of the catalyst.¹⁷ Also, we examined the effect of *para*-substituents of the 2-methoxy-methyl-6-methylphenyl (**4c**) and 2-methoxy-ethyl-6-methylphenyl (**4d**) groups on the catalytic activity (Figure 3). When the imidazolium salt (**4c**) containing 2-methoxy-methyl-6-methylphenyl groups was employed, the electron-donating methyl group proved to be a suitable *para*-substituent and the methyl-substituted precatalyst (**4c-Me**) showed higher activity than the precatalyst (**4c**). The catalytic activity of the precatalyst (**4c-Me**) was 1.2-fold higher than that of **4c** ($k_{4c-Me} = 3.21 \times 10^{-2} \text{ min}^{-1}$). On the other hand, the catalytic activity of *para*-bromo substituted precatalyst (**4c-Br**) was lower than that of **4c** ($k_{4c-Br} = 0.78 \times 10^{-2} \text{ min}^{-1}$). In contrast, imidazolium salts (**4d**) with 2-methoxy-ethyl-6-methylphenyl groups showed a trend opposite to that of the 2-methoxy-methyl-6-methylphenyl-type precatalyst with respect to the *para*-substituents. Although the catalytic activity of the *para*-methyl substituted precatalyst (**4d-Me**) was lower than that of unsubstituted precatalyst (**4d**) ($k_{4d-Me} = 3.24 \times 10^{-2} \text{ min}^{-1}$), the catalytic activity of the *para*-bromo substituted precatalyst (**4d-Br**) was higher than that of **4d** ($k_{4d-Br} = 4.51 \times 10^{-2} \text{ min}^{-1}$). These results suggest that the length of the alkyl linker in the *N*-aryl *ortho*-substituent contributes to the *para*-substituent effect on the catalyst activity.

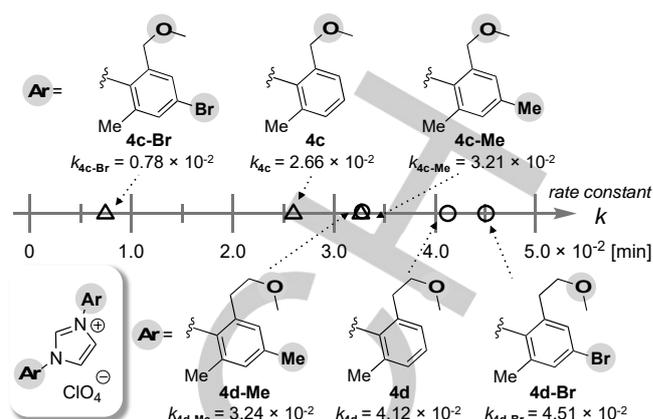
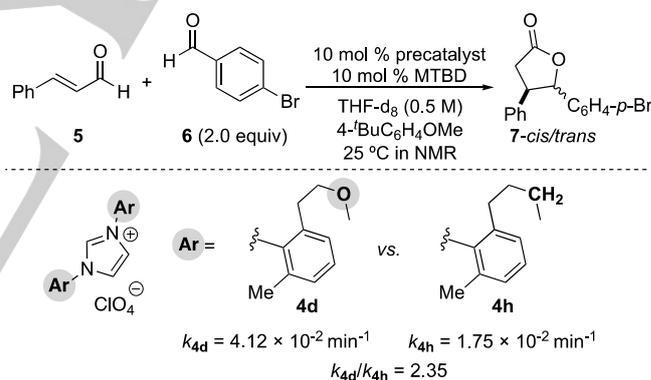


Figure 3. Effect of *para*-substituents of *N*-aryl groups on the catalytic activities.

We conducted a competition experiment between ether-linked precatalyst (**4d**) and the precatalyst (**4h**) bearing a methylene linker (Scheme 3). Under the same conditions, the ether-type precatalyst (**4d**) has higher catalytic activity than the methylene-type precatalyst (**4h**) ($k_{4h} = 1.75 \times 10^{-2} \text{ min}^{-1}$), demonstrating the significant effect in this reaction of the pendant alkoxy groups.



