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Remote Electronic Tuning of Chiral N-Heterocyclic Carbenes

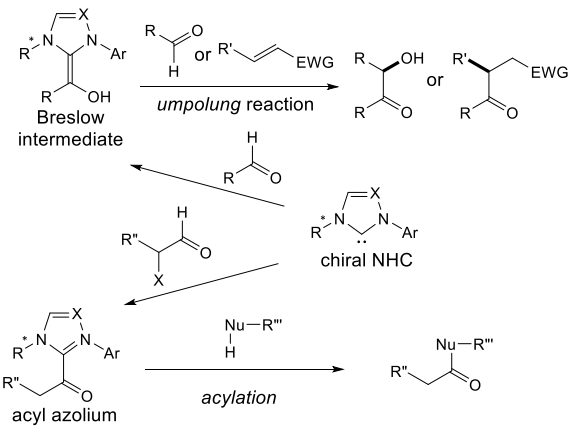
Tsubasa Inokuma,[a,b] and Ken-ichi Yamada*[a,b]

Abstract: Our recent efforts to develop novel *N*-Heterocyclic carbene (NHC)-catalyzed asymmetric reactions are described. During our investigation for development of the acylation reactions via acylazoliums generated by the reactions of NHCs and α-oxidized aldehydes, we have observed significant effects of substitution at a remote site of the carbene carbon of NHCs. In addition, we also observed a significant enhancement of the enantioselectivity by the addition of carboxylate anions. From this observation, we proposed a novel working hypothesis involving a formation of a complex of the substrate and additive to reinforce the recognition of the catalyst for enhancement of the catalytic performance of the asymmetric *N*-heterocyclic carbene system. By applying this concept, we achieved the kinetic resolutions of both cyclic and acyclic alcohols in excellent enantioselectivities. The effects of the remote substitution were also observed in intramolecular Stetter reaction and intermolecular benzoin reaction. In these reactions, the comparison of the catalytic performance of the NHCs bearing variable remote substitutions provided insights into the reaction mechanism because the remote substitution tuned the electronic nature of NHCs without affecting the steric and electrostatic factors around the reaction site. We also developed an intramolecular benzoin condensation involving two aldehydes, which is challenging to realize. Using the substrates bearing proper protecting groups, we succeeded in the stereo divergent synthesis of a variety of inososes, which are important intermediates for the synthesis of biologically active cyclitols.

1. Introduction

The development of asymmetric organocatalysis is one of the major research topics in the field of synthetic organic chemistry.[1] A chiral N-heterocyclic carbene (NHC) is a well-known organocatalyst used in various asymmetric reactions (Scheme 1).[2] NHCs are widely utilized for reactions in which *Umpolung* of aldehyde is involved, such as benzoin condensation[3] or a Stetter reaction.[4] Treatment of NHC with α-oxidized aldehyde produces the corresponding acylazolium species, which acts as a chiral acylation reagent.[5]

In 1943, Ukai discovered the catalytic activity of thiazolium salt in benzoin reaction under basic conditions.[6] Later, Breslow proposed that the deprotonation of thiazolium formed an NHC, acting as a catalyst for the umpolung reaction.[7] The first breakthrough came in 1996 when Enders et al. reported triazolium-derived NHC as a suitable catalyst for the condensation of formaldehyde[8] due to the improved stability of the carbene compared to that derived from thiazolium salt.[9] This report promoted many chemists to develop new triazolium-derived chiral NHCs. In 2002, Rovis et al. reported a highly enantioselective intramolecular Stetter reaction catalyzed by a chiral aminoindanol-derived triazolinylidene NHC.[10] After this pioneering work, a number of reactions using this type of NHC have been reported. The structural modification of NHC was performed to improve catalytic activity. A conventional strategy to tune the catalytic activity of NHCs is substitution on the *N*-aryl group directly connected to the triazolium rings.[11] However, such substitutions affect not only the electronic character of the NHCs but also the steric and electrostatic natures around the reactive carbene sites; therefore, it would cause undesirable effect on catalytic activities. During our efforts to develop the novel asymmetric catalytic reactions,[12] we found that an electron-withdrawing substituent at the indane benzene ring, which is far from the carbene carbon atom, significantly improved the performance of NHC (Figure 1).[13] We were pleased but surprised by this finding because the long distance



Scheme 1. Typical reactions using chiral NHC.

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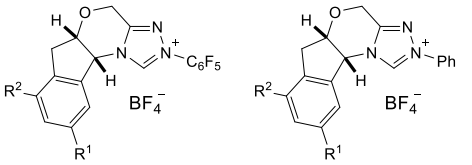
between the carbene carbon and the substituted site seemed to be beyond the range of the inductive effect. Nevertheless, we refer to this new strategy to electronically tune NHCs by introducing variable substituents at the remote position as the remote electronic tuning. The advantage of this strategy is that we can tune the electron density of the reactive site without affecting their steric and electrostatic factors. We have demonstrated that this strategy enabled the development of novel and effective catalysis.[14] In addition, a precise comparison of the catalytic performance of the series of the tuned catalysts could provide further insights into the mechanisms of certain NHC-catalyzed reactions. Herein, we summarize our recent contributions based on the concept of the remote electronic tuning of NHCs.



R^1 = Me, R^2 = H (**1a**)
R^1 = H, R^2 = H (**1b**)
R^1 = Br, R^2 = H (**1c**)
R^1 = NO_2, R^2 = H (**1d**)
R^1 = NO_2, R^2 = Br (**1e**)

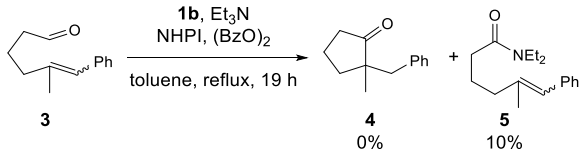
R^1 = H, R^2 = H (**2a**)
R^1 = Br, R^2 = H (**2b**)
R^1 = NO_2, R^2 = H (**2c**)
R^1 = NO_2, R^2 = Br (**2d**)

Figure 1. The NHC precursors bearing varieties of substitutions at the remote site.

