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Late-Stage Diversification of Chiral N-Heterocyclic-Carbene Precatalysts for Enantioselective Homoenolate Additions

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Dedicated to Professor Eiichi Nakamura on the occasion of his 60th birthday

Abstract: A library of chiral triazolium salts has been prepared by late-state diversification of a triazolium amine salt. By utilizing a primary amine as a functional handle, a single triazolium salt can be transformed into a variety of chiral N-heterocyclic carbene precatalysts. This approach makes the preparation of chiral N-heterocyclic carbenes possible by a single-step modification of a triazolium salt, rather than the usual need for multistep organic synthesis and challenging heterocycle formation for each member of a catalyst library. We have screened these catalysts for control of diastereo- and enantioselectivity in a γ-lactam-forming reaction between α,β-unsaturated aldehydes and cyclic ketimines.

Keywords: carbenes · asymmetric catalysis · heterocycles · homoenolates · N-heterocyclic carbenes

Introduction

Homoenolates are synthetically important reactive species for the construction of both linear and cyclic stereochemical assemblies. In contrast to their enolate counterparts, which can be generated under a larger number of catalytic and stoichiometric conditions, there are relatively few general methods for the preparation of homoenolates and their addition to suitable electrophiles. The first general stoichiometric methodology for homoenolate additions was pioneered by Nakamura, Kuwajima et al.[1] who demonstrated that cyclopropane silyl hemiketals serve as homoenolate equivalents under strong Lewis acid catalysis. Other advances in the preparation of homoenolates under stoichiometric conditions include Hoppe's γ-deprotonation of carbamates facilitated by (−)-sparteine[2] and a single report on the use of a β-trimethylsilyl ester[3] as a homoenolate precursor. Unlike the increasingly mild and general methods for enolate generation,[4] the majority of protocols for the use of homoenolates require harsh conditions and strong reagents, which limits both their synthetic appeal and their options for the development of catalytic, enantioselective variants.

In 2004, both our group[5] and that of Glorius[6] independently reported the first catalytic method for the generation of homoenolate equivalents by the combination of α,β-unsaturated aldehydes and a N-heterocyclic carbene (NHC) catalyst. This mild and simple protocol catalytically generates homoenolates at ambient temperature without the need for stoichiometric additives or exclusion of water. Following our initial report on the use of this chemistry for the preparation of γ-lactones, NHC-catalyzed homoenolate formation has been extended to the synthesis of γ-lactams and related heterocycles,[7] spiro γ-butyrolactones,[8] and pyridazinones[9] (see Scheme 1). Similar conditions and catalysts can be used to prepare cyclopentenes and cyclopentane derivatives in good yield and with high enantioselectivity, but more-complex mechanisms, rather than a simple homoenolate equivalent, may be involved in those processes.[10]

The most synthetically valuable products obtained from NHC-catalyzed homoenolate generation are arguably the γ-lactone and γ-lactam products. These two structural motifs feature prominently in several classes of biologically active natural products and pharmaceuticals. For example, γ-lactams constitute the core of natural products, including clausenamide,[11] salinosporamide,[12] and the polychlorinated

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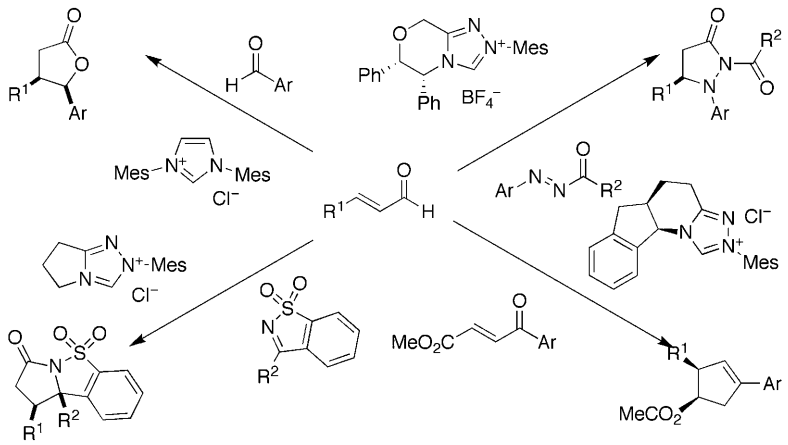


Scheme 1. Selected NHC-catalyzed homoenolate additions of enals to various electrophiles.