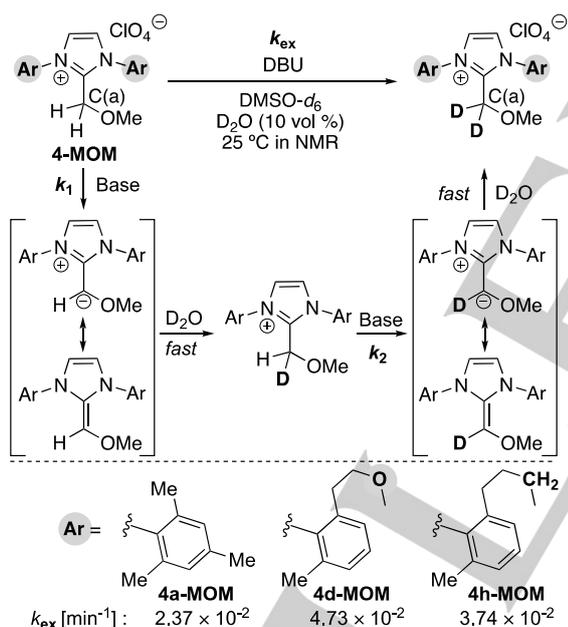
Scheme 3. Kinetic studies with **4d** and **4h**.

To explore the turnover-limiting steps in the reaction using precatalyst (**4d**), the H/D KIE studies were conducted under standard conditions using 1-deuterated cinnamaldehyde (**5-D**) (>95%-d) (see the Supporting Information). The value of k_H/k_D for the precatalyst (**4d**) was 2.38, which indicates that hydrogen-transfer from tetrahedral intermediate is at least partially turnover-limiting in this reaction.

We next analyzed the proposed kinetic relevance of the hydrogen-transfer step which generating the conjugated Breslow intermediate in the homoenolate annulation. The rate constants of deuterium exchange at the C(α)-H position in the tetrahedral intermediate model were assessed by ¹H NMR spectroscopy using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMSO-*d*₆ and 10 vol% D₂O (Scheme 4). Deuterium exchange studies

were carried out with **4a-MOM**¹⁸ derived from IMes (**4a**), **4d-MOM** derived from the ether-type precatalyst **4d**, and **4h-MOM** derived from the methylene-type precatalyst **4h**. In each case, deuteride-catalyzed exchange of C(α)-H to C(α)-D could be monitored without any side reactions and **4d-MOM** showed a higher rate constant than the **4a-MOM** and **4h-MOM** ($k_{\text{ex } 4\text{a-MOM}} = 2.37 \times 10^{-2} \text{ min}^{-1}$, $k_{\text{ex } 4\text{d-MOM}} = 4.73 \times 10^{-2} \text{ min}^{-1}$, $k_{\text{ex } 4\text{h-MOM}} = 3.74 \times 10^{-2} \text{ min}^{-1}$) for the deuterium exchange. Even in the absence of DBU, 5% deuterium exchange was observed with the ether-type **4d-MOM** after 12 days, while this exchange was not observed with **4a-MOM** and **4h-MOM**. These results suggest that the oxygen atom in the N-aryl *ortho*-substituent of **4d-MOM** facilitates the deuterium exchange. We speculated that the proximity effects of Lewis base functionality could play an important role in the enhanced rate of deuterium exchange for **4d-MOM**.¹⁹

Figure 4 shows the ¹H NMR analysis of **4d-MOM** and **4h-MOM** in CDCl₃. This shows that the C(α) protons of **4d-MOM** are non-equivalent while the C(α) protons of **4h-MOM** are chemically equivalent. This suggests that the pendant methoxy groups in **4d-MOM** could interact with acidic C(α) protons, restricting rotation about the C-C bond. This was supported by X-ray crystallographic analysis of **4d-MOM**.²⁰



Scheme 4. Deuterium exchange study of the tetrahedral intermediate model. Starting conditions: NHC-MOM (0.005 M), DBU (0.025 M), in DMSO-*d*₆: D₂O = 9:1 at 25 °C.

