DOI: 10.1002/chem.200800942

Cyclophane-Type Imidazolium Salts with Planar Chirality as a New Class of N-Heterocyclic Carbene Precursors

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Abstract: Cyclophane-type imidazolium salts with planar chirality were synthesized from enantiopure 2-amino alcohols, of which the N(1) and N(3) positions were connected with a bridge. The structural profiles of the imidazolium salts and their derivative N-heterocyclic carbenes (NHCs) were investigated by means of several analyses. The chiral NHCs derived from these imidazolium salts were found to catalyze the asymmetric cross-annulation of an α,β-unsaturated aldehyde with a ketone by means of the "conjugated" umpolung of the enal to give the target γ-lactone with good to excellent enantioselectivity (up to 94% *ee*). Based on the expected structure of the NHCs and their intermediates, together with the absolute configuration of the products, a plausible mechanism for the stereocontrol was proposed.

Keywords: carbenes · chirality · cyclophanes · heterocycles · umpolung

Introduction

Topological chirality, as represented by helical, axial, and planar chiralities, has been regarded as a key principle in overcoming the limits of traditional tetrahedral chirality and expanding the scope of chiral molecular devices.[1] In every field of chiral technology, topologically chiral molecules often provide useful chiral materials, such as ligands,[2a,g] auxiliaries,[2b] selectors,[2d,e] and sensors.[2c,f] Their well-defined, three-dimensionally dissymmetric shape seems to be advantageous not only for chirality induction/recognition but also for further development of materials with an optimized structure and elucidation of mechanisms. As representative examples, numerous metal-based catalysts with topologically chiral ligands have been developed to date,[2a] and recently the utility of topological chirality has been also proved in the realm of organocatalysis.[3]

Among various classes of organocatalysts, N-heterocyclic carbenes (NHCs) have attracted exceptional attention. These offer a unique carbon–carbon bond-forming ability by means of the umpolung of aldehydes.[4] Because most of these reactions feature the creation of a stereogenic carbon atom(s) in products, the stereocontrol of these reactions by chiral NHCs has been a challenging target over the last decade.[4] At the earlier stage of the development of NHC precursors, simple azolium/azolinium salts with chiral N substituent(s) were studied extensively,[5] and more recently NHC precursors with topological chirality have appeared, including polycyclic (**A**–**C**),[6] axially chiral (**D**–**F**),[7] planarly chiral (**G**–**I**),[8] oligopeptidyl (**J**),[9a] rotaxane-containing (**K**),[9b] and chirality-relayed (**L**)[9c] azolium/azolinium salts. In fact, some of these examples were found to provide NHC organocatalysts for the benzoin condensation and the Stetter reaction, of which the chirality induction ability was superior to that of traditional NHCs with simple point chirality.

Through our ongoing study on the development of novel NHC precursors with topological chirality, we focused on imidazolium salts (**1a**–**c**) with cyclophane-type planar chirality, of which the N(1) and N(3) positions are bridged with a chiral linker. When the two nitrogen atoms of an imidazolium ring are linked by a dissymmetric bridge with a proper length, the steric demand forces the bridge to cover either of the two faces of the prochiral imidazolium ring, and as a result, a planar-chiral cyclophane-type molecule will be readily generated without resorting to complicated/bulky substituent(s).[10,11] Because planar-chiral cyclophanes with such a structure are anticipated to easily isomerize by means of the rope-skipping motion of the bridge going over the imidazolium ring, a sufficient chiral auxiliary might be required to distinguish two atrop isomers in stability and/or reactivity; either of the two isomers would work as a net reac-

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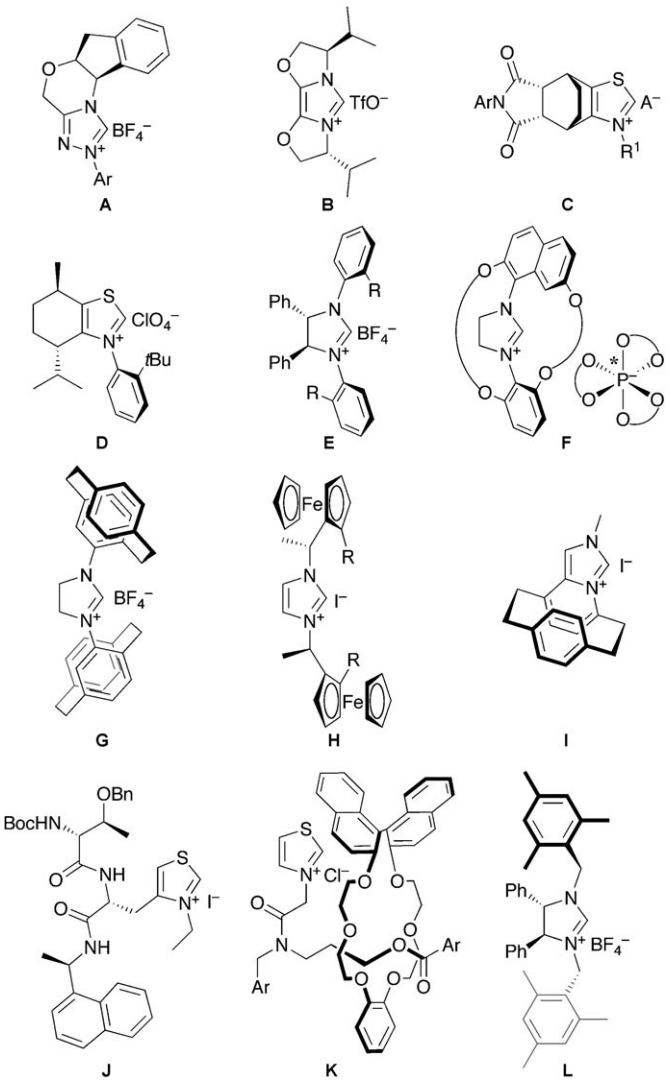
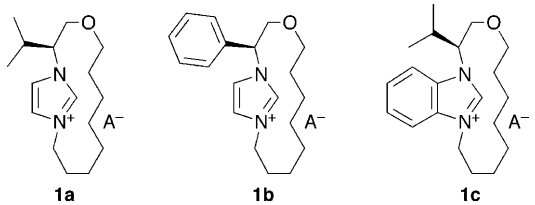
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200800942.

