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C2 Symmetric chiral *N*-heterocyclic carbene catalyst for asymmetric intramolecular Stetter reaction

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Abstract—The asymmetric intramolecular Stetter reaction of ω-formyl α,β-unsaturated carbonyl compounds was catalyzed by a C2 symmetric chiral carbene, generated from (4*S*,5*S*)-diphenyl-1,3-bis(mesitylmethyl)-4,5-dihydro-1*H*-imidazolium tetrafluoroborate, to afford 2-substituted cyclopentanones in good enantioselectivity of up to 80%.

Chiral ligands with C2 symmetry have proven to nicely control metal-catalyzed asymmetric reactions as exemplified by DIOP,[1] BINAP,[2] BOX,[3] and TADDOL[4] etc. We have also experienced such advantages of C2 symmetric chiral ligands in the asymmetric dihydroxylation of olefins[5] and conjugate addition reaction of α,β-unsaturated carbonyl compounds.[6] For example, a chiral diether **1**[7] was designed to form a chelate **3** with organolithiums, resulting in a chiral environment around lithium cation by placing the methyl groups on oxygen atoms on the up and down faces of **3** (Fig. 1).

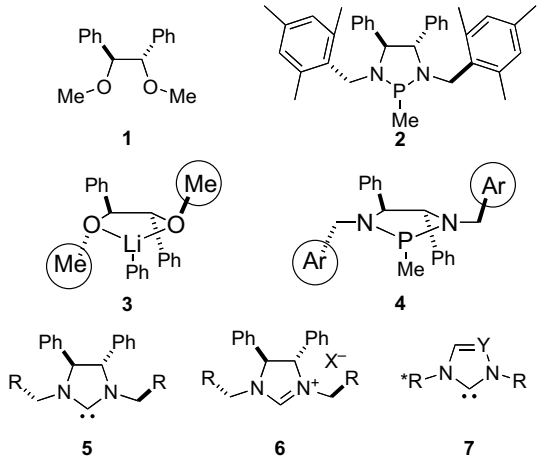

Figure 1. Chiral C2 symmetric structures.

Phosphorous compound **2**,[8] a ligand for the copper-catalyzed conjugate addition of organozincs, also fixes mesityl groups on the up and down faces of a five membered ring giving the similar chiral environment around phosphorus as shown in **4**. We extended such a design of a C2 symmetric chiral environment to an *N*-heterocyclic carbene (NHC) **5** that is generated from dihydroimidazolium salt **6** by treating with a base.

NHC[9]-mediated asymmetric transformations are the recent topics of brilliant success as have been shown by transesterification,[10] benzoin condensation,[11,12] and Stetter reaction.[13,14] Although imidazolidene and triazolidene carbenes **7** (Y = CH, N) are the frequently used organocatalysts in these transformations, dihydroimidazolidenes (**5**) are not sufficiently surveyed yet.[15,16] Since **5** is anticipated to be less stable than **7** due to electronic reason, we began our studies with the asymmetric Stetter reaction of a formylenoate **8** following Rovis's procedure[14] to evaluate the catalytic reactivity and enantioselectivity of C2 symmetric **5**.

The dihydroimidazolium tetrafluoroborate **6a** (R = mesityl, X = BF_4) was prepared in 76% yield by the reaction of (1*S*,2*S*)-1,2-diphenyl-N^1,N^2-bis(mesitylmethyl)ethane-1,2-diamine,[8] triethyl orthoformate, and ammonium tetrafluoroborate.[17] To a suspension of **6a** (20 mol %) in toluene was added *n*-butyllithium (19 mol %) in hexane at −20 °C and the whole suspension was stirred at rt for 0.5 h. Then a toluene solution of a formylenoate **8a** was added to the above suspension. The consumption of **8a** and formation of **9a** were not observed by TLC at rt and also at 50 °C. However,

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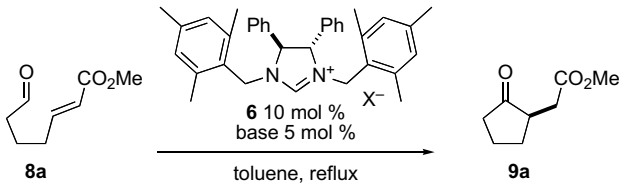
Table 1. Asymmetric Stetter reaction with **6**-*n*-BuLi or KH



