Homogeneous Catalysis

DOI: 10.1002/ange.200503885

Asymmetric Intramolecular Crossed-Benzoin Reactions by N-Heterocyclic Carbene Catalysis**

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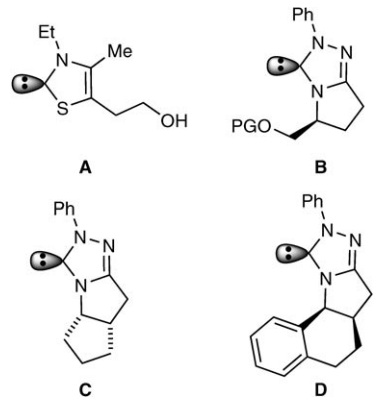
The discovery of stable carbenes in the last decade of the 20th century[1] has brought about extensive research on the chemistry of N-heterocyclic carbenes. With respect to the biochemistry of the coenzyme thiamine (vitamin B_1, a natural thiazolium salt), where the catalytically active species has been proposed to be a carbene, investigations on N-heterocyclic carbenes focussed on the catalysis of organic reactions[2] side by side with their use as ligands for organometallic chemistry.[3]

The powerful catalytic capacities of N-heterocyclic carbenes have been demonstrated by new organocatalytic transformations, for example, conjugate nucleophilic acylations,[4] transesterifications,[5] and polymerizations.[6] Great efforts have been made to conduct carbene-catalyzed reactions in an enantioselective way, and the 21st century has already witnessed remarkable achievements, such as, the efficient enantioselective benzoin condensation,[7] the asymmetric intramolecular Stetter reaction,[8] and the stereoselective intermolecular aldehyde-imine cross-coupling.[9]

The crossed-benzoin reaction also belongs to the family of nucleophilic acylation reactions. Chemoselectivity and stereocontrol were first reached with the thiamine-dependent enzyme benzoylformate decarboxylase that linked various, mostly aromatic, aldehydes to acetaldehyde to form the corresponding 2-hydroxy ketones.[10] Synthetic thiazolium salts developed by Stetter and co-workers, and similar to thiamine itself,[11] have been used successfully by Suzuki and co-workers for the first intramolecular crossed-aldehyde-ketone benzoin reactions in the course of an elegant natural product synthesis.[12] Stereocontrol was exerted by preexisting stereocenters in these specific substrates—the catalysts being achiral.

As it was highly desirable to develop a general protocol for the intramolecular benzoin reaction, we started investigations on simple aldehyde-ketones as substrates for the carbene-catalyzed intramolecular crossed-benzoin condensation. We were able to show that various five- and six-membered cyclic acyloins could be obtained in moderate to good yields by employing a commercially available thiazolium salt as precatalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine as the base to generate the carbene (**A**, Scheme 1).[13] Synchronously to our report, Suzuki and co-workers published similar results emphasizing that the competing intramolecular aldol reaction could be suppressed when a substoichiometric amount of base was employed relative to the precatalyst.[14]



Scheme 1. Carbenes derived from thiazolium and triazolium salts. PG = protecting group.

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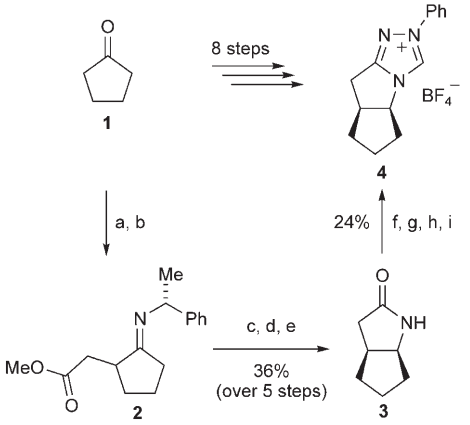
[**] This work was supported by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm Organokatalyse) and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, Bayer AG, and Wacker Chemie for the donation of chemicals.

With the crossed intramolecular aldehyde-ketone benzoin condensation thus established as a synthetic method, we continued our research to further optimize the reaction and to devise an enantioselective variant. We report herein the synthesis of various novel enantiopure polycyclic triazolium salts and their application as efficient chiral N-heterocyclic carbene catalysts of type **B**–**D** (Scheme 1) for the first enantioselective intramolecular crossed-benzoin reaction creating a quaternary stereocenter.[15]

Unfortunately the bicyclic triazolium salt that had successfully been used in our research group for the enantioselective intermolecular benzoin condensation[7] did not show any catalytic activity in the intramolecular reaction. We thus searched for alternative, easily accessible enantiopure polycyclic γ-lactams as precursors for the synthesis of novel triazolium salts. The rigid polycyclic structure of the catalysts should allow for high asymmetric inductions in catalysis.