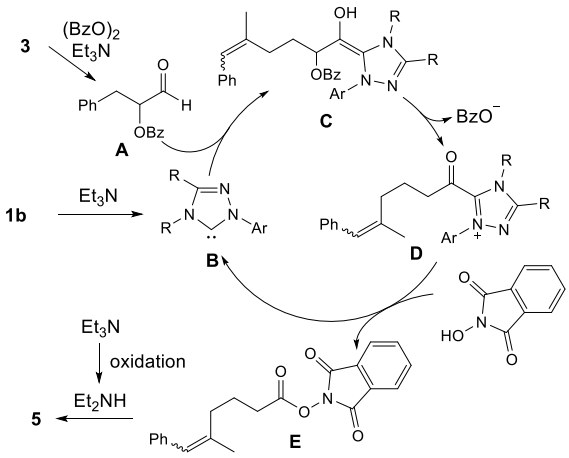
2. Remote electronic tuning in the NHC-catalyzed acylation reactions via acylazolium

2.1. Generation of acylazolium from NHC and application to the synthesis of amide from aldehyde

We have been engaged in the development of new radical reactions.[15] During the investigation, we attempted to apply chiral NHC catalysis to a radical reaction with the expectation that hydrogen atom abstraction from a Breslow intermediate would generate the corresponding chiral radical species and enable asymmetric radical reactions.[16] However, instead of the expected radical reaction to produce cyclopentanone derivative **4**, we observed production of the corresponding amide **5** from aldehyde **3** and triethylamine that was used to generate NHC from the corresponding azolium salt **1b** when we used N-hydroxyphthalimide (NHPI) and benzoyl peroxide as a hydrogen transfer catalyst and a radical initiator, respectively (Scheme 2). We speculated that this reaction would proceed as shown in Scheme 3. First, α-benzyloxy aldehyde **A** is formed by base-mediated α-oxidation of aldehyde **3** with $(BzO)_2$.[17] Then, **A**



Scheme 2. Attempted radical reaction.



Scheme 3. Plausible reaction mechanism of amide formation from **2**.

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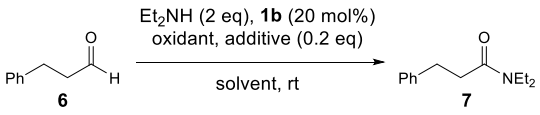
reacts with NHC **B** derived from **1b** to form acylazolium **D** via the elimination of the benzoyloxy group from the allylic position of the Breslow intermediate **C**.[18,19] Thus-produced acylazolium **D** acted as an acylating reagent for NHPI to produce activated ester **E**, which in turn reacts with diethylamine that could be produced by oxidation of triethylamine to yield amide **5**. This observation prompted us to develop NHC-catalyzed reactions involving acylazolium species.[20]

First, we optimized this NHC-catalyzed amidation[21] of aliphatic aldehyde (Table 1). When aliphatic aldehyde **6** was treated with NHC precursor **1b**, Et_2NH, NHPI, and $(BzO)_2$, the corresponding aide **7** was produced in 29% yield (entry 1). The decreased amount of $(BzO)_2$ gave a lower yield as expected from the estimated mechanism (entry 2), and further improvement was achieved using 1-hydroxybenzotriazole (HOBt) instead of NHPI (entry 3). When *N*-chlorosuccinimide (NCS) was used instead of $(BzO)_2$, the yield of **7** was significantly improved (entry 4). Finally, the excellent yield was realized using Et_3N as an additional base (entry 5).

During the optimization of the reaction conditions, we observed intriguing phenomenona, that is, the switching of chemoselectivity depending on the structure of NHC (Scheme 4).When the conversion of **6** to **7** was performed using bicyclic NHC precursor **8** instead of **1b**, the yield of **7** decreased, and instead, the corresponding carboxylic acid **10** was obtained in 14% yield. Triazolium **9** produced both **7** and **10** in similar yields, but the yields were varying. The carboxylic acid **10** was preferentially produced in 83% yield using **9** by addition of H_2O.

In addition, we achieved chemoselective oxidation of aliphatic aldehyde in the presence of aromatic aldehyde. The amidation of the aliphatic aldehyde site of **11** proceeded under the condition using **1b** as an NHC precursor, while the same functional group could be converted to carboxylic acid by changing the NHC precursor from **1b** to **9** (Scheme 5). Under both conditions, the aromatic formyl group did not react, which clearly indicates that oxidation of the Breslow intermediate by NCS is not involved in the generation of the acylazoium species and supports our estimated mechanism. This chemoselectivity is contrastive to those of the previously reported methodologies in which aromatic aldehyde preferably reacts rather than aliphatic aldehyde.

Table 1. NHC-catalyzed amidation of aldehyde.

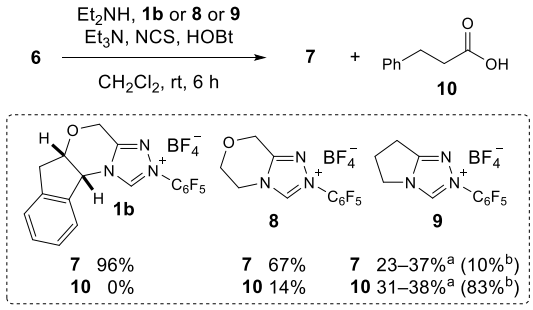


entry	solvent	oxidant (eq)	additive	time (h)	yield (%)
1	toluene	$(BzO)_2$ (1)	NHPI	19	29
2	toluene	$(BzO)_2$ (0.6)	NHPI	20	20
3	toluene	$(BzO)_2$ (1)	HOBt	18	45
4	CH_2Cl_2	NCS (1.3)	HOBt	6	76
5[a]	CH_2Cl_2	NCS (1.3)	HOBt	6	96

[a] Et_3N (1.2 eq) was added.