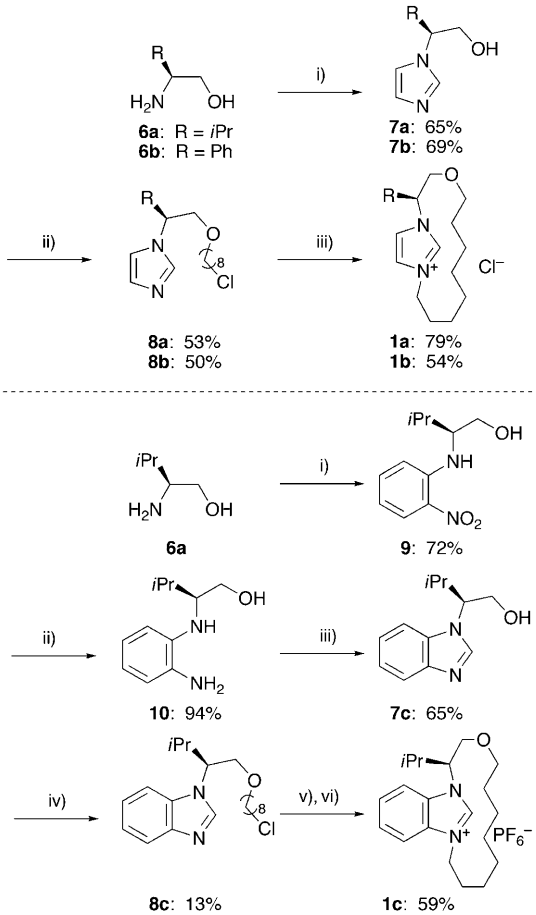


tive species. In the context of chirality type, **1a–c** might be classified in the same category as the types **G–I** (planar chirality). However, the carbene moiety of **1a–c** is incorporated in a macrocyclic structure, which seems to be advantageous in directly controlling spatial environment around the carbene reaction center. Despite such a simple and promising structure, NHCs derived from imidazolium salts like **1a–c** have not yet been explored so far. Here we report the synthesis, characterization, and application of a new type of NHC/NHC precursor with cyclophane-type planar chirality.



Results and Discussion

Synthesis of cyclophane-type imidazolium salts: The N(1)–N(3)-bridged imidazolium salts **1a–c** were synthesized as shown in Scheme 1. According to the procedure we have recently reported,[12] the imidazoles **7a** and **7b** with a chiral N substituent were directly synthesized by the cyclocondensation of the enantiopure 2-amino alcohols **6a** and **6b** with glyoxal, formaldehyde, and ammonium acetate. On the other hand, the analogous benzimidazole **7c** was prepared by the following series of reactions: the nucleophilic substitution of 1-fluoro-2-nitrobenzene with **6a**, the hydrogenolysis of the nitro group into an amino group, and the condensation of the resultant 1,2-diaminobenzene derivative with triethyl orthofomate.[13] The imidazoles **7a–c** thus obtained were then treated successively with sodium hydride and 1,8-dichlorooctane to afford the 8-chlorooctylated imidazoles **8a–c**. Finally, the intramolecular quaternization of the resultant imidazoles **8a–c** gave the cyclophane-type imidazolium salts **1a–c**.[10a,b,d] For the last step, a highly elevated tempera-



Scheme 1. Synthesis of cyclophane-type imidazolium salts **1a–c**. Top: i) glyoxal, HCHO, NH_4OAc, MeOH/H_2O, 80 °C, 5 h; ii) NaH, $Cl(CH_2)_8Cl$, DMF, 0 to 55 °C, 20 h; iii) DMAc, 150 °C, 48 h. Bottom: i) 1-fluoro-2-nitrobenzene, DMSO, RT, 60 h; ii) Pd/C, H_2 (1 atm), MeOH, RT, 40 h; iii) $CH(OEt)_3$, *p*-TsOH·H_2O, 100 °C, 44 h; iv) NaH, $Cl(CH_2)_8Cl$, DMF, 0 to 55 °C, 17 h; v) DMAc, 150 °C, 140 h; vi) KPF_6, CH_3CN, RT, 10 h.

ture was required to ensure a reasonable reaction rate, because the length of the alkyl chain had little margin to connect the two imidazolium nitrogen atoms. Although the intermolecular quaternization was a possible undesired side reaction, only a small amount of a mixture of oligomers was generated, as long as the initial concentration was at an order of 10–100 mM. In addition, the extensive degas of oxygen from the system before heating efficiently prevented side reactions, most likely caused by the heat-promoted generation of NHCs and a subsequent reaction with internal oxygen.