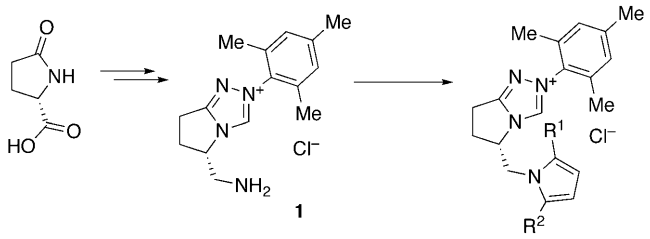
dysidamides.[13] NHC-catalysis offers a direct, one-step route to the core of a number of these molecules. However, these protocols largely remain limited to racemic products; despite considerable effort, there have been few successful reports of highly enantioselective NHC-catalyzed syntheses of γ-lactones and γ-lactams through NHC-catalyzed homoenolate generation.[14] This is surprising because other reaction manifolds promoted by NHC-catalysts, such as benzoin[15] and Stetter reactions,[16] formal cycloadditions,[17] and protonation reactions,[18] may be effected with high enantioselectivity by using a number of chiral catalysts.[19]

The difficulty in identifying superior catalysts for NHC-catalyzed γ-lactam and γ-lactone formation lies partly in the synthetic complexity of preparing chiral NHCs or, more precisely, their azolium-salt precursors.[15d,20,21] The best catalysts often require numerous steps for their preparation, many of which require re-optimization after even modest changes in the structures. The relatively harsh conditions needed for the formation of the imidazolium or triazolium ring limit the choice of pendant functionality compatible with the known synthetic protocols. This limitation is particularly true for the formation of azolium salts bearing sterically hindered *N*-mesityl groups, which have been shown to be essential for most NHC-promoted homoenolate reactions. In seeking to further the development of chiral NHC catalysts, we sought an approach for the late-stage variation of the catalyst structure by elaborations after the installation of the azolium ring. Similar late-stage modifications have proven to be highly effective in the synthesis and screening of other catalyst types, including ligands for transition-metal-catalyzed reactions[22] and thioureas.[23] This approach, however, has seen less use with chiral azoliums or NHC-carbene ligands, owing to potential difficulties of synthetic manipulations and purifications of molecules containing the azolium salts.

Herein, we report the preparation of *N*-mesityl-substituted triazolium **1**, which contains a chiral aminomethyl functionality that is poised for further elaboration (Scheme 2).[24] This synthetic handle was exploited in the introduction of various pendant groups, including pyrroles, thioureas, and tertiary amines, to quickly generate a small library of chiral azolium salts. These precursors to chiral NHC catalysts were screened for enantioselectivity against a particularly challenging γ-lactam formation that used saccharine-derived ketimines as electrophiles.

Results and Discussion

Ongoing work from our laboratory has employed chiral bicyclic triazolium salts similar to those originally prepared by Knight and Leeper[21] in asymmetric benzoin and Stetter reactions. Subsequent efforts by Rovis and co-workers[25] and Enders and Han[20] have improved the synthesis of these structures, and provide catalysts that offer excellent enantioselectivity in reactions that occur through acyl anion equivalents. In our studies that required an *N*-mesityl moiety on the triazolium ring, we often found that bicyclic precatalyst **7**, derived from (*S*)-phenylalanine, gave the best results, albeit still with suboptimal levels of stereoselectivity. Unfortunately, modification of the benzyl group was a long and costly process that required the prior synthesis of the corresponding enantiopure amino acid followed by seven steps for each catalyst derivative. For example, the naphthyl-containing triazolium **6** was prepared over seven steps from the commercially available, but rather expensive, unnatural amino acid **2** (Scheme 3). The same—or similar—procedures were used for the preparation of several other triazolium precatalysts (**7**–**20**), some of which were previously reported by ourselves or others. To confirm that epimerization did not occur during this sequence, triazolium salt **7** and its enantiomer were prepared with the chiral counteranion (*S*)-(+)-binaphthyl-2,2′-diyl phosphate.[26] The resulting diastereomeric salts had distinctly different ^{1}H NMR and ^{13}C NMR spectra.