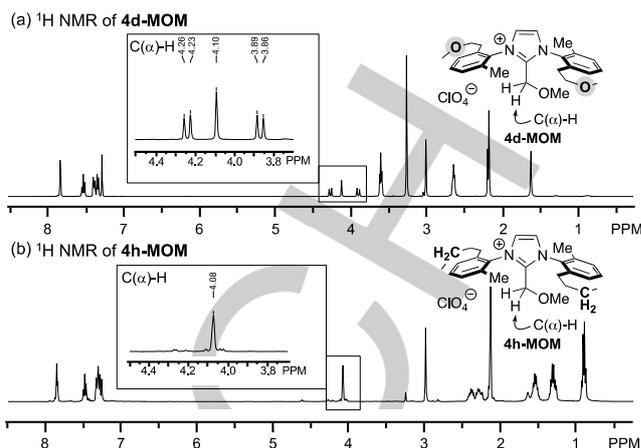
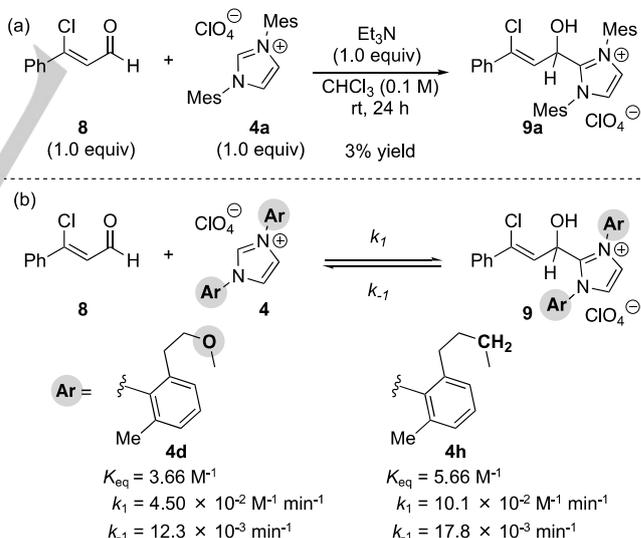


Figure 4. ¹H NMR spectra (CDCl₃, 400 MHz) of (a) **4d-MOM** and (b) **4h-MOM**.

Next, we sought to investigate the proximity effects of the alkoxy groups on the formation of tetrahedral intermediates. Although the detection and isolation of the NHC-aldehyde adducts derived from aryl aldehydes has been reported,^{13b, 13c, 21} the adducts derived from enals have not been identified. In seeking to synthesize the enal-derived adducts, we found that the combination of β -chlorocinnamaldehyde (**8**) and IMes delivered the desired adduct (**9a**) in 3% isolated yield (Scheme 5a).²²



Scheme 5. (a) Isolation of IMes- α,β -enal adduct **9a**. (b) Equilibrium experiments for tetrahedral intermediate. Starting concentration: β -chlorocinnamaldehyde **8** (0.043 M), precatalyst **4** (0.043 M), Et₃N (0.043 M) in CDCl₃ at 25 °C.