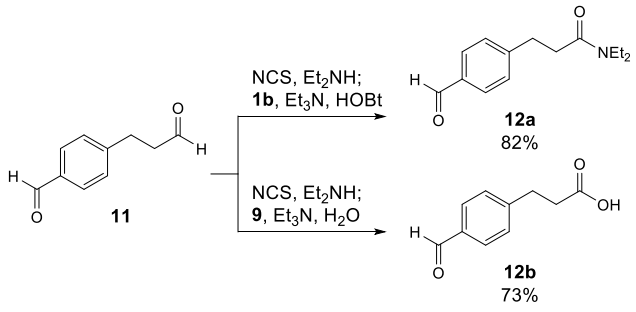
2.2. The remote electronic effect on the kinetic resolution of chiral cyclic 1,2-diols and related compounds

In the above amidation reaction, the chiral acylazolium intermediate reacts with achiral HOBt and generate the corresponding achiral activated ester. We next envisioned that a chiral acylazolium can recognize chirality of alcohols and undergo enantioselective acylation to realize the kinetic resolution of racemic alcohol.[19] Kinetic resolution of racemic alcohols is an efficient methodology because you can obtain both enantiomers of the chiral alcohol using the same substrate and asymmetric catalyst.[22] To date, a myriad of methods to resolve racemic alcohol using asymmetric catalysts such as nucleophilic[23] or acidic[24] catalysts as well as enzymatic[25] processes have been developed. Recently, the chiral tin or copper catalyzed versions were also achieved.[26] In contrast to these reports, kinetic resolution using the NHC-catalyzed redox acylation system had been relatively unexplored.[11e,27] Therefore, we examined the kinetic resolution of racemic *trans*-cycloalkane diols, which are less-explored for kinetic resolution study, to demonstrate the potential of the chiral acylazolium as chiral acylation reagents.



[a] Range of three reactions. [b] H_2O was added.

Scheme 4. Switching of the chemoselectivity depending on the structure of NHC.

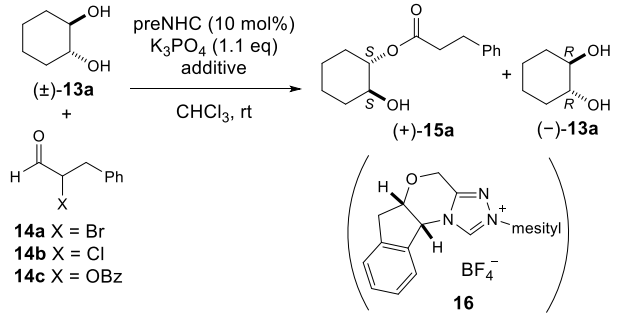


Scheme 5. Chemoselective synthesis of carboxylic acid derivetaives **12a** and **12b** from the same substrate.

Acylation of racemic diol **13a** was performed using a chiral NHC and aldehyde **14** bearing various leaving groups at their α-position (Table 2).[13a] When aminoindanol-derived chiral NHC precursor **2a** and α-bromo aldehyde **14a** were used, (+)-**13a**, derived from *S*,*S*-configured diol, was acylated 20 times faster (*s* = 20) than (−)-**13a** (entry 1). According to a convention, we tested NHCs bearing different proximal *N*-aryl groups but the enantioselectivity decreased especially when **1b**, bearing an electron-deficient aryl group, was used (entries 2 and 3).

We found an interesting additive effect during screening of a leaving group. The reaction using **14b**, bearing a chloro group of lower leaving ability, was slower (46% conversion in 8 h, entry 4) than that using **14a** (54% conversion in 4 h, entry 1). However,

Table 2. Kinetic resolution of *trans*-cyclohexane diol **5a**.



entry	**14**	pre NHC	additive	time	conv. (%)[a]	*s*[b]
1	**14a**	**2a**	none	6 h	54	20
2	**14a**	**1b**	none	12 h	60	2
3	**14a**	**16**	none	12 h	41	14
4	**14b**	**2a**	none	8 h	46	18
5	**14c**	**2a**	none	3 h	51	29
6[c]	**14a**	**2a**	4-$Me_2NC_6H_4CO_2H$ (1 eq)	2 min	47	39
7[c]	**14a**	**2b**	4-$Me_2NC_6H_4CO_2H$ (1 eq)	1 min	40	62
8[c]	**14a**	**2c**	4-$Me_2NC_6H_4CO_2H$ (1 eq)	1 min	51	85
9[d,e]	**14a**	**2c**	4-$Me_2NC_6H_4CO_2H$ (0.1 eq)	48 h	35	239

[a] Conversion, *C* was calculated as follows: $C = ee_{13a}/(ee_{13a} + ee_{15a})$. [b] The *s* value was calculated as follows: $s = \ln[(1 - C)(1 - ee_{13a})]/\ln[(1 - C)(1 + ee_{13a})]$, where ee was determined by HPLC analysis. [c] K_3PO_4 (2.1 eq) was used. [d] Proton sponge (1.2 eq) was used instead of K_3PO_4. [e] The reaction was performed at −20 °C.

the use of benzoyloxy group-containing aldehyde **14c**, which was expected to be a more-slowly-reacting substrate based on the ability of BzO group as a leaving group, improved not only reaction rate but also enantioselectivity (51% conversion in 3 h, *s* = 29; entry 5). From the observation by TLC analysis that the reaction proceeded slowly in an initial stage and gradually accelerated, we anticipated that the liberated benzoate anion might play an important role in achieving the fast and enantioselective reaction. As expected, the addition of an external benzoate anion, generated in situ from the corresponding benzoic acid under the basic condition, significantly improved both the reactivity and the enantioselectivity (entry 6). This is the first example of using a Brønsted base additive for enhancing the reactivity and enantioselectivity of NHC-catalyzed asymmetric reactions.