Structural profiles of the cyclophane-type imidazolium salts: The structural profiles of the cyclophane-type imidazolium salts **1** were investigated by ^{1}H NMR spectroscopy, X-ray crystallography, and molecular modeling. The ^{1}H NMR spectroscopy signals for the methylene protons at the middle of the N(1)–N(3) bridge in **1a** were observed at an upfield-shifted region ($\Delta\delta \approx 0.5$ ppm, overlapped with the signal of the isopropyl group (CH_3)$_2$CH−), which indicates that the bridge overlays the imidazolium ring to suffer a shielding effect.[10,14] Given such a "hover-overed" structure, two atrop isomers (diastereomers) arising from the planar chirality of the imidazolium ring are possible for **1a** (S_p and R_p). In good agreement with this expectation, a theoretical calculation at the HF/6-31G level gave two constitutions with a "hover-overed" structure minimal in potential energy, both of which correspond to two possible conformers (Figure 1a). Moreover, an X-ray crystallographic study revealed that **1a** takes one of the two conformations ((R_p)-**1**) in the crystalline state (Figure 1b).[14] However, variable-temperature (VT) ^{1}H NMR spectroscopy measurements clearly proved that the isomerization by means of the rope-skipping motion of the N(1)–N(3) bridge easily takes place in a solution; **1a** showed one set of sharp signals at a temperature range from 25 to −80 °C, and even at −95 °C only partial broadening of signals was observed.[10a,b,14] The phenomenon

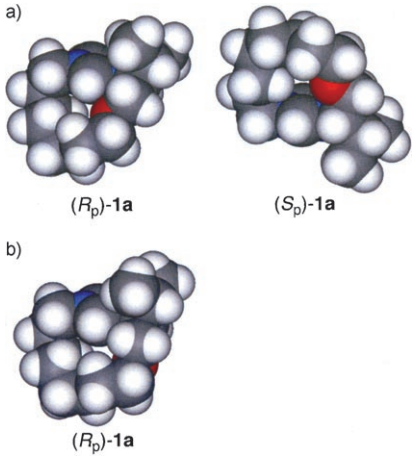
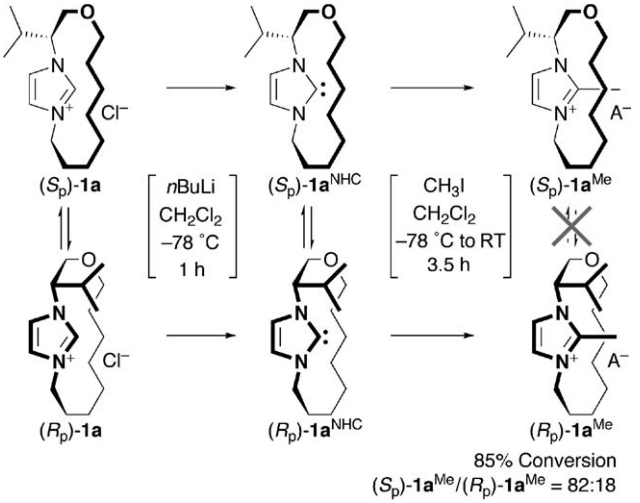


Figure 1. Structure of cyclophane-type imidazolium salt **1a**. a) Optimized structure (HF/6-31G level) of the two conformers of **1a** with cyclophane-type planar chirality of R_p (left) and S_p (right). b) X-ray crystal structure of **1a** (bromide salt). The counteranion is omitted for clarity.

suggests that the activation energy for the rope-skipping process is rather low. The above-mentioned molecular modeling also indicates that the rope-skipping process easily takes place at the C(2) side of the imidazolium ring, even though the bridge barely goes through the C(4)/C(5) side because of steric hindrance.

Considering the structural similarity between imidazolylidenes and their parent imidazoliums, it might be reasonable to anticipate that the imidazolylidene **1a**^{NHC}, derived from **1a**, also exists as a mixture of two atrop isomers ((S_p)- and (R_p)-**1a**^{NHC} in Scheme 2) that are isomerizable into each



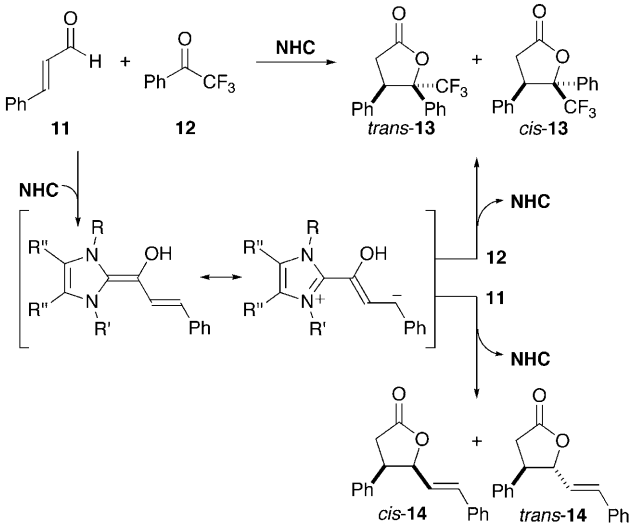
Scheme 2. Relative reactivity of two conformers of **1**^{NHC}.

other. However, there seems to be large difference in nucleophilicity between (S_p)- and (R_p)-**1a**^{NHC}, because of the difference in steric congestion around the carbene moieties. In the case of (R_p)-**1a**^{NHC}, the isopropyl group on the stereogenic carbon in the bridge would overlay the C(2) to reduce the nucleophilicity of this NHC species. Contrary to this, (S_p)-**1a**^{NHC} seems to have enough space around the C(2) to facilitate nucleophilic attack toward electrophiles such as aldehydes.