Scheme 2. Late-stage modification of **1**.

In seeking less-expensive starting materials and a route amenable to late-stage modification, ideally following the introduction of the *N*-mesityl moiety and the completion of

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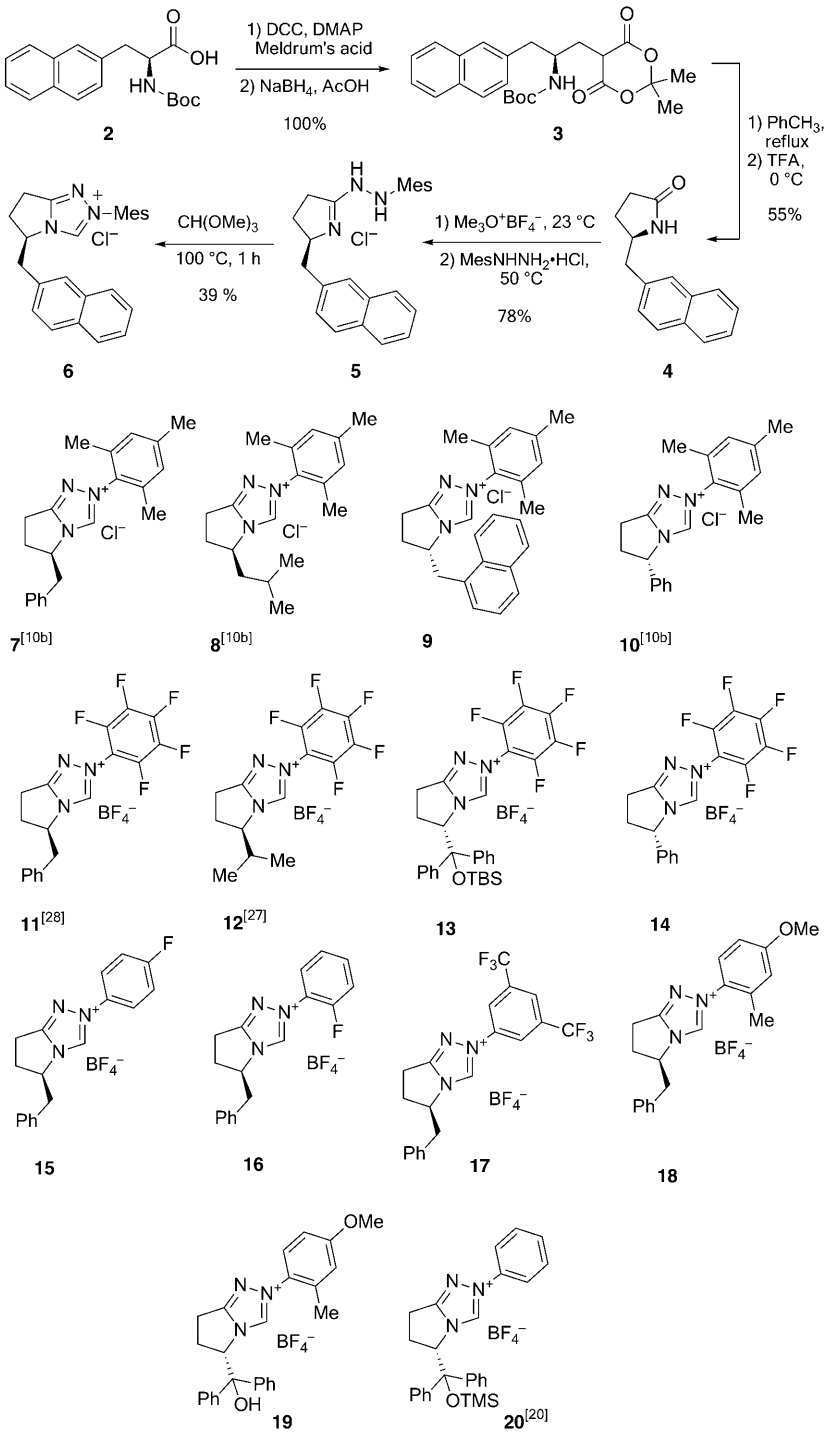
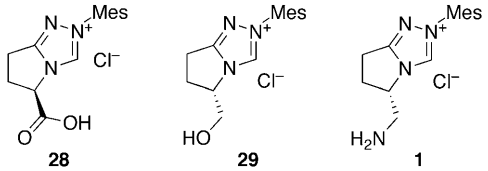