Entry	6	R	X	Base	Time (h)	Yield (%)	ee (%)
1[a,b]	**6a**	Mes	BF_4	*n*-BuLi	17	93	32
2[b]	**6a**	Mes	BF_4	*n*-BuLi	10	74	76
3[b]	**6b**	Mes	PF_6	*n*-BuLi	10	6	72
4[b]	**6c**	Mes	Cl	*n*-BuLi	10	85	6
5[b]	**6d**	Mes	Br	*n*-BuLi	10	0	
6[c,d,e]	**6a**	Mes	BF_4	KH	16	85	20
7[c,e]	**6b**	Mes	PF_6	KH	3	83	45
8[c]	**6d**	Mes	Br	KH	5	71	72

[a] 20 mol % of **6a** and 19 mol % of *n*-BuLi.
[b] Generation of **5** at rt.
[c] Generation of **5** at reflux.
[d] **8a** was added at 50 °C and then the whole was stirred for 1 h at 50 °C and then refluxed.
[e] 18-Crown-6 (50 mol %) was added as an additive.

we were very pleased to find that heating at reflux for 17 h gave (*R*)-**9a**[18] in 93% yield (Table 1, entry 1). The enantioselectivity was determined to be 32% ee by a chiral GC (chirasil dex CB). Although the less reactivity was expected by the comparison of the electronic nature of **5** and **7**, the enantioselectivity was unexpectedly low. Then we checked the % ee at 2 h reflux and found that **9a** was produced in 76% ee, suggesting the occurrence of racemization during the reaction at such high temperature. Racemization was almost sufficiently suppressed by lowering the loading of base to 5 mol % of *n*-butyllithium against 10 mol % of **6a**, giving **9a** with 76% ee in 74% yield (entry 2).[19] It is remarkable that such a good enantioselectivity was observed at such a high temperature of refluxing toluene. It is also important to note that imidazolium salt **6a** was recovered in 80% yield and was reusable.

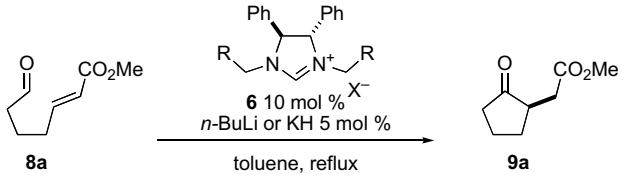
Other salts **6b–d** bearing PF_6, Cl, Br as a counter anion were unsuitable choices, giving lower yield or poorer % ee (entries 3–5). Since the lithium salts, produced during the generation of an NHC **5** from **6** with *n*-butyllithium, have been known to form a complex with **5**,[20] we then examined potassium hydride as an NHC generating base.

Treatment of **6a** with potassium hydride at reflux for the generation of **5** and subsequent reaction with **8a** gave **9a** in reasonably high yields regardless of the counter anion (entries 6–8). However, enantioselectivity suffers from racemization except in the case of bromide **6d** (72% ee, entry 8). The production and no production of **9a** depending on the use of potassium hydride and *n*-butyllithium with **6d** suggest the high affinity of lithium cation for **5**, which upon complexation loses its reactivity (entries 5 and 8).

The enantioselectivity evaluation of some NHC **5** bearing the different size of substituent RCH_2 on nitrogen atoms was carried out by treating **6** with *n*-butyllithium or potassium hydride at reflux for the generation of **5** (Table 2). The dihydroimidazolium salts **6e** and **6f** bearing neopentyl groups on nitrogen atoms gave **9a** with 68% ee and 56% ee, respectively, although the combination of bromide salt and potassium hydride base is superior in the chemical yield (entries 1 and 2). Mesitylethyl substituent (**6g**), one carbon longer than mesithylmethyl group (**6a**), gave (*R*)-**9a** with 20% ee in 91% yield, indicating the importance of the conformational fixing of a stereocontrolling group R (entry 3). Direct attachment of a phenyl group to each nitrogen atom (**6h** and **6i**) is not beneficial to enantioselectivity giving (*S*)-**9a** of the opposite absolute configuration with 6% and 7% ees (entries 4 and 5).