An individually synthesized sample of the C(2)-methylated imidazolium salt **1a**^{Me} revealed that the isomerization of (S_p)- and (R_p)-**1a**^{Me} hardly occurs, even when standing at room temperature for several months; the methyl group is bulky enough to suppress the rope-skipping of the N(1)–N(3) bridge across the imidazolium plane. To confirm the deduction described above, the following model reaction was conducted. The imidazolium salt **1a** was treated with butyllithium to generate the imidazolylidene **1a**^{NHC}, which was then electrophilically trapped with methyl iodide to give **1a**^{Me}.[15] The conformation of the S_p and R_p isomers should be locked after the C(2)-methylation (Scheme 2). As a result, we could roughly but directly estimate the relative reactivity of the two imidazolylidene conformers (S_p)- and (R_p)-**1a**^{NHC} from the product ratio of (S_p)- and (R_p)-**1a**^{Me}. We should emphasize here that, because the isomerization is

such a fast process as estimated by variable-temperature NMR spectroscopy, the product ratio will not be governed by the population of the two imidazolylidene conformers, but will reflect their relative reactivity.

Through the deprotonation and the subsequent methylation at the C(2) position, **1a** gave (S_p)-**1a**^{Me} as the main product (85% conversion, $S_p/R_p = 82:18$). The absolute configuration of the major isomer (determined by an X-ray crystallographic study) is in good agreement with our expectation that (S_p)-**1a**^{NHC} would be more reactive than (R_p)-**1a**^{NHC}.[10d] In the cases of the other imidazolium salts **1b** and **1c**, essentially the same results (by means of ^{1}H NMR spectroscopy and molecular modeling) were obtained as those of **1a**, which strongly implies a general tendency in the reactivity order (S_p isomer > R_p isomer), regardless of the side-chain residue on the stereogenic carbon and of the substituents at the C(4) and C(5) positions. Thus, (S_p)-**1** was found to preferentially react even with methyl iodide relatively little in comparison with carbonyl compounds widely used as substrates in NHC-catalyzed reactions.



Scheme 3. Cross-annulation of the enal **11** and the ketone **12** by means of the conjugated umpolung catalyzed by NHC, and a possible side reaction.

Cross-annulation of the enal 11 and the ketone 12 catalyzed by the NHC derived from imidazolium salt 1b: With these cyclophane-type imidazolium salts **1a–c** in hand, we next applied them as the precursors of chiral NHC organocatalysts. For the first attempt the NHC-catalyzed annulation of cinnamaldehyde (**11**) and 2,2,2-trifluoroacetophenone (**12**) was selected, because only those from imidazoliums are known to catalyze this reaction efficiently among four types of NHCs based on triazolium, thiazolium, imidazolium, and imidazoliunium salts.[15b] The annulation involves multiple steps, such as the generation of an acyl anion equivalent through the NHC-catalyzed umpolung of the enal unit, the conversion of the acyl anion equivalent into a homoenolate equivalent through the conjugation, the electrophilic trapping of this homoenolate by the carbonyl compound, and the intramolecular nucleophilic attack of the resultant alkoxide on an activated ester moiety (Scheme 3).[16] Despite the synthetic importance of this annulation, attempts to extend the reaction to an enantioselective version are at a premature stage.[6f,g,17,18] Thus, this reaction seemed to be a suitable entry to demonstrate the utility of our imidazolium salts **1** as precursors of chiral NHC organocatalysts.

The effect of reaction conditions on the efficiency and selectivity of this reaction was thoroughly investigated by using **1b** (Table 1). The NHC **1b**^{NHC} was generated in situ by treatment of **1b** (0.2 equiv) with a base (0.2 equiv), which was directly used for the annulation of **11** (1.0 equiv) and **12** (4.0 equiv). In all entries, the target cross-annulated lactone **13**, the self-annulated lactone **14**,[19] and the starting materials **11** and **12** were isolated from the reaction mixture (Scheme 3), whereas other possible byproducts generated from an acyl anion equivalent such as acyloins and the Stetter products were not detected at all. The homoenolate generated showed undesired chemoselectivity (i.e., the cross-annulation/self-annulation ratio) to lower the yield of the target lactone **13**; this problematic side reaction has been commonly observed in the cases of other imidazolidene catalysts.[15a] However, upon raising the reaction temperature, the cross-/self-annulation ratio was improved to some extent (from 26:74 to 46:54, Table 1, entries 2–4).

The stereochemical outcomes of the cross-annulation exhibited an unexpected dependence on the reaction conditions. The diastereomeric ratio (*trans*-**13**/*cis*-**13**) showed little dependence on the reaction temperature, solvent, and base. On the other hand, the enantiomeric excesses of *trans*- and *cis*-**13** significantly increased as the reaction temperature became higher, which is a contrast to the commonly observed tendency of asymmetric reactions.

Overall, the conditions given in entry 4 in Table 1 were found to be optimal from the viewpoints of yield and selec-

Table 1. Cross-annulation of the enal **11** and the ketone **12** catalyzed by **1b**^{NHC}.