Scheme 3. Chiral triazolium salts synthesized by our group or others and used in this study. DCC = *N,N'*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, Meldrum's acid = 2,2-dimethyl-1,3-dioxane-4,6-dione, Boc = *tert*-butoxycarbonyl, TFA = trifluoroacetic acid. For previous syntheses of **7**-**8** and **10**,[10b] **11**,[28] **12**,[27] and **20**[20] see references, respectively.

the triazolium ring, we wanted to prepare a structure with a suitable synthetic handle. Earlier work in our group on chiral carboxylic acid **28** established the viability of such a route, but was plagued by epimerization of the chiral center. Azolium precatalyst **29**, which bears a primary alcohol, has also been prepared, but simple derivatization reactions to give esters afford products that were not always stable to the conditions of NHC-catalyzed reactions. Therefore, we targeted the chiral aminomethyl-substituted triazolium **1**, which we believed could be elaborated by reactions at the primary amine as the final step in the precatalyst synthesis (see Scheme 4).

Our synthesis began from readily available (*S*)-pyroglutamic acid methyl ester **21**. Selective reduction of the ester to the primary alcohol followed by mesylation and displacement with sodium azide afforded **23**, a sequence previously reported by Bateman et al.[29] In an analogy to the protocol described by Knight and Leeper[21] and ourselves,[30] **23** was methylated with Meerwein's salt to give neutral imidate **24** in 85% yield. Condensation with *N*-mesitylhydrazine hydrochloride afforded **26**, which was further used without purification to generate *N*-mesityl triazolium chloride **27**. In our hands, reduction of the azide to the amine was best effected by zinc metal in aqueous ethanol followed by careful workup to separate the hydrochloride salt of the product from unreacted zinc metal. These procedures could be executed on a 5–10 gram scale, although care in the final azide reduction was necessary.

Conversion of primary amines into pyrroles by the Paal–Knorr reaction was particularly valuable in the combinatorial synthesis of chiral catalysts, and we chose this reaction for our initial elaborations (Scheme 5).[23] Although the