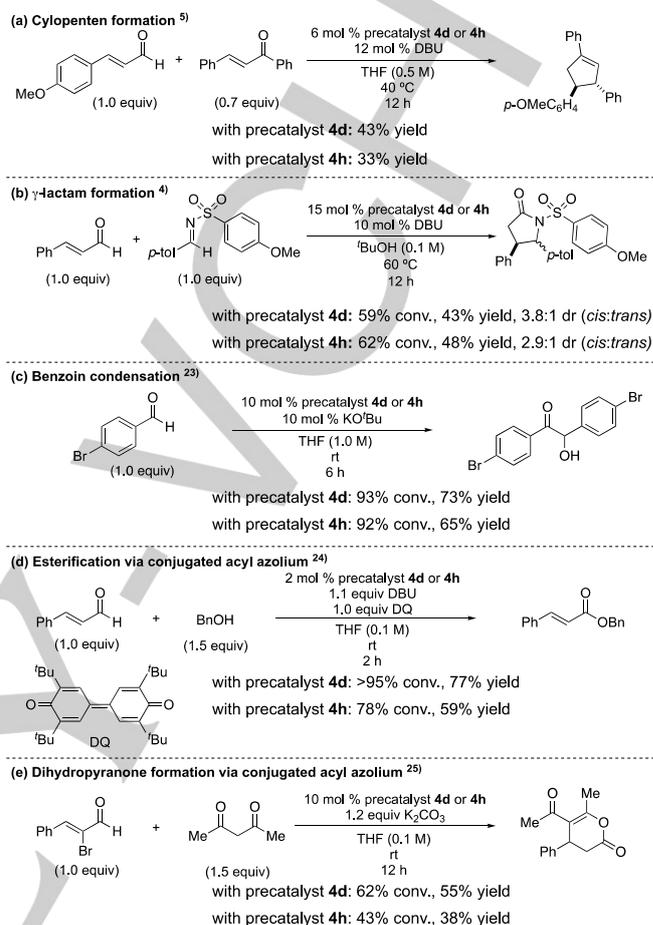
With successful results produced by β -chlorocinnamaldehyde, we monitored by ¹H NMR spectroscopy, the stoichiometric reactions of each catalyst (**4d** or **4h**) with an equimolar amount of **8** and Et₃N under pre-steady-state

conditions in CDCl_3 (0.043 M) at 25 °C (Scheme 5b). Kinetic analysis of the reaction profile, which could be monitored without side reactions, allowed the determination of pseudo-second-order rate constants (k_1 , $\text{M}^{-1} \text{min}^{-1}$) and equilibrium constants (K_{eq} , M^{-1}) for tetrahedral intermediate formation. The pseudo-first-order rate constants (k_1 , min^{-1}) for dissociation of the tetrahedral intermediate were calculated from $K_{\text{eq}} = k_1/k_{-1}$. The observed rate constant of the forward reaction with the ether-type precatalyst (**4d**) was $k_1 = 4.50 \times 10^{-2} \text{ M}^{-1} \text{ min}^{-1}$, half that of the methylene-type precatalyst (**4h**) ($k_1 = 10.1 \times 10^{-2} \text{ M}^{-1} \text{ min}^{-1}$), indicating that the pendant alkoxy groups have a negative effect on the nucleophilic attack of NHCs to enals. This is probably due to the electronic repulsion between oxygen atoms in the N-aryl groups and the chlorine atom of **8**. Interestingly, the dissociation constant k_{-1} of **4d** was also lower than that of **4h**. This lower dissociation constant of **4d** can be attributed to the proximity effects of pendant alkoxy groups on the NHC-enal adducts, which can impede the dissociation process, even with the similar electronic repulsion. Even though the equilibrium constant of **4d** is smaller than that of **4h**, **4d** shows the higher catalytic activity (Scheme 3). Thus, we concluded that the pendant alkoxy group contributes mainly to the formation of the conjugated Breslow intermediate rather than to the formation of the tetrahedral intermediate.

To confirm the utility of the catalyst design, we conducted reaction competition studies using the precatalysts **4d** and **4h** of well-known NHC-catalyzed reactions proceeding via a Breslow intermediate or a conjugated Breslow intermediate (Scheme 6). In all cases, the reaction conditions screened were identical and with the exception of the catalyst structure, no attempts were made to optimize the reaction conditions. The precatalyst **4d** gave a higher yield than precatalyst **4h** for the cyclopentene formation via homoenolate addition (Scheme 6a).⁵ On the other hand, the formation of γ -lactam⁴ was slightly favored with precatalyst **4h** over **4d** (Scheme 6b). This can presumably be attributed to the protonation of pendant alkoxy groups in the protic solvent which suppresses the proximity effects. Similarly, comparison of precatalysts **4d** and **4h**, shows that the reactivity of precatalyst **4d** was higher than that of precatalyst **4h** in terms of the chemical yields of benzoin condensation via an acyl anion equivalent,²³ esterification with an oxidant²⁴ or dihydropyranone formation via a conjugated acyl azolium intermediate²⁵ (Schemes 6c–6e). These results suggest that the precatalyst **4d** with pendant alkoxy groups is effective not only in γ -butyrolactone formation but also in various NHC-catalyzed reactions.