Entry[a]	Solvent	Base	T [°C]	Conv.[b] [%]	Ratio[b] **13**/**14**	Yield[c] (ee[d]) [%] *trans*-**13**	*cis*-**13**
1	THF	$KN(SiMe_3)_2$	−78	<1	–	–	–
2	THF	$KN(SiMe_3)_2$	−20	59	26:74	6 (19)	3 (29)
3	THF	$KN(SiMe_3)_2$	0	62	31:69	8 (32)	3 (51)
4	THF	$KN(SiMe_3)_2$	25	>99	46:54	21 (43)	9 (69)
5	CH_2Cl_2	$KN(SiMe_3)_2$	25	69	41:59	14 (25)	4 (44)
6	THF	$LiN(SiMe_3)_2$	25	60	43:57	13 (20)	3 (45)

[a] Conditions: NHC generation: **1b** (0.2 equiv), a base (0.2 equiv), a solvent, −78 °C for 1 h. Cross-annulation: NHC, **11** (1.0 equiv), **12** (4.0 equiv), a solvent, from −78 °C to a temperature in a period of 30 min and then at that temperature for 16 h. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Determined by chiral HPLC. In all entries, (4*R*,5*R*)- and (4*R*,5*S*)-**13** were obtained as the major enantiomers of *trans*- and *cis*-**13**, respectively.

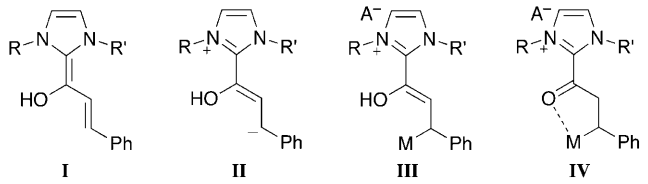


Figure 2. Possible reactive intermediates in the present reaction.

tivity. By taking account of the unexpected changes in enantioselectivity depending on the reaction temperature and on the metal cation, the reactive intermediates might include a metal homoenolate complex (Figure 2, **III** and/or **IV**), in addition to the Breslow intermediate and its tautomer (**I** and **II**).

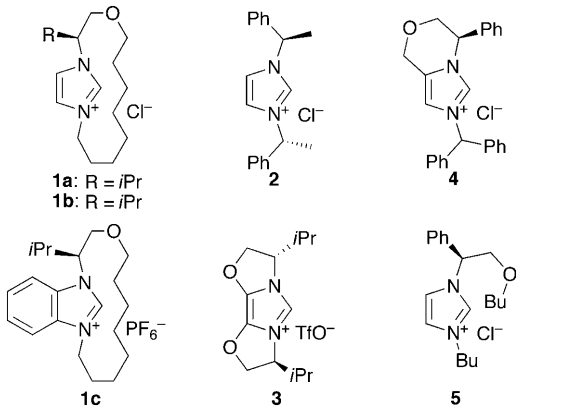
Cross-annulation of the enal 11 and the ketone 12 catalyzed by the NHCs derived from various imidazolium salts 1–5: To address the characteristic profile of the cyclophane-type planarly chiral NHCs $\mathbf{1}^{NHC}$, the same reaction was conducted by using conventional chiral NHCs based on the imidazolium salts **2–5**; C_2-symmetric **2** is one of the most widely used chiral imidazolium precatalysts,[5c,d] whereas the tricyclic and bicyclic imidazolium salts (**3** and **4**) are limited examples of precedent chiral imidazolium precatalysts with a fused ring structure. In addition to them, an open-chained analogue of **1b** (**5**) was also employed as a precatalyst, which would clarify the effect of the cyclophane structure in **1** (Table 2).

Table 2. Cross-annulation of the enal **11** and the ketone **12** catalyzed by NHCs from the imidazolium salts **1–5**.

Entry[a]	Precat.	Conv.[b] [%]	Ratio[b] **13**/**14**	Yield[c] (*ee*[d]) [%]	
				trans-**13**	*cis*-**13**
1	**1a**	93	45:55	10 (57)	10 (89)
2	**1b**	>99	46:54	21 (43)	9 (69)
3	**1c**	79	59:41	16 (74)	17 (94)
4	**2**	>99	45:55	22 (23)	7 (45)
5	**3**	94	>99:1	48 (28)	20 (14)
6	**4**	>99	44:56	23 (66)	5 (58)
7	**5**	>99	36:64	16 (18)	6 (31)

[a] Conditions: NHC generation: imidazolium precatalyst (Precat.) (0.2 equiv), $KN(SiMe_3)_2$ (0.2 equiv), THF, −78 °C for 1 h. Cross-annulation: NHC, **11** (1.0 equiv), **12** (4.0 equiv), THF, from −78 °C to 25 °C in a period of 30 min and then at 25 °C for 16 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Determined by chiral HPLC. In all entries except for entry 6, (4*R*,5*R*)- and (4*R*,5*S*)-**13** were obtained as the major enantiomer of *trans*- and *cis*-**13**, respectively. In entry 6, the absolute configuration of the major enantiomers were inverted for both of *trans*- and *cis*-**13**.

The conversion of the enal **11** revealed that the NHCs $\mathbf{1a–c}^{NHC}$ exhibited a sufficient catalytic activity comparable to that of the conventional NHCs $\mathbf{2–4}^{NHC}$, although the reactivity of the NHC $\mathbf{1c}^{NHC}$ was lower than that of the others to some extent (Table 2, entries 1–3 versus entries 4–6). Despite the adequate amount of catalytic activity thus observed, the NHCs $\mathbf{1a–c}^{NHC}$ as well as the NHCs $\mathbf{2}^{NHC}$ and $\mathbf{4}^{NHC}$ could not achieve sufficient yield of the cross-annulated lactone **13** because of unsatisfactory chemoselectivity required to generate a considerable amount of the self-annulation product **14** (Scheme 3).[19] Among $\mathbf{1a–c}^{NHC}$, $\mathbf{1c}^{NHC}$ showed better cross-annulation selectivity (entries 1 and 2 versus entry 3), which might be elucidated as follows. Because of the electron-withdrawing and/or charge-delocalizing effect of the benzo moiety, $\mathbf{1c}^{NHC}$ generates a homoenolate equivalent with lower nucleophilicity than do $\mathbf{1a}^{NHC}$ and $\mathbf{1b}^{NHC}$, and the resultant homoenolate species prefers the electronically favorable electrophile **12** rather than the sterically favorable electrophile **11** (Scheme 3).