Although the use of NHC precursor **1b**, bearing an electron-withdrawing *N*-aryl substituent, drastically decreased the enantioselectivity (entry 2), to our delight, **2b** bearing an electron-withdrawing bromo group on the remote benzene ring gave a higher enantioselectivity (entry 7). The introduction of a more electron-withdrawing nitro group further improved the selectivity (entry 8). Finally, we observed the highest selectivity up to s value of 239 when the reaction was performed at −20 °C using a proton sponge as a base (entry 9).

Our reaction system involving NHC and benzoate additive was applicable to kinetic resolution of wide varieties of cycloalkane 1,2-diols consisting of various numbers of ring structures (Figure 2). Although the *s* value of the kinetic resolution of 5-membered diol **13b** was lower than that of 6-membered substrate **13a**, which is still the highest value to date. Seven- and eight-membered diols **13c** and **13d** proceeded in excellent enantioselectivities. Cyclohexene diol **13e** was also applicable. In addition, one of the hydroxy groups could be replaced with CbzNH, and we applied our resolution system to prepare optically active 1,2-amino alcohols **13f** and **13g**.

We assumed the role of the carboxylate additive as follows based on the DFT analysis (Figure 3). The carboxylate anion would interact with both the diol and acylazolium via the formation of hydrogen bonding and electrostatic interaction, respectively, to capture the diol and recruit it to the cationic acylating species. From the viewpoint of the chiral acylazolium species, the number of recognition site increases in the presence of the carboxylate anion, resulting in the higher

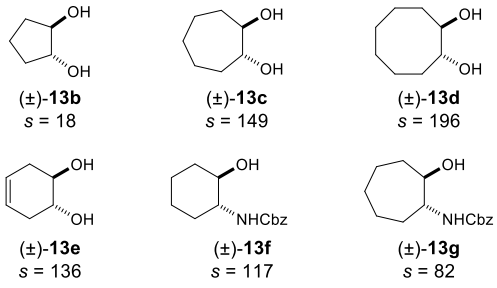


Figure 2. Substrate scope of the kinetic resolution of cyclic diol and cyclic amino alcohol derivatives.

enantioselectivity. The enantioselectivity is likely correlated to the distance of the azolium cation and carboxylate anion in the transition state (TS) for each enantiomer (3.34 Å in the TS consisting of *S*,*S*-diol and 3.83 Å in that of *R*,*R*-diol, respectively). The improved reactivities and enantioselectivities observed using electron-rich carboxylate or electron-poor NHC can be rationalized by the enhancement of this electrostatic interaction. Although the improvement of reactivity or enantioselectivity by a Lewis or Brønsted additive has already been reported,[28] the idea that the external additive benefits the recognition of chiral catalyst with the substrate component has yet to be reported (Figure 4).

2.3. Application to Kinetic Resolution of acyclic α-hydroxythioamide and α-hydroxyamide

Next, we applied the concept of the carboxylate-enhanced recognition to the kinetic resolution of acyclic substrates, which is more challenging (Table 3).[13b] When the racemate of α-hydroxythioamide **17a** was subjected to a similar condition to that for cyclic substrates, acylation of (*R*)-configured substrate proceeded preferentially to give *R*-**18a** in 26% conversion, and the *s* value was determined to be 68 based on the ees of the acylated product **18a** and recovered **17a** (entry 1). The introduction of an electron-withdrawing substituent at the proximal site of the carbene carbon significantly decreased the enantioselectivity also in this reaction (entry 2). In contrast, installing an additional electron-withdrawing group at the remote site improved both the reactivity and enantioselectivity (entry 3). We further optimized the reaction and achieved *s* value of 142 by using **2d** and 9-julolidinecarboxylic acid as NHC precursor and additive, respectively (entry 4). This protocol could be applied to substrates bearing various substituents at the α-position of thioamide moiety except for substrate **17h**, which has a phenyl group directly connected to the chiral center (Figure 5).

In this kinetic resolution, a hydrogen-bonding complex of the substrates and carboxylate is likely formed before the reaction with acylazolium species as proposed for cyclic diols (Figure 6). This assumption is supported by the observation of the mass peaks corresponding to the complex in analyses of electron spray ionization mass spectrometry (ESI-MS). The diffusion-ordered NMR spectroscopy (DOSY) analysis also supported the formation of the complex between the α-hydroxythioamide and carboxylate. In the transition state, the electrostatic interaction between the carboxylate and azolium part is likely crucial; the carboxylate derived from less acidic carboxylic acid is a better

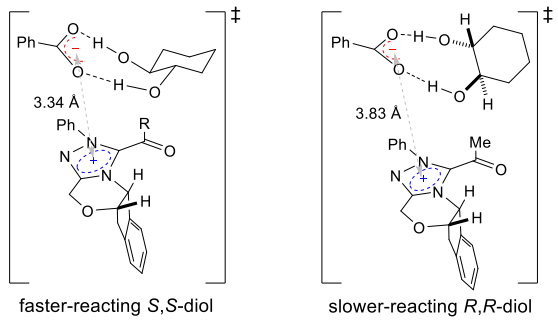


Figure 3. The transition state models of the kinetic resolution of cycloalkane 1,2-diol calculated by DFT.