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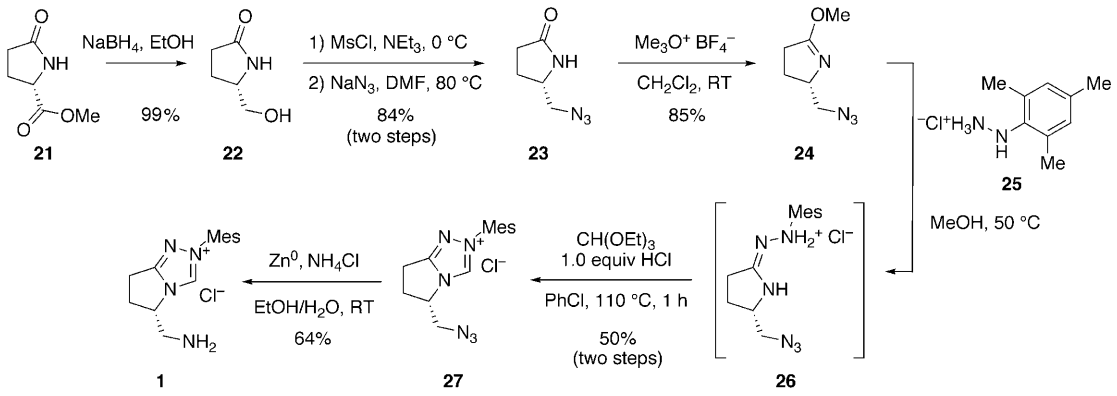
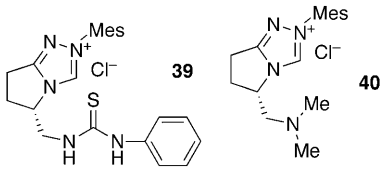


Scheme 4. Synthesis of **1** from (*S*)-methyl pyrroglutamate. Ms = methanesulfonyl, DMF = *N*,*N*-dimethylformamide, Mes = mesityl.

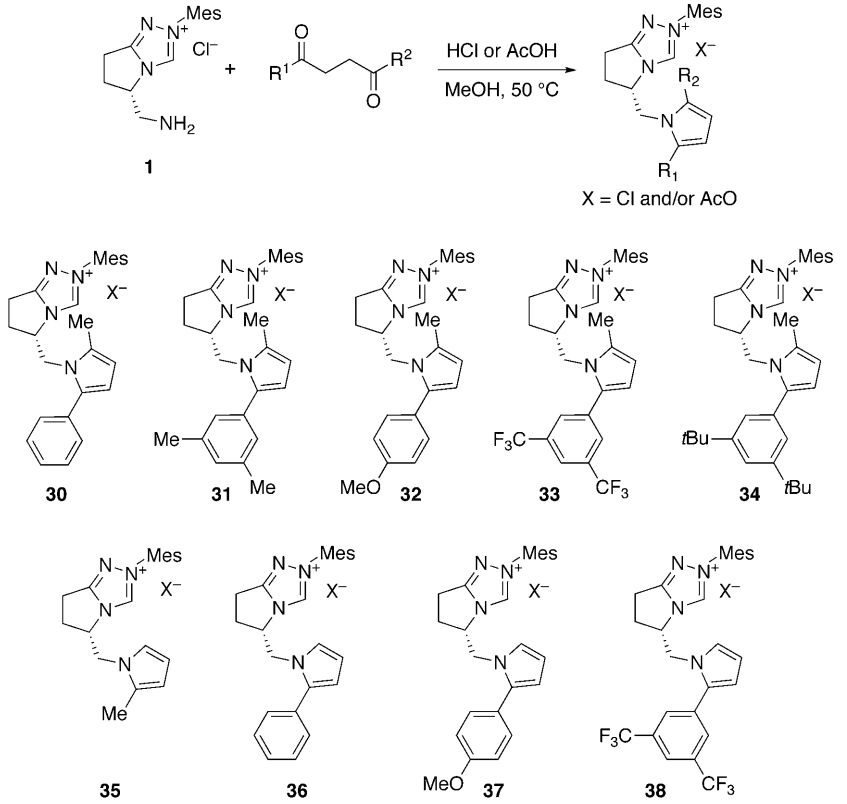
use of the azolium salt initially complicated the reactions and isolations, successful procedures were identified after some experimentation. For bis(ketones), the optimal conditions employed one equivalent of HCl in methanol, and provided products **30**–**34** in 23–29% yield. However, the same conditions applied to 1,4-ketoaldehydes only resulted in decomposition of the starting materials. A survey of other conditions for the Paal–Knorr synthesis led to an improved procedure that employs acetic acid to afford the desired products **35**–**38** in 39–67% yield. Other modifications of primary amine **1** were conversion into thiourea **39** by reaction with an isothiocyanate, as well as dimethylation to give **40** (Scheme 6).