For the diastereoselectivity of this reaction catalyzed by NHCs, it is generally known that the isomer possessing two aromatic groups at the same side of the γ-lactone ring (*trans*-**13**) is more predominantly formed than is the other isomer (*cis*-**13**). In good agreement with this propensity, $\mathbf{1b}^{NHC}$ afforded *trans*-**13** as the major product in a *trans*/*cis* ratio of around 70:30 (entry 2, Table 1). Worth noting is the peculiar diastereoselectivity of $\mathbf{1a}^{NHC}$ and $\mathbf{1c}^{NHC}$, the cyclophane-type NHCs bearing an isopropyl group on the stereogenic center; the ratio of the *cis* isomer increased, and the diastereomer ratio reached around 50:50 (entries 1 and 3, Table 2). Because such a peculiar diastereoselectivity was not observed for $\mathbf{1b}^{NHC}$, the bulky isopropyl group on the stereogenic carbon of $\mathbf{1a}^{NHC}$ and $\mathbf{1c}^{NHC}$ was likely to contribute to suppress the formation of *trans*-**13**.

Quite interestingly, the NHCs derived from the N(1)–N(3)-bridged imidazoliums **1a–c** showed exceptionally high enantioselectivity (entries 1–3, Table 2) compared with conventional chiral NHCs. Especially, the enantiomeric excesses of *trans*- and *cis*-**13** obtained by the reaction catalyzed by $\mathbf{1c}^{NHC}$ were no less than 74 and 94%, respectively (entry 3). To the best of our knowledge, these are the highest enantioselectivity (*ee*) values for this reaction up to now.[6f,g,17,18] A control experiment using the analogous ring-opened $\mathbf{5}^{NHC}$ strongly suggests that such high enantioselectivities are ascribable to the conformationally constrained cyclophane structure (entry 2 versus entry 7).

Elucidation of the mechanism of the present stereocontrolled lactone formation: Direct γ-lactone formation by means of the conjugated umpolung of enals is expected to

become an important benchmark reaction to evaluate the potential of chiral NHCs, especially those derived from chiral imidazolium salts. For the detailed elucidation of the mechanism for chirality induction, the determination of the absolute configuration of the annulation products would be highly necessary. Up to now, however, studies on the absolute configuration of 4,5-diaryl-γ-lactones have been limited to a few reports dealing with the simplest type of 4,5-diphenyl-γ-lactone.[20] Moreover, all of these conventional assignments were deduced from the pattern of circular dichroism spectra. Therefore, we tried to determine the absolute configuration of the enantiomers of *trans*- and *cis*-**13** by an unequivocal method based on the chromatographic separation of the enantiomers, their derivation by the aminolysis with (*R*)-1-phenylethylamine, and the X-ray crystallography of the resultant γ-hydroxypentanamides. As a result, the major enantiomers of *trans*- and *cis*-**13** obtained by the NHC catalysts **1a**–**c**^{NHC} were found to be 4*R*,5*R* and 4*R*,5*S*, respectively (Figure 3).[14]

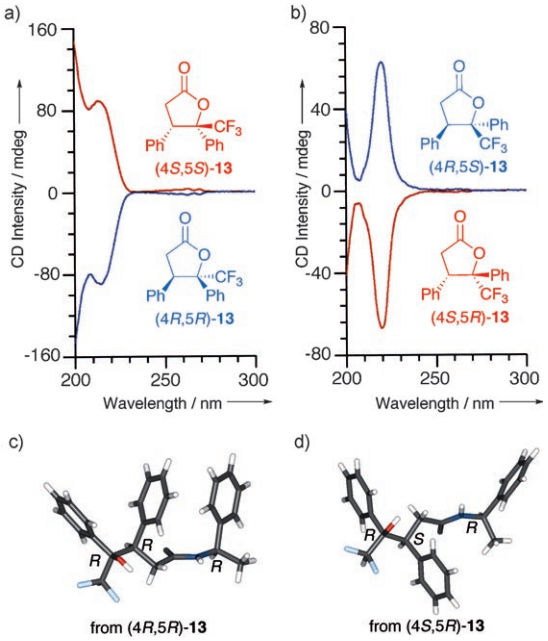
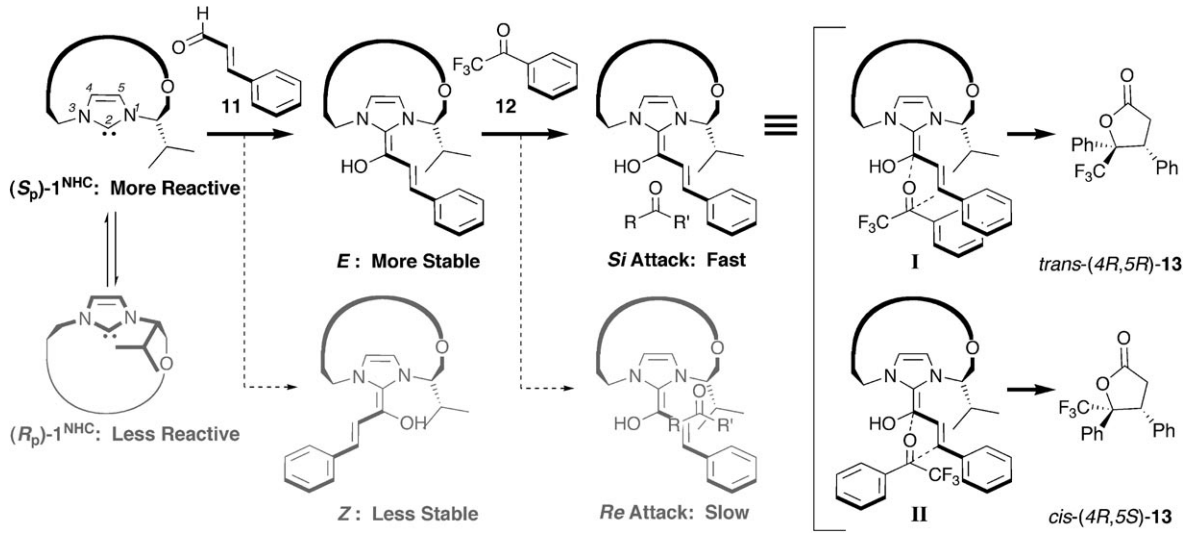