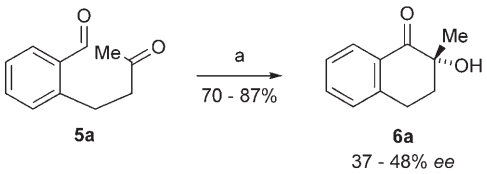
A first target was found in the *cis*-bicyclic lactam **3** which was obtained in a diastereo- and enantioselective manner in five steps starting from cyclopentanone (**1**) in 36% yield following a modified procedure developed by Omar and Frahm (Scheme 2).[16] After α-alkylation of **1** with methyl



Scheme 2. Preparation of the tricyclic triazolium salt **4**. a) LDA, $BrCH_2CO_2Me$, THF, DMPU, −78 °C to RT, 18 h; b) (*R*)-phenethylamine, cyclohexane, 4-Å molecular sieves, room temperature, 72 h; c) Raney Ni/H_2 (20 bar), EtOH, room temperature, 16 h; d) 3 N NaOH, MeOH, room temperature, 1 h; e) Li, liq. NH_3, THF/*t*BuOH (9:1), −78 °C, 20 min; f) Me_3OBF_4, CH_2Cl_2, room temperature, 24 h; g) $PhNHNH_2$, THF, 80 °C, 3 h; h) HBF_4/Et_2O, CH_2Cl_2, room temperature, 30 min; i) $HC(OMe)_3$, MeOH, 80 °C, 12 h. LDA = lithium diisopropylamide, DMPU = 1,3-dimethylhexahydro-2-pyrimidone.

bromoacetate and subsequent condensation with (*R*)-phenethylamine, the resulting imine **2** was diastereoselectively hydrogenated, cyclized, and deprotected to give lactam **3**. The *cis*-tricyclic triazolium salt **4** was then obtained as a solid in 24% yield by a modified three-step procedure reported by Knight and Leeper.[17]

The asymmetric intramolecular benzoin condensation with model substrate **5a** and the chiral triazolium salt **4** as precatalyst gave rise to the desired acyloin **6a** in good yields by utilizing toluene as solvent and DBU or KO*t*Bu as the base (Scheme 3). Unfortunately only moderate enantiomeric excess (37–48%) could be achieved, even at 5 °C (Table 1).



5a **6a**
37 - 48% *ee*

Scheme 3. First investigations with model substrate **5a**. a) **4**, base, toluene (0.1 M).

Table 1: Asymmetric intramolecular crossed-benzoin reaction with **4**.

4 [mol%]	Base (mol%)	*t* [h]	*T*	Yield [%]	*ee* [%][a] (config.)[b]
10	DBU (10)	3	RT	76	38 (*R*)
10	KO*t*Bu (10)	3	RT	87	37 (*R*)
20	DBU (20)	24	5 °C	70	48 (*R*)

[a] Determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD). [b] Based on the measured optical rotation value in comparison with the literature data.[18]

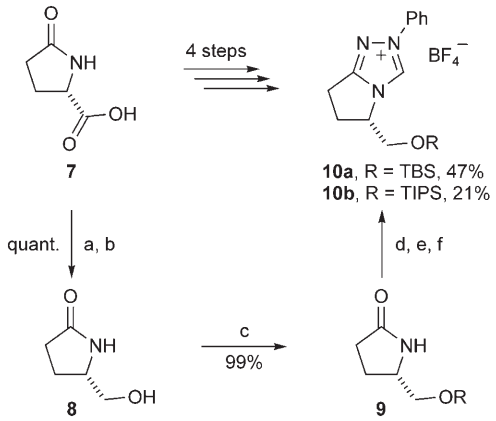
Two different concepts were chosen to increase the steric demand of the carbene catalysts and thus increase the asymmetric induction. A triazolium salt synthesis starting from L-pyroglutamic acid (**7**), which is among the cheapest chiral sources available, might generate an extremely flexible catalyst system. Furthermore, the promising results with precatalyst **4** showed that modifications of this structure could also be fruitful.