Scheme 6. Other chiral-amine derivatives prepared from **1**.

In 2008, we reported the direct annulation of α,β-unsaturated aldehydes with ketimines derived from saccharine (Scheme 7) to give γ-lactams.[7d] Our preliminary studies showed that the catalyst structure had a profound effect on the stereochemical outcome. Interestingly, the azolium precatalysts that gave the highest enantioselectivities gave the poorest diastereoselectivity. Chiral variants **42**, **43**, and **44** gave rise to the γ-lactams with excellent diastereoselectivity in transformations that favored the *cis* isomer.

As an initial test of our catalyst library, which consisted of the compounds shown in Schemes 3 and 5, we screened these azolium salts for their ability to promote the γ-lactam-forming annulation between cinnamaldehyde and phenyl-substituted saccharine derivative **46** (Table 1). For initial work, we selected conditions employing 5–10 mol% of the catalyst and 20 mol% DBU at 25 °C in dichloromethane. The conversion into the product, diastereoselectivity, and enantioselectivity of the major *cis* diastereomer were directly as-



Scheme 5. Paal–Knorr synthesis of pyrrole-functionalized precatalysts. Ac = acetyl.

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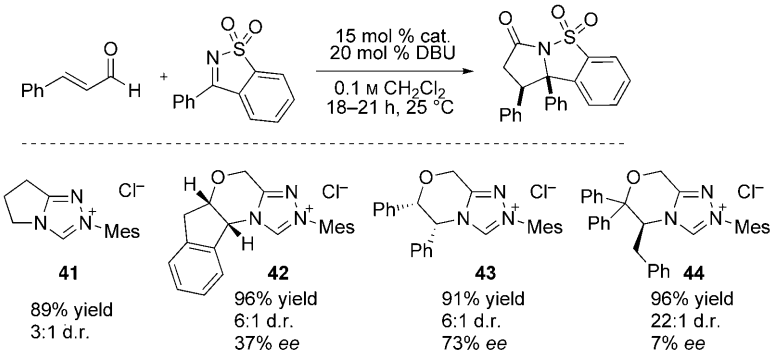
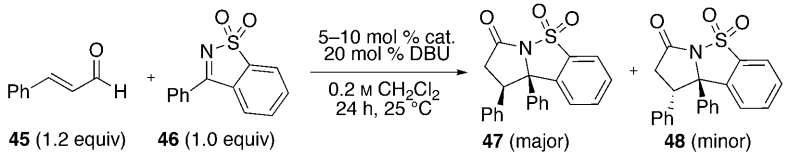


Scheme 7. Previous attempts at enantioselective γ-lactam formation by triazolium-catalyzed homoenolate additions to saccharine-derived ketimines. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 1. Screening of chiral-azolium catalysts for enantioselective annulation of cinnamaldehyde and ketimine **46**.



Entry	Catalyst	Conversion [%][a]	d.r.[b]	*ee* [%] (major)
1	6[c]	61	13:1	53
2	7[c]	57	24:1	57
3	8[c]	100	13:1	52
4	9[c]	100	5:1	34
5	10[c]	87	3:1	42
6	11[c]	98	12:1	58
7	12[c]	10	nd	42
8	13[c]	n.r.		
9	14[c]	10	nd	28
10	15[c]	70	3:1	38
11	16[c]	70	2:1	41
12	19[c]	51	3:1	61
13	20[c]	17	5:1	56
14	30[d]	89	6:1	25
15	31[d]	98	7:1	23
16	32[d]	100	5:1	23
17	33[d]	19	10:1	23
18	34[d]	n.r.	–	–
19	35[d]	41	9:1	45
20	36[d]	96	13:1	55
21	37[d]	n.r.	–	–
22	38[d]	80	8:1	53
23	39[c]	100	2:1	27
24	40[c]	100	8:1	43

[a] Relative conversion determined with SFC. Direct comparison of the area under the peak for **46**, the limiting reagent, versus the combined areas of **47** and **48**. [b] Diastereomeric ratio determined by direct comparison of the area of the two enantiomers of **47** and **48**. [c] 5 mol % catalyst used [d] 10 mol % catalyst used.

sayed by supercritical fluid chromatography (SFC) with chiral columns.