Figure 3. Circular dichroism spectra of the enantiomers of a) *trans*- and b) *cis*-**13** in acetonitrile at RT and X-ray crystal structures of the γ-hydroxypentanamides derived from c) *trans*-(4*R*,5*R*)- and d) *cis*-(4*S*,5*R*)-**13** by treatment with (*R*)-1-phenylethylamine.

Based on the configurations as determined above, a plausible reaction path elucidating the enantioselection by **1**^{NHC} can be proposed; it involves the *Si*-selective attack of the *E* homoenolate (Scheme 4, **I** and **II**). Although **1**^{NHC} is likely to exist as a mixture of the R_p and S_p isomers easily isomerizable into each other, the S_p isomer was proved to be the net reactive species of **1**^{NHC}, as described above (Scheme 2). Apparently, the *Z* homoenolate might seem to be more favorable than the *E* isomer as an intermediate of the first step, considering steric congestion around the N(1) of the NHC moiety. However, we believe that the *E* homoenolate is more stable owing to the following "strain-relayed" mechanism; our hypothesis is strongly supported by the X-ray crystal structure of a homoenolate-intermediate analogue (the PF_6^- salt of (S_p)-**1a**^{Me}), of which the C(2) substituent is replaced with a methyl group (Figure 4).[10d] Taking account of steric repulsion, the bulky side-chain residue on the stereogenic carbon (*i*Pr for **1a**,**c**^{NHC} and Ph for **1b**^{NHC}) should orient perpendicularly to the imidazolium ring (Figure 4, arrow *i*). In addition, the ether unit in the N(1)–N(3) bridge might restrict the conformation around the N(1) end of the bridge, owing to the partial sp^2 character of the oxygen atom. These conformational demands would relay to the neighboring atoms in the bridge (arrows *ii* and *iii*). To cancel the strain thus accumulated, the other end of the bridge adjacent to the N(3) is pushed out to the C(2) side, which induces the N(3) end of the bridge to occupy the space around the C(2) (arrow *iv*). Such a dissymmetrically distorted structure of the N(1)–N(3) bridge seems to be suitable



Scheme 4. A plausible reaction path for the stereocontrolled cross-annulation of the enal **11** and the ketone **12** catalyzed by NHCs from **1a**,**c**.

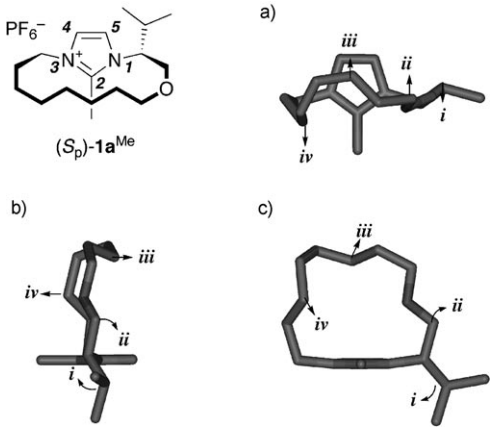


Figure 4. X-ray crystal structure of (S_p)-**1a**^{Me} (PF_6^- salt): a) top view, b) side view, and c) front view. Hydrogen atoms, counteranions, and the other symmetrically independent imidazolium cations in a unit cell are omitted for clarity.[10d]

for the preferential formation of the *E* homoenolate. According to the molecular modeling of the *E* homoenolate, the *Re* face is significantly shielded by the N(1)–N(3) bridge of the imidazolylidene moiety, whereas there is essentially no steric hindrance on the *Si* face. Consequently, the electrophilic attack of **12** occurs mainly on the *Si* face of the homoenolate to generate the γ-lactone with *R* configuration at the C(4) position. The expected stereochemical outcome is in good agreement with that observed for both of the *trans* and *cis* isomers (Scheme 4).