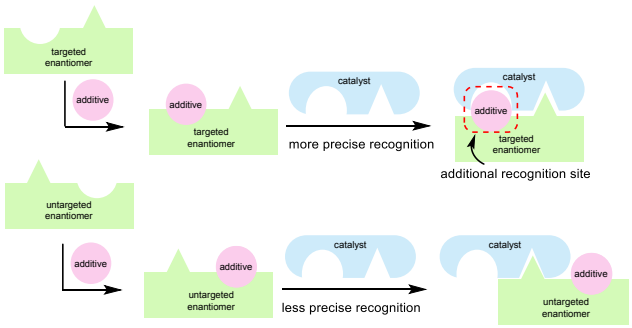
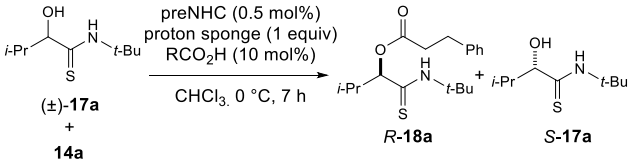


Figure 4. Concept of the more precise recognition of the substrate caused by external additive.

Table 3. Kinetic resolution of α-hydroxythioamide **17a**.



entry	NHC precursor	RCO_2H	conv. (%)[a]	s[b]
1	**2c**	4-$Me_2NC_6H_4CO_2H$	26	68
2	**1d**	4-$Me_2NC_6H_4CO_2H$	24	9
3	**2d**	4-$Me_2NC_6H_4CO_2H$	39	92
4	**2d**	9-julolidinecarboxylic acid	28	142

[a] Conversion, *C* was calculated as follows: $C = ee_{17a}/(ee_{17a} + ee_{18a})$. [b] The *s* value was calculated as follows: $s = \ln[(1 - C)(1 - ee_{17a})]/\ln[(1 - C)(1 + ee_{17a})]$, where ee was determined by HPLC analysis.

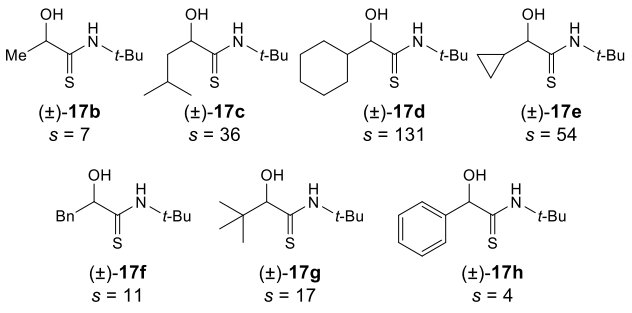


Figure 5. Substrate scope of the kinetic resolution of acyclic α-hydroxy thioamide **17**.

additive than those from more acidic ones due to the reinforcement of this interaction. The result that more electron-deficient NHC gave better enantioselectivity could also be explained by the same model.

α-Hydroxyamide substrates were also applicable for this kinetic resolution (Scheme 6).[13c] We observed the enhancement of conversion and stereoselectivity by introducing remote electron-withdrawing substituents similar to the reaction of α-hydroxythioamide. Although an *s* value of the reaction of **19** was slightly lower than that of the corresponding thioamide **17a**, the amide substrate gave still high enantioselectivities. The decreased selectivity probably reflects the inferior hydrogen bond donor ability.

3. The remote electronic effect on the NHC-catalyzed umpolung reactions

3.1. The remote electronic effect on the intramolecular Stetter reaction and structural revision of products

Having demonstrated the remote electronic tuning in the acylation of hydroxy groups, we next investigated the remote electronic effect on asymmetric C-C bond formations. The Stetter reaction[29] is a nucleophilic addition of acyl anion equivalent to olefine activated by an electron-withdrawing group.[4,30] Mechanism of the Stetter reaction is well-studied, and the rate-determining step is believed to be the proton transfer of **F** to form **G** (Scheme 7).[31] The density-functional theory (DFT) calculation analysis strongly supported the hypothesis.[32] We anticipated that if a substituent at the remote site affects the acidity of the transferred hydrogen atom, the introduction of an electron-withdrawing group should increase reaction rate of the Stetter reaction.

We investigated the performance of the series of NHCs bearing variable remote substituents in an intramolecular Stetter reaction of α,β-unsaturated esters **21** (Table 4).[13d] When α,β-unsaturated ester **21a** was subjected to the reaction with **1b** and proton sponge in 1,2-dichloroethane at 0 °C for 100 min, cyclized product **22a** was produced in 53% yield with 96% ee (entry 2). After investigating NHCs with various substituents at the indane ring, we found that the more electron-deficient NHC provided better conversion (entries 1-5). Surprisingly, the remote electron-withdrawing group improved not only the reactivity but also the enantioselectivity. Therefore, we also investigate the reactions of trisubstituted alkene **21b** to exclude the possibility of product-racemization through enolization, and the same tendency was observed in the reaction of **21b** (entries 6-10). Using the electron-deficient NHC derived from **1e**, we could successfully synthesize cyclohexanone derivative **22b** bearing all-carbon quaternary stereogenic center in high yield with excellent enantioselectivity (entry 10).

To elucidate the reason for the enantioselectivity improved by the remote electron-withdrawing substituents, we performed a DFT study (Figure 7). In the transition state to give the major enantiomer, the benzylic hydrogen of the indane moiety formed a hydrogen bond with the carbonyl oxygen atom of the ester (magenta dash line), which is not observed in the transition state to form the minor enantiomer. We speculate that the introduction of the electron-withdrawing group at the indane moiety would enhance this interaction and stabilize the transition state to the major enantiomer.