Despite a wide scope in the appendages of the azolium catalysts, this annulation reaction was remarkably intransigent to improved enantioselectivity, with no catalysts giving greater than 70% enantiomeric excess (*ee*). Chiral triazolium precatalysts bearing the *N*-mesityl moiety and various substituted pyrrolidine rings gave similar results despite considerable changes in the size of the pendant group (Table 1, entries 1–5). Variation of the triazolium *N*-substituted (Table 1, entries 6–13) gave similar enantioselectivity but lowered the conversion and diastereoselectivity. With the exception of **11**, the perfluorophenyl-substituted triazolium compounds were ineffective as catalysts. These electron-deficient azoliums are usually poor catalysts for NHC-catalyzed reactions that occur through homoenolate equivalents.[10b]

We were pleased to find that the pyrrole-substituted triazolium salts (entries 14–22) were effective catalysts because these structural motifs have not previously been employed in NHC-catalyzed processes. Although they did not offer improved selectivity in this (particularly challenging) case, their synthetic availability and late-stage diversification should prove valuable in other enantioselective reactions promoted by this class of catalysts.

Conclusions

We have described the preparation of a number of novel triazolium precatalysts for NHC-catalyzed reactions. We disclosed the preparation of *N*-mesityl-substituted triazolium amine **1** and its late-stage, one-step conversion into various pyrrole-substituted precatalysts by Paal–Knorr synthesis on the intact triazolium salt. The success of this reaction as the last step in the synthetic sequence suggests that further functionalization of the amine or other functional groups will be possible, which should aid the rapid generation of structurally diverse libraries of chiral NHC catalysts and ligands.

Experimental Section

Preparation of (*S*)-5-(azidomethyl)-2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium chloride (27): A flame-dried 1 L round-bottomed flask was charged with a magnetic stirrer bar, (*S*)-5-(azidomethyl)-2-pyrrolidone (23, 6.0 g, 43 mmol, 1.0 equiv), CH_2Cl_2 (300 mL), and trimethyloxonium tetrafluoroborate (7.0 g, 47 mmol, 1.1 equiv). The tan mixture was stirred at ambient temperature under an atmosphere of nitrogen for 17 h. The solution was cooled to 0 °C and quenched by the slow, portionwise addition of $NaHCO_3$ (saturated aqueous, 300 mL) over a period of 1.5 h; stirring was maintained