On the other hand, the relative stereochemistry at the C(4) and C(5) positions (i.e., the diastereocontrol) of **13** might be mainly determined by the inherent nature of substrates **11** and **12**. Considering the favorable arrangement of the dipoles of the homoenolate equivalent and the ketone **12**, as well as π–π interaction between the electron-rich and electron-deficient phenyl groups, the transition states of **I** in Scheme 4 are expected to be the most favorable. The subsequent electrophilic trapping of the homoenolate and lactone formation would give the *trans* isomer, which is in good agreement with the general tendency of this reaction including our observations. The exceptional bias in the diastereoselectivity observed for the reactions catalyzed by **1a**^{NHC} and by **1c**^{NHC} might be explained in terms of steric repulsion between the bulky isopropyl group in the imidazolylidene and the phenyl group in **12**.

Conclusion

Imidazolium salts with cyclophane-type planar chirality (**1a**–**c**) were developed as precursors of a novel class of chiral NHCs. The structural profiles of the imidazolium salts and their derivative NHCs were investigated by several methods, which revealed that one of the two possible conformers for the imidazolylidenes acted as a main active species. The NHCs derived from these imidazoliums showed remarkably high enantioselectivity in the cross-annulation reaction of an enal and a ketone (up to 94% *ee*), owing to their characteristic cyclophane structure. As far as we know, this is the first attempt to apply planar chirality to the development of NHC-based chiral organocatalysts. Although the yield of the target lactone was unsatisfactory at present, the *ee* values observed here were at the highest level for this reaction. Considering the easy access, simple and well-defined structure, and the high chirality induction ability, the cyclophane-type planarly chiral imidazolium salts developed here would provide us a new structural motif in the field of NHC chemistry.

Experimental Section

Chemicals: Chemicals were purchased and used as delivered unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium wire and benzophenone before use. Dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), and dimethylsulfoxide (DMSO) were distilled from CaH_2 and stored over activated molecular sieves. *N*,*N*′-Dimethylformamide (DMF) was dried over P_2O_{10}, distilled from CaH_2, and stored over activated molecular sieves. *N*,*N*′-Dimethylacetamide (DMAc) was distilled just before use. Cinnamaldehyde (**11**) and 2,2,2-trifluoroacetophenone (**12**) were distilled just before use. A solution of potassium hexamethyldisilazane in toluene was purchased and used as received. Imidazolium salts **2**–**4** were prepared according to the literature cited in the Supporting Information. For the synthesis of the cyclophane-type imidazolium salts **1a**–**c** and the open-chained analogue **5**, see the Supporting Information.

C(2)-methylation of the imidazolium salt 1a: A solution of butyllithium in hexane (1.56 M, 0.24 mL, 0.36 mmol) was added dropwise to a solution (3 mL) of **1a** (90 mg, 0.30 mmol) in CH_2Cl_2 at −78 °C, and the mixture was stirred at −78 °C for 1 h. After adding a solution (1.5 mL) of methyl iodide (70.2 mg, 0.49 mmol) in CH_2Cl_2, the mixture was stirred at −78 °C for 30 min and then at RT for 3 h. The insoluble materials were filtered off (ADVANTEC filter paper 5A), and the filtrate was concentrated under reduced pressure to give a crude mixture of (S_p)- and (R_p)-**1a**^{Me}, and unreacted **1a** (85% conversion, (S)-**1a**^{Me}/(R_p)-**1a**^{Me} = 82:18, determined by ^{1}H NMR spectroscopy).

Typical procedure for the cross-annulation of the aldehyde 11 and the ketone 12: A solution of potassium hexamethyldisilazane in toluene (0.50 M, 200 μL, 0.10 mmol) was added dropwise to a suspension of **1a** (30.1 mg, 0.10 mmol) in THF (3 mL) at −78 °C under an argon atmosphere, and the mixture was stirred at that temperature for 1 h. Then, 2,2,2-trifluoroacetophenone (**11**, 280 μL, 2.0 mmol) and cinnamaldehyde (**12**, 65 μL, 0.50 mmol) were successively added to the mixture at −78 °C. The mixture was stirred at that temperature for 30 min, and then allowed to warm up to RT. After being stirred at RT for 16 h, the mixture was treated with methanol (0.5 mL) and concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography (eluent: hexane/CH_2Cl_2 = 2:1, v/v) to give a mixture of *trans*- and *cis*-**13** as a pale yellow oil (29.0 mg, 0.09 mmol, 19%). The ratio of *trans*- and *cis*-**13** was 50:50 (estimated by a ^{1}H NMR spectroscopy measurement), and the enantiomeric excesses of *trans*- and *cis*-**13** were 57 and 89%, respectively (estimated by a chiral HPLC measurement). Chiral HPLC conditions: column, Daicel CHIRALCEL AS-H (4.6 × 153 mm); eluent, hexane/2-propanol (90:10, v/v); flow rate, 1.0 mL min^{-1}; detection, UV absorption at λ = 210 nm; retention time, 8.41 and 13.16 min for *trans*-**13** and 14.06 and 23.44 min for the *cis*-**13**.

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[18] By using special electrophiles such as nitrobenzene/nitrone/1-acyl-2-aryldiazene in this reaction (ref. [17]), good to excellent enantioselectivity was often achieved (up to 93% *ee*, ref. [17a]). However, it is still difficult to realize satisfactory selectivity by using a simple aldehyde/ketone/aldimine as an electrophile (up to 66% *ee*, ref. [6g]).

[19] By using the NHC catalyst generated from **1a**, the self-annulation of **12** to form **14** proceeded with appreciable diastereo- and enantioselectivities. The optimization of the reaction conditions for the self-annulation is under progress. Details will be reported elsewhere in the near future.

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Received: May 17, 2008
Published online: August 27, 2008