Comparing the experimental data and the DFT calculation, we found that the absolute configuration reported in the previous paper and that predicted by the DFT calculation were opposite. Therefore, we confirmed the configuration by X-ray crystallo-

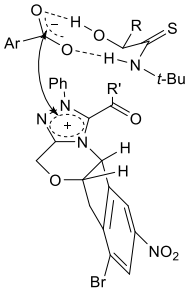
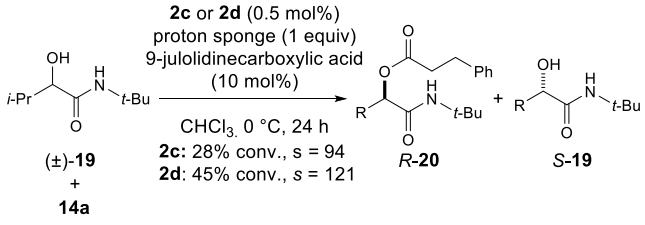
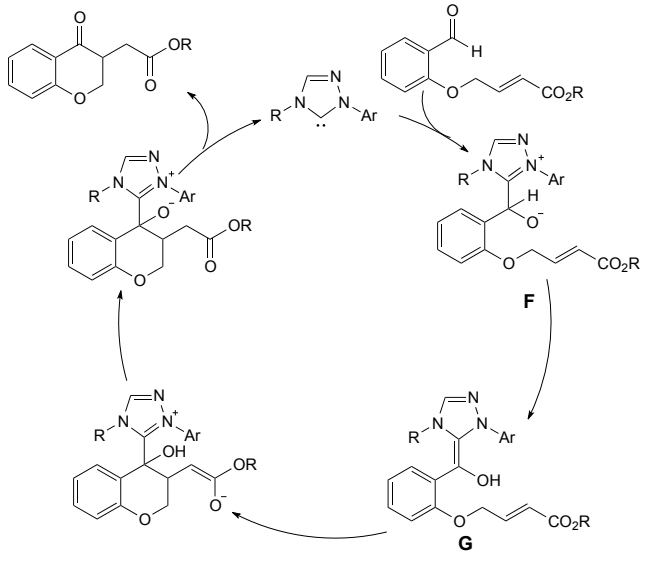


Figure 6. Proposed structure of the complex forming during the reaction.



Scheme 6. Kinetic resolution of acyclic α-hydroxyamide.

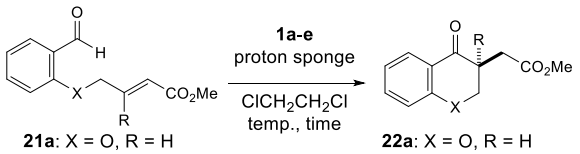


Scheme 7. Proposed mechanism of NHC-catalyzed Stetter reaction.

graphic analysis and found that the absolute configuration in the previous report was misassigned. Our finding revised the stereochemistry of more than 80 compounds whose configuration was assigned based on the same report.

We also found that the NHC derived from **1e** could apply to the synthesis of a highly enolizable product. The asymmetric intramolecular Stetter reaction of **21c** is challenging because the resulting product **22c** is prone to enolize under basic conditions.[10,30a] Although the product with good ee was obtained after 2 h, the prolonged reaction time decreased the ee when the relatively electron-rich NHC derived from **1a** was used (Scheme 8). In contrast, the NHC derived from **1e** bearing electron-withdrawing groups at the indane moiety gave quite high enantioselectivity, and the decrease of ee in prolonged reaction was suppressed probably due to the low basicity of NHC.

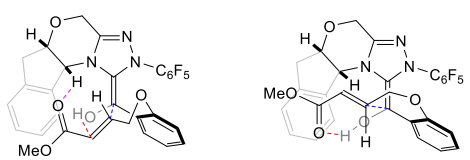
Table 4. NHC-catalyzed asymmetric intramolecular Stetter reaction of **21**.



21a: X = O, R = H
21b: X = NTs, R = Me

22a: X = O, R = H
22b: X = NTs, R = Me

entry	21	1	condition	yield (%)	ee (%)
1	**21a**	**1a** (1 mol%)	0 °C, 100 min	50	92
2	**21a**	**1b** (1 mol%)	0 °C, 100 min	53	96
3	**21a**	**1c** (1 mol%)	0 °C, 100 min	73	97
4	**21a**	**1d** (1 mol%)	0 °C, 100 min	85	98
5	**21a**	**1e** (1 mol%)	0 °C, 100 min	89	98
6	**21b**	**1a** (20 mol%)	40 °C, 7 h	44	74
7	**21b**	**1b** (20 mol%)	40 °C, 7 h	52	78
8	**21b**	**1c** (20 mol%)	40 °C, 7 h	70	86
9	**21b**	**1d** (20 mol%)	40 °C, 7 h	77	92
10	**21b**	**1e** (20 mol%)	40 °C, 7 h	83	95



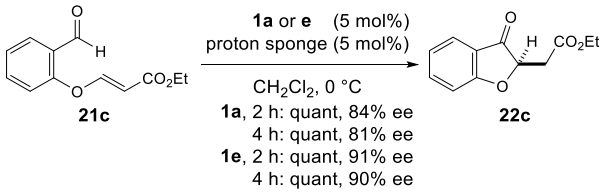
TS to give **22a** TS to give *ent*-**22a**

Figure 7. The transition state models of the intramolecular Stetter reaction of **21a** calculated by DFT.