The *tert*-butyldimethylsilyl (TBS) and triisopropylsilyl (TIPS) protected lactams **9** could be synthesized in almost quantitative yields from L-pyroglutamic acid (**7**) by reduction to the hydroxymethyl-substituted lactam **8** and subsequent reaction with the silyl chlorides.[19] The bulkiness at the stereogenic center might be modified by a simple exchange of the protecting group. Conversion into the triazolium salts could be achieved by following an optimized one-pot procedure recently reported by Rovis and co-workers.[20] The lactams **9** were methylated with Meerwein's reagent to form the corresponding amidates. These were treated in situ with phenylhydrazine to yield the hydrazonium salts, which were directly cyclized with trimethyl orthoformate in methanol to give the triazolium salts **10** in moderate yields as crystalline solids (Scheme 4).

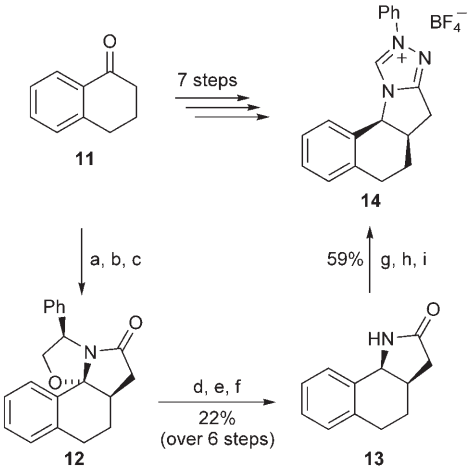
For the structural optimization of the tricyclic triazolium salt **4** the *cis*-tricyclic lactam **13** was chosen as the precursor for the synthesis of the tetracyclic triazolium salt **14**. The diastereo- and enantiopure γ-lactam **13** was synthesized following a procedure reported by Ennis et al. (Scheme 5).[21]

α-Tetralone (**11**) was α-alkylated with ethyl bromoacetate and subsequently hydrolyzed to the corresponding carboxylic acid. Condensation with (*R*)-phenylglycinol yielded the lactam **12** as a single stereoisomer. Stereoselective reduction, dehydration of the alcohol, and acid-catalyzed enamine hydrolysis provided the *cis*-tricyclic lactam **13**. The one-pot procedure that had previously been successful in the synthesis of **10** also gave access to the chiral tetracyclic triazolium salt **14**, which was obtained as a solid in 59% yield.

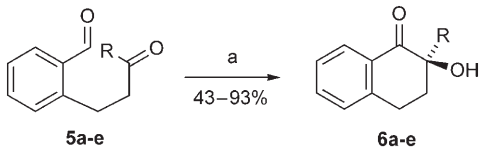
With these novel chiral carbene precursors in hand, several aldehyde ketones **5a**–**e** could be transformed into



Scheme 4. Preparation of triazolium salts **10** derived from pyroglutamic acid. a) $SOCl_2$, MeOH, −15 °C, 2 h; b) $NaBH_4$, EtOH, 0 °C, 12 h; c) RCl, imidazole, DMF, room temperature, 20 h; d) Me_3OBF_4, CH_2Cl_2, room temperature, 3 h; e) $PhNHNH_2$, CH_2Cl_2, room temperature, 3 h; f) $HC(OMe)_3$, MeOH, 80 °C, 12 h.



Scheme 5. Preparation of the tetracyclic triazolium salt **14**. a) LDA, $BrCH_2CO_2Et$, THF, DMPU, −78 °C to RT, 18 h; b) $LiOH{\cdot}H_2O$, THF/H_2O (2:1), room temperature, 20 h; c) (*R*)-phenylglycinol, toluene, 4-Å molecular sieves, reflux, 20 h; d) Et_3SiH, $TiCl_4$, CH_2Cl_2, −78 °C to RT, 3 h; e) $LiOH{\cdot}H_2O$, DMSO, 140 °C, 72 h; f) 1 N HCl, THF, reflux, 8 h; g) Me_3OBF_4, CH_2Cl_2, room temperature, 3 h; h) $PhNHNH_2$, CH_2Cl_2, room temperature, 3 h; i) $HC(OMe)_3$, MeOH, 80 °C, 12 h.



Scheme 6. Asymmetric intramolecular crossed-benzoin reaction with substrates **5a–e**. a) Precatalyst **10** or **14**, solvent (0.1 M), base, 1 day.

the corresponding six-membered acyloins **6a–e** (Scheme 6, Table 2).

The use of 10 mol% of the TBS-substituted catalyst **10a** and stoichiometric amounts of DBU in toluene at room temperature enabled the methyl-substituted acyloin **6a** to be obtained in high yield (92%) but with only moderate enantioselectivity (61%). Application of the TIPS-substituted catalyst **10b** under the same conditions resulted in an increased enantiomeric excess of 77%, which could be further improved to 84% with almost unchanged yields by performing the reaction at 5 °C.