In conclusion, we have successfully identified novel NHC catalysts suitable for homoenolate annulation of α,β -unsaturated aldehydes and arylaldehydes by the functionalization of N-aryl substituents facilitating the generation of the conjugated Breslow intermediate. The key to this success is the installation of the oxygen atoms at the appropriate position of N-aryl substituents. Comparative studies and structural analyses indicated that pendant alkoxy groups are involved in the hydrogen-transfer step, thereby accelerating the formation of the conjugated Breslow intermediate from the catalytically generated tetrahedral intermediate. Since the utility of this catalyst can also be found in a wide range of NHC-catalyzed reactions which proceed via Breslow intermediates, these studies provide a new approach to

increasing the NHC catalyst activity where the hydrogen-transfer of the tetrahedral intermediate is the turnover-limiting step.



Scheme 6. Reaction competition studies using precatalyst **4d** and **4h**.

Acknowledgements

This research was supported by a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from The Ministry of Education, Culture, Sports, Science and Technology, Japan. R.K. is grateful for the Amano Institute of Technology scholarship. We are grateful to Dr. Hiroyasu Sato (Rigaku) for the assistance in X-ray crystal analysis.

Conflict of interest

The authors declare no conflict of interest.

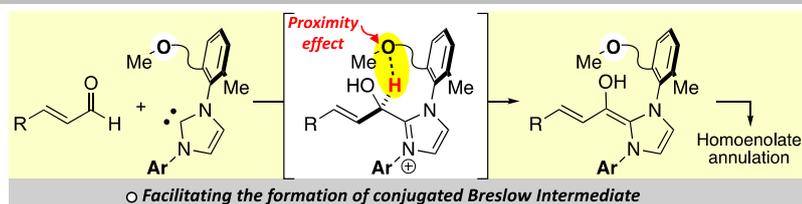
Keywords: N-heterocyclic carbenes • organocatalysis • annulation • kinetic study • umpolung

[1] For selected recent reviews on NHC catalysis, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; c) M. N.

- Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; d) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307; e) R. S. Menon, A. T. Biju, V. Nair, *Beilstein J. Org. Chem.* **2016**, *12*, 444; f) M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2016**, *55*, 14912; *Angew. Chem.* **2016**, *128*, 15134; g) C. Zhang, J. F. Hooper, D. W. Lupton, *ACS Catal.* **2017**, *7*, 2583; h) Y. Wang, D. Wei, W. Zhang, *ChemCatChem* **2018**, *10*, 338; i) X.-Y. Chen, Q. Liu, P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2018**, *57*, 3862; *Angew. Chem.* **2018**, *130*, 3924.
- [2] a) C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; *Angew. Chem.* **2004**, *116*, 6331; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370.
- [3] P.-C. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* **2009**, *131*, 8714.
- [4] M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131.
- [5] V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736.
- [6] V. Nair, M. Poonoth, S. Vellalath, E. Suresh, R. Thirumala, *J. Org. Chem.* **2006**, *71*, 8964.
- [7] J. Liu, D. K. Das, G. Zhang, S. Yang, H. Zhang, X. Fang, *Org. Lett.* **2018**, *20*, 64.
- [8] a) S. Urban, M. Tursky, R. Fröhlich, F. Glorius, *Dalton Trans.* **2009**, 6934; b) J. Kaebamrung, J. W. Bode, *Org. Lett.* **2009**, *11*, 677.
- [9] R. Kyan, K. Sato, N. Mase, N. Watanabe, T. Narumi, *Org. Lett.* **2017**, *19*, 2750. The value is lower than that of IMesCl ($k_{\text{IMes}} = 3.57 \times 10^{-2} \text{ min}^{-1}$)⁹ from ref 9 probably due to the different reaction conditions.
- [10] V. R. Yatham, J.-M. Neudörfl, N. E. Schlörer, A. Berkessel, *Chem. Sci.* **2015**, *6*, 3706.
- [11] a) E. M. Higgins, J. A. Sherwood, A. G. Lindsay, J. Armstrong, R. S. Massey, R. W. Alder, A. C. O'Donoghue, *Chem. Commun.* **2011**, *47*, 1559; b) R. S. Massey, C. J. Collet, A. G. Lindsay, A. D. Smith, A. C. O'Donoghue, *J. Am. Chem. Soc.* **2012**, *149*, 20421; c) Z. Li, X. Li, J.-P. Cheng, *J. Org. Chem.* **2017**, *82*, 9675; d) Y. Niu, N. Wang, A. Muñoz, J. Xu, H. Zeng, T. Rovis, J. K. Lee, *J. Am. Chem. Soc.* **2017**, *139*, 14917; e) Z. Wang, F. Wang, X.-S. Xue, P. Ji, *Org. Lett.* **2018**, *20*, 6041.
- [12] a) T. Rovis, *Chem. Lett.* **2008**, *37*, 2; b) J. Mahatthananchai, J. W. Bode, *Chem. Sci.* **2012**, *3*, 192.
- [13] a) J. L. Moore, A. P. Silvestri, J. R. de Alaniz, D. A. DiRocco, T. Rovis, *Org. Lett.* **2011**, *13*, 1742; b) C. J. Collett, R. S. Massey, O. R. Maguire, A. S. Batsanov, A. C. O'Donoghue, A. D. Smith, *Chem. Sci.* **2013**, *4*, 1514; c) C. J. Collett, R. S. Massey, J. E. Taylor, O. R. Maguire, A. C. O'Donoghue, A. D. Smith, *Angew. Chem. Int. Ed.* **2015**, *54*, 6887; *Angew. Chem.* **2015**, *127*, 6991; d) A. Levens, F. An, M. Breugst, H. Mayr, D. W. Lupton, *Org. Lett.* **2016**, *18*, 3566.
- [14] L. Hintermann, *Beilstein J. Org. Chem.* **2007**, *3*, No. 22.
- [15] J. H. Kim, K. A. Jo, Y. S. Son, S. R. Park, K.-H. Ahn, E. J. Kang, *Bull. Korean Chem. Soc.* **2009**, *30*, 2464.
- [16] We speculate that a significant positive intercept with precatalyst (**4e**) reflects a complex system of very early stages of the reaction.
- [17] See the Supporting Information for the details.
- [18] A. Berkessel, S. Elfert, V. R. Yatham, J.-M. Neudörfl, N. E. Schlörer, *Angew. Chem. Int. Ed.* **2012**, *51*, 12370; *Angew. Chem.* **2012**, *124*, 12537.
- [19] Another possible explanation is that the inductive effects of the pendant methoxy groups that would increase the acidity of C(α)-H of the intermediate.
- [20] See the Supporting Information for the details.
- [21] T. E. Reynolds, C. A. Stern, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 2581.
- [22] See the Supporting Information for details of structural analysis.
- [23] D. Enders, U. Kalfass, *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; *Angew. Chem.* **2002**, *114*, 1822.
- [24] S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190.
- [25] F.-G. Sun, L.-H. Sun, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 3134.

Entry for the Table of Contents

COMMUNICATION



R. Kyan, K. Sato, N. Mase, T. Narumi*

Page No. – Page No.

Pendant Alkoxy Groups on N-Aryl Substitutions Drive the Efficiency of Imidazolyliene Catalysts for Homoenate Annulation from Enal and Aldehyde

The formation of conjugated Breslow intermediate is a turnover-limiting step in the NHC-catalyzed γ -butyrolactone formation via homoenate addition. Structural and mechanistic studies including deuterium exchange experiments revealed that the formation of conjugated Breslow intermediate is facilitated by the proximity effects of pendant alkoxy groups on *ortho*-N-aryl groups of imidazolyliene catalyst.