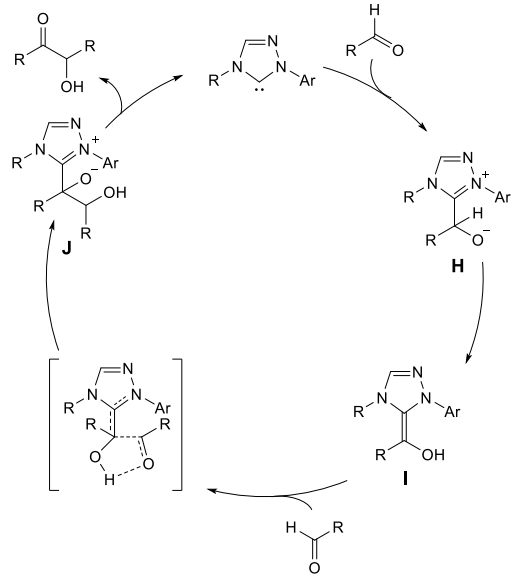
3.2. The remote electronic effect on the Intermolecular benzoin condensation

We next applied the remote electronic tuning to benzoin condensation[3], another Umpolung reaction that chiral NHCs efficiently work.[33] The mechanism of intermolecular benzoin condensation of aldehyde was proposed by Breslow in 1958[7] and is still accepted today (Scheme 9). According to the kinetic study reported by Leeper, all three steps, including (1) addition of NHC to aldehyde, (2) proton transfer of **H** to generate the Breslow intermediate **I**, and (3) addition of **I** to aldehyde to form **J** are partially rate-determining steps.[34]

We tested **1a**–**e** to asymmetric benzoin condensation of three benzaldehydes **22** (Table 5).[13e] In contrast to the Stetter reaction, the benzoin condensation of non-substituted benzaldehyde **22a** was most effectively catalyzed by moderately electron-withdrawing substituent-containing catalyst **1c**, and the electron-deficient catalyst **1e**, which is the most reactive catalyst in the Stetter reaction, gave the lowest yield among the tested



Scheme 8. Intramolecular Stetter reaction for the synthesis of enolizable product **22c**.

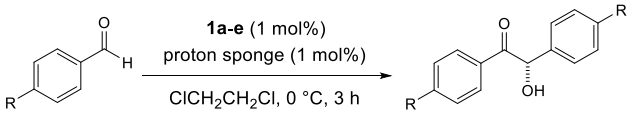


Scheme 9. Proposed mechanism and rate-determining step of NHC-catalyzed benzoin condensation.

catalysts (entries 1–5). When electron-deficient benzaldehyde **22b** was used, the highest yield was achieved by **1b**, and the introduction of electron-withdrawing groups to NHC catalysts resulted in slower reactions (entries 6–10). A similar tendency was observed in the benzoin condensation of electron-rich benzaldehyde **22c** to produce **23c** (entries 11–15). These results are consistent with the previously reported kinetic study, which indicates that the rate-determining step is likely interchangeable.[34]

The benzoin condensation of electron-deficient aldehydes, such as **23d**, often suffers from the racemization of products.[35] When **1b** was used, the ee after reaction for 5 min was 57%, while the ee decreased to 42% in the reaction for 3 h (Scheme 10). It is worth noting that the use of the electron- deficient NHC can prevent the racemization even in the prolonged reaction time (73% and 72% ee in 15-min and 3-h reactions, respectively) as well as the case in the above-mentioned intramolecular Stetter reaction.

Table 5. Observation of the effect of the remote electron-tuning on asymmetric benzoin condensation of **23**.



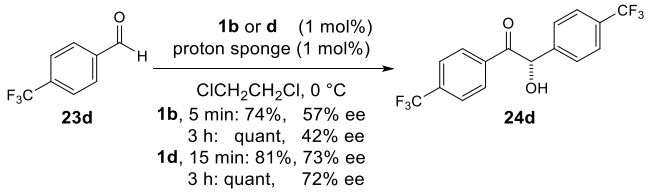
23a–c **24a–c**

entry	R (**23**)	**1**	**24**	yield (%)	ee (%)
1	H (**23a**)	**1a**	**24a**	29	89
2	H (**23a**)	**1b**	**24a**	56	93
3	H (**23a**)	**1c**	**24a**	65	93
4	H (**23a**)	**1d**	**24a**	63	94
5	H (**23a**)	**1e**	**24a**	29	95
6	Cl (**23b**)	**1a**	**24b**	70	78
7	Cl (**23b**)	**1b**	**24b**	86	78
8	Cl (**23b**)	**1c**	**24b**	60	81
9	Cl (**23b**)	**1d**	**24b**	54	86
10	Cl (**23b**)	**1e**	**24b**	48	86
11	Me (**23c**)	**1a**	**24c**	8	90
12	Me (**23c**)	**1b**	**24c**	23	93
13	Me (**23c**)	**1c**	**24c**	35	93
14	Me (**23c**)	**1d**	**24c**	32	94
15	Me (**23c**)	**1e**	**24c**	28	95

3.3. Development of the Intramolecular benzoin condensation for the stereodivergent synthesis of inososes

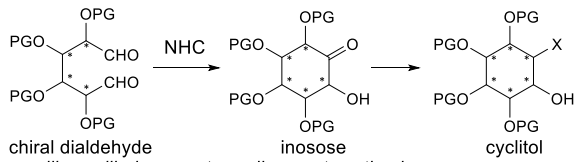
The originally developed benzoin condensation, which gives homo dimer of aldehydes, has a narrow product scope; therefore, the development of cross-benzoin condensation is demanded. The intramolecular version of this reaction is an attractive transformation because it can access cyclic α-hydroxy ketone, a useful chiral building block for the preparation of biologically important compounds. While the intramolecular reactions involving aldehydes and ketones are well-established,[11c, 36] the reports using dialdehyde were rare, probably because of unstable nature of dialdehyde.[11d,37] We anticipated that if stereo divergent synthesis of inosose is realized via intramolecular cross-benzoin condensation of dialdehyde readily available from alditols, the thus-obtained polyols can be used as chiral building blocks for a divergent synthesis of structurally important cyclitols (Scheme 11).[38]