The olefin activating group of **8** influenced the enantioselectivity. The more bulky *t*-butyl ester **8b** was

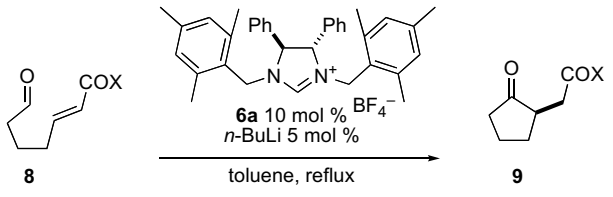
Table 2. Asymmetric Stetter reaction with **6** bearing the different size of substituents



Entry	6	RCH_2	X	base	Time (h)	Yield (%)	ee (%)
1[a]	**6e**	*t*-$BuCH_2$	BF_4	*n*-BuLi	10	5	68
2[b]	**6f**	*t*-$BuCH_2$	Br	KH	5	67	56
3[a]	**6g**	$Mes(CH_2)_2$	BF_4	*n*-BuLi	10	91	20
4[a,c]	**6h**	Ph	BF_4	*n*-BuLi	10	20	6
5[b,c]	**6i**	Ph	Br	KH	5	58	7

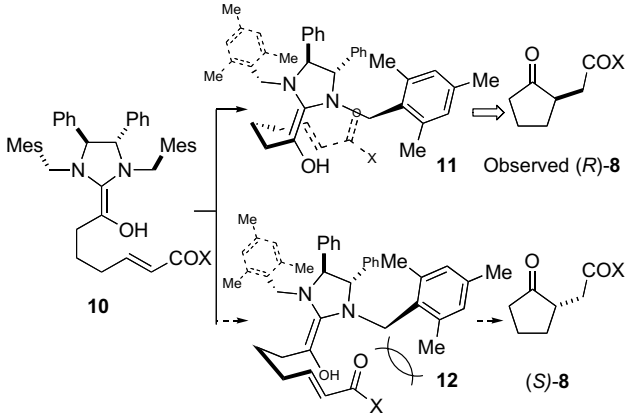
[a] Generation of **5** at rt.
[b] Generation of **5** at reflux.
[c] The product was (*S*)-**9a**.

Table 3. Effects of an acceptor moiety on enantioselectivity



Entry[a]	8	X	Time (h)	Yield (%)[b]	ee (%)
1	**8a**	MeO	10	74	76
2	**8b**	*t*-BuO	9	59	80
3	**8c**[c]	Ph	10	33	63

[a] Generation of NHC at rt.
[b] Recovery of **8a** (16%), **8b** (35%), and **8c** (50%).
[c] Absolute configuration was not determined.



Scheme 1. Stereochemical control.

converted to **9b** with 80% ee (Table 3, entry 2). A phenylketone **8c** was converted to **9c** with 63% ee (entry 3).

The sense of asymmetric induction is predictable by the models **11** and **12** (Scheme 1). The reaction of an NHC **5** with **8** would give a so-called Breslow intermediate **10**,[21] from which an intramolecular enamine-Michael-type reaction takes place via **11** and **12**. The sterically less demanding **11** would be the major conformer to give (*R*)-**9** with the observed absolute configuration. The C2 symmetry in fixing stereocontrolling mesityl groups may be the origin of relatively high enantioselectivity at such high reaction temperature.

In conclusion we have developed a chiral C2 symmetric *N*-heterocyclic carbene from a dihydroimidazolium that behaves as a chiral organocatalyst. It is remarkable to note that relatively high enantioselectivity of up to 80% was obtained even at the high temperature of toluene reflux. Encouraged by this result, further studies directed toward the development of C2 symmetric chiral carbene–metal complex for catalytic asymmetric reactions are in progress in our laboratories.

Acknowledgments

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19. Table 1, entry 2: To a suspension of **6a** (234 mg, 0.41 mmol) in 88 mL of toluene was added dropwise *n*-BuLi (0.13 mL, 0.21 mmol) in hexane at −20 °C and the mixture was stirred at rt for 0.5 h. A solition of **8a** (635 mg, 4.1 mmol) in toluene (8 mL) was added over a period of 5 min. The mixture was stirred for 2 h at rt, for 2 h at 50 °C, and for 10 h at reflux, and then quenched with 2% aq NH_4BF_4 (10 mL). The aqueous phase was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4. Concentration and silica gel column chromatography (Et_2O/hexane = 1/3) gave **9a** as a colorless oil (472 mg, 74%) of $[\alpha]_D^{25}$ +102 (*c* 0.98, MeOH), and **8a** (16% recovery). The ee of **9a** was determined to be 76% ee by gas chromatography (chirasil dex CB column with constant 95 °C oven temperature. 17.1 min and 17.9 min for minor and major).
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