The reactions with the tetracyclic catalyst **14** were conducted in THF for better solubility. Furthermore, DBU was found to cause side reactions which could be suppressed when KO*t*Bu was used in substoichiometric amounts (9 mol%). Product **6a** could be obtained in high yield (93%) with an excellent enantiomeric excess of 94%. Attempts to increase the *ee* value further by performing the reaction at 5 °C gave only very low conversion even after five days, presumably because of the low activity of the catalyst at this temperature.

The increased steric demand at the ketone function of the substrates **5** resulted in the reaction rate being much lower and reaction times of two days were necessary. Furthermore, higher catalyst loadings were required to achieve good conversions. We were pleased to see that the steric bulk of the ketone function had a significant influence on the enantiomeric excess, and almost complete inductions could be achieved. α-Hydroxy-α-ethyl tetralone (**6b**) was obtained with 95% *ee* and in still excellent yields. An excellent enantiomeric excess of 98% was obtained with the *n*-butyl- and *iso*-butyl-substituted substrates **5c**,**d**. The α-butyl-α-hydroxytetralone (**6c**) could be synthesized in excellent yields with only 10 mol% of the catalyst **14**. A significant decrease in the chemical yield, albeit with the enantiomeric excess remaining very good (93%), was observed when the benzyl-substituted aldehyde ketone **5e** was used.

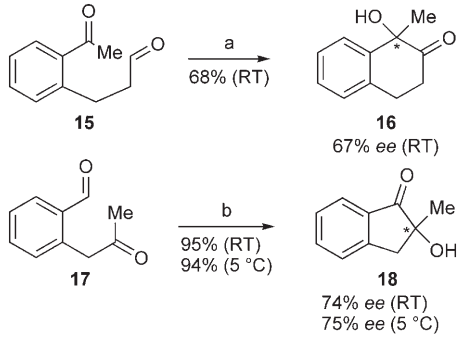
In general, the TIPS-substituted triazolium salt **10b** derived from pyroglutamic acid delivered lower enantiomeric excess values than the tetracyclic carbene precursor **14**. However, the ease of its preparation and the low price of L-pyroglutamic acid also make it an attractive catalyst. Reaction times are less than catalyses performed with **14**, and the reaction can be performed at 5 °C for better enantioselectivity.

Table 2: Asymmetric intramolecular crossed-benzoin reaction with **5**.

5	R	Catalyst (mol%)	Base (mol%)	*T*	Yield [%]	*ee* [%][a] (config.)[b]
a	Me	**10a** (10)[c]	DBU (10)	RT	92	61 (*S*)
a	Me	**10b** (10)[d]	DBU (10)	RT	89	77 (*S*)
a	Me	**10b** (10)[d]	DBU (10)	5 °C	90	84 (*S*)
a	Me	**14** (10)[c]	KO*t*Bu (9)	RT	93	94 (*S*)
b	Et	**14** (20)[c]	KO*t*Bu (19)	RT	90[e]	95 (*S*)
c	*n*Bu	**10b** (10)[d]	DBU (10)	RT	88	79 (*S*)
c	*n*Bu	**14** (10)[c]	KO*t*Bu (9)	RT	85[e]	98 (*S*)
d	*i*Bu	**14** (20)[c]	KO*t*Bu (19)	RT	91[e]	98 (*S*)
e	Bn	**10b** (10)[d]	DBU (10)	RT	90	63 (*R*)
e	Bn	**14** (20)[c]	KO*t*Bu (19)	RT	43[e]	93 (*R*)

[a] Determined by GC (Lipodex E) or HPLC (Daicel Chiralpak AD) with a chiral stationary phase. [b] Based on the measured optical rotation value in comparison with the literature data,[18] adaptation of computational calculations,[22] and assuming a uniform reaction mechanism. [c] Reaction in THF (0.1 M). [d] Reaction in toluene (0.1 M). [e] Reaction time 2 days.

Investigations to widen the scope of the asymmetric intramolecular benzoin reaction by utilizing aldehyde-ketone **15**, where the aldehyde and the ketone function are interchanged relative to **5**, show a promising 67% *ee* for the resulting acyloin **16** as well as high yields (68%). First experiments with substrate **17** to synthesize the five-membered cyclic acyloin **18** resulted in an excellent yield and a good enantiomeric excess (74%). When the reaction was carried out at 5°C, the enantiomeric excess could be slightly increased to 75% (Scheme 7).