We found that the C_2-symmetrical D-mannitol-derived dialdehyde **25a** could be converted to the inosose **26a**, bearing *R* configuration at the newly generated carbinol stereo center, in good yield as a sole stereoisomer by using the NHC generated from **1b** and Et_3N (Scheme 12-a).[39,40a] We also found that the reaction using **25b**, bearing more bulky protecting groups than **25a**, and structurally simpler NHC precursor **9** proceeded in an opposite stereoselective fashion to give **26b** presumable (Scheme 12-b). The similar conditions were applicable to the NHC-catalyzed cross-benzoin condensation of unsymmetrical dialdehyde[40b]. The NHC generated by sodium-benzoate-mediated deprotonation of **28** efficiently catalyzed the reaction, and **29a** was obtained as a major product in high site- and diastereoselectivity (Scheme 12-c). On the other hand, **27b**



23d **24d**

Scheme 10. Asymmetric benzoin reaction for the synthesis of readily racemizable product **24d**.



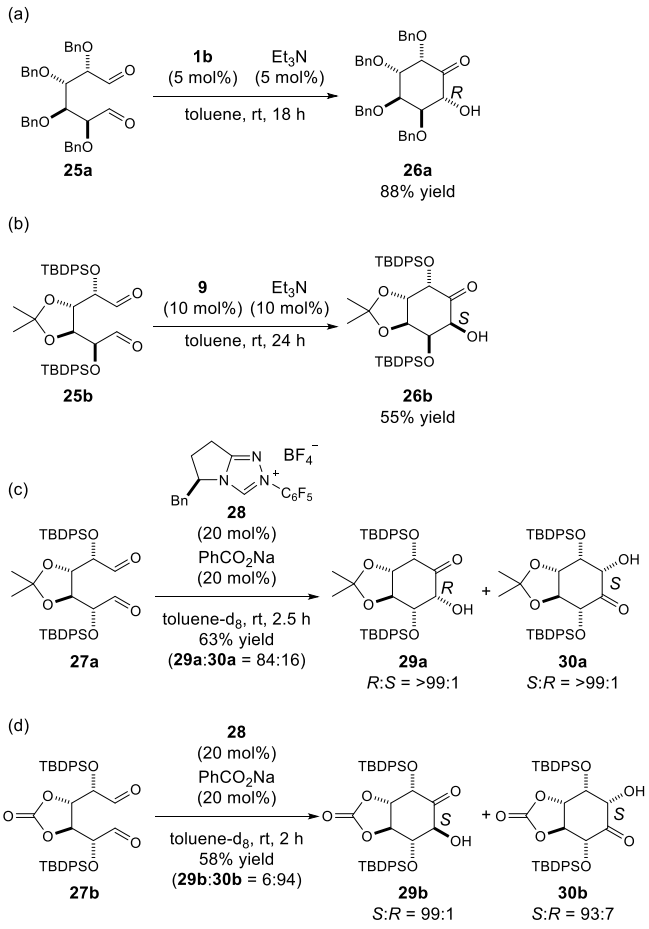
chiral dialdehyde *readily availbale from alditol* — inosose *stereodivergent synthesis controled by the NHC catalyst and PGs* — cyclitol

Scheme 11. Intramolecular cross benzoin condensation of dialdehyde to form the chiral inosose and versatile transformation of the chiral cyclitol.

bearing a carbonate moiety at the hydroxy groups of C3 and C4 could be converted to **30b** in high selectivity under the same condition as described in Scheme 12-c (Scheme 12-d). Further investigation based on the remote electronic tuning of NHC is currently underway to improve the reaction efficacy.

4. Summary and Outlook

In conclusion, we have developed novel chiral NHCs based on the concept of the remote electronic tuning. In spite of the long distance between the substituted site and carbene carbon, the substitution significantly affects the catalytic performance of NHCs to realize a highly enantioselective Stetter reaction, benzoin condensation, and kinetic resolution of racemic secondary alcohols. In addition, this modification contributed to deeper understanding of the mechanisms of NHC-catalyzed reactions. Elucidation of the basic mechanism and further application of the concept to development of new reactions is currently underway and will be reported in the near future.



Scheme 12. Intramolecular benzoin condensation of dialdehyde.

Acknowledgements

This research was supported in part by JSPS (KAKENHI 24790011, 26105732, 26460005, 18K06579, 20K06965, and 22H05569), the Mochida Memorial Foundation for Medical and Pharmaceutical Research, Tokushima University (a research program for the development of an intelligent Tokushima artificial exosome (iTEX), and Research Clusters programs 1802001 and 2201004), Takeda Science Foundation, Uehara Memorial Foundation, and the Japan Science Society (Sasakawa Scientific Research Grant). The authors thank all co-workers.

Keywords: organocatalysis • umpolung • *N*-heterocyclic carbene • kinetic resolution • asymmetric catalysis

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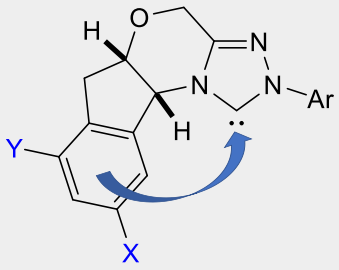
Entry for the Table of Contents (Please choose one layout)

Layout 1:

PERSONAL ACCOUNT

During our research toward the development of novel asymmetric organocatalysis, we established an original concept involving the remote electronic tuning in chiral N-heterocyclic carbene catalysis. In this personal account, we described our recent progress in the development of novel catalysts based on the concept and its application to kinetic resolution via stereoselective *O*-acylation, intramolecular Stetter reaction, and benzoin reactions.



Remote electronic tuning affecting reaction rate and stereoselectivity

*Tsubasa Inokuma, and Ken-ichi Yamada**

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