Scheme 7. Further substrate scope for the asymmetric intramolecular crossed-benzoin reaction. a) **14** (20 mol%), KO*t*Bu (19 mol%), THF (0.1 M), room temperature, 4 days; b) **14** (10 mol%), KHMDS (10 mol%, 0.5 M in toluene), THF (0.1 M), 2 days. KHMDS = potassium hexamethyldisilazide.

The absolute configuration of the produced quarternary stereocenter of the acyloin **6a** was determined to be *S* by comparison of the measured optical rotation value with the corresponding literature data.[18] This stereochemical outcome might be explained by the transition state shown in Figure 1, which is an adaptation of the transition state

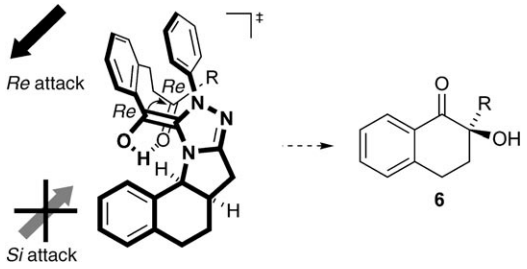


Figure 1. Proposed transition state.

proposed by Dudding and Houk on the basis of computational calculations.[22] The *Si* face of the Breslow intermediate,[23] which is formed as its *E* isomer in the hypothetical catalytic cycle, would be sterically shielded by the tetrahydronaphthalene residue of the tetracyclic catalyst. The *Re* face of the intermediate would attack the ketone function at its *Re* face (R ≠ Bn). Furthermore, a favorable pre-arrangement for the formation of the C–C bond might be caused by the activation of the ketone function by an intramolecular H bridge. Thus, the *S* configuration of the new stereocenter would be preferred, which in fact is observed.

In conclusion we have developed the first enantioselective intramolecular crossed-benzoin reaction catalyzed by novel chiral N-heterocyclic carbenes. The tetracyclic triazolium salt **14** catalyzes the cyclization with generation of a quaternary stereocenter in high yields and excellent enantiomeric excess. An interchange of the functional groups of the title α-hydroxy-substituted tetralones is possible as well as the synthesis of the corresponding α-hydroxyindanone derivatives with still good enantiomeric excess values.

Experimental Section

Typical procedure for the asymmetric intramolecular crossed-benzoin reaction, as exemplified for the formation of **6d**: Precatalyst **14** (20.6 mg, 0.055 mmol, 20 mol%) was suspended with anhydrous THF (1.7 mL) in a Schlenk tube under argon at room temperature. A solution of freshly sublimed KO*t*Bu (5.9 mg, 0.052 mmol, 19 mol%) in anhydrous THF (0.6 mL) was added slowly, and the solution was stirred for 5 min. Aldehyde-ketone **5d** (60 mg, 0.275 mmol) was dissolved in anhydrous THF (0.5 mL) and added to the carbene solution. The reaction mixture was stirred for 48 h, diluted with CH_2Cl_2, quenched with water, extracted two times with CH_2Cl_2, and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (dichloromethane/*n*-pentane 2:1) to yield **6d** (54 mg, 91%) as a colorless liquid. *ee* = 98% (determined by HPLC on a chiral stationary phase (Daicel Chiralpak AD)). $[\alpha]_D^{23} = -30.0$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 0.85$ (d, 3H, $J = 6.6$ Hz, CH_3CH), 0.96 (d, 3H, $J = 6.9$ Hz, CH_3CH), 1.50 (dd, 1H, $J = 5.5$, 14.3 Hz, $CHHCH$), 1.68 (dd, 1H, $J = 4.7$, 14.6 Hz, $CHHCH$), 1.84–1.97 (m, 1H, CH), 2.15 (ddd, 1H, $J = 6.0$, 13.5, 13.5 Hz, $CCHH$), 2.36 (ddd, 1H, $J = 2.2$, 5.0, 13.5 Hz, $CCHH$), 2.93–3.17 (m, 2H, CH_2), 3.92 (s, 1H, OH), 7.24–8.00 ppm (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.5$, 23.7, 24.7, 26.5, 34.7, 43.8, 75.9, 126.7, 127.8, 128.8, 130.4, 133.7, 143.1, 202.5 ppm.

The analytical and spectroscopic data of all new compounds were correct.

Received: November 3, 2005
Published online: January 3, 2006

Keywords: asymmetric synthesis · benzoin reaction · heterocycles · homogeneous catalysis · N-heterocyclic carbenes

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