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for an additional 1 h. The biphasic mixture was transferred to a separatory funnel, and the organic phase was isolated, dried over Na_2SO_4, filtered, and concentrated to afford the crude iminoether (5.6 g, 85%) as a brown oil, which was used without further purification. A flame-dried 500 mL round-bottomed flask was charged with the crude iminoether (5.5 g, 35 mmol, 1.0 equiv), a magnetic stirrer bar, 2- mesitylhydrazinium chloride[30] (6.6 g, 35 mmol, 1.0 equiv), and MeOH (140 mL), which resulted in a deep-red–orange solution that was stirred at 50°C under an atmosphere of nitrogen for 1 h. The reaction was allowed to cool to ambient temperature, and then concentrated under reduced pressure to afford the hydrazone as a crude orange solid. The crude material was suspended in EtOAc and placed in a sonicating bath for 30 minutes. The light-orange precipitate (recovered 2-mesitylhydrazinium hydrochloride) was removed by suction filtration. The filtrate was concentrated under reduced pressure to afford crude hydrazone **26** (8.7 g, 79%) as an orange foam. Triethylorthoformate (38 mL, 280 mmol, 10 equiv), chlorobenzene (28 mL), and anhydrous HCl (4 M in 1,4-dioxane, 7.0 mL, 28 mmol, 1.0 equiv) were added to the round-bottomed flask that contained the crude hydrazone. The reaction vessel was equipped with a water-jacketed condenser, and stirred at 100°C for 50 min under an atmosphere of nitrogen. The brown solution was allowed to cool to ambient temperature and concentrated under reduced pressure. The crude brown solid was purified by flash column chromatography on silica gel (gradient elution, CH_2Cl_2/acetone, 10:1 to 5:1 to 2:1 to 1:1) to give the title compound (4.45 g, 50%) as a tan powder. $[\alpha]_D^{20}=1.47$ ($c=8.23$, MeOH); IR(KBr): $\tilde{\nu}=2919$, 2108, 1586, 1442, 1388, 1331, 1290, 1037, 854 cm^{-1}; ^1H NMR (500 MHz, [D_6]DMSO): $\delta=10.77$ (s, 1H,), 7.16 (s, 2H), 5.03 (s, 1H), 4.18–4.12 (m, 1H), 3.95–3.94 (m, 1H), 3.34–3.18 (m, 3H), 2.96–2.89 (m, 1H), 2.37 (s, 3H), 2.08 ppm (s, 6H); ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta=162.7$, 141.8, 141.2, 134.8,131.9, 129.3, 59.5, 52.0, 30.0, 21.3, 20.7, 16.9 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{19}N_6^+$: 283.1666 $[M]^+$, found: 283.1671.

Preparation of (*S*)-5-(aminomethyl)-2-mesityl-6,7-dihydro-5H-pyrrolo-[2,1-c][1,2,4]triazol-2-ium chloride (1): NH_4Cl (0.847 g, 13.0 mmol, 1.3 equiv) and Zn powder (1.39 g, 25.9 mmol, 2.3 equiv) were added to a solution of **27** (3.18 g, 9.97 mmol, 1.0 equiv) in EtOH/H_2O (3:1, 10 mL). Vigorous stirring was maintained for 1 h at ambient temperature. Dimethyl sulfoxide (DMSO, 10 mL) was added, and the insoluble solids were removed by suction filtration and washed with DMSO (5 mL). A magnetic stirrer bar was added to the filtrate, and Et_2O (100 mL) was added with vigorous stirring, which resulted in the formation of an oil. To induce product precipitation, EtOH (20 mL) was added with vigorous stirring. The heterogeneous mixture was placed in an ultrasound bath until all traces of the initially formed oil had dissolved. The resultant precipitate was collected by suction filtration and washed with EtOAc to afford the title compound (1.85 g, 64%) as a white powder. Note: the product may contain some inorganic salts (ZnCl and NH_4Cl). IR(KBr): $\tilde{\nu}=3434$, 3330, 3252, 3049, 2992, 1588, 1402, 1234, 1134, 1023, cm^{-1}; ^1H NMR (500 MHz, [D_6]DMSO): $\delta=7.05$ (s, 2H), 4.60 (q, 1H, $J=8.5$ Hz), 3.36–3.14 (m, 2H), 3.06 (dd, 1H, $J=16.5$, 9.0 Hz), 2.75–2.71 (m, 2H), 2.40–2.34 (m, 1H), 2.32 (s, 3H), 2.08 (s, 3H), 1.99 ppm (s, 3H); ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta=172.9$, 160.0, 139.4, 135.4, 134.9, 128.7, 128.6, 57.0, 44.8, 31.7, 30.7, 21.2, 20.7, 17.2, 17.0 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{21}N_4^+$: 257.1761 $[M]^+$, found: 257.1746.

General Procedure for the Paal–Knorr Pyrrole Synthesis/Preparation of (*S*)-2-mesityl-5-((2-methyl-5-phenyl-1H-pyrrol-1-yl)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium chloride (30): Compound **1** (100 mg, 0.34 mmol, 1.0 equiv) and anhydrous HCl (85 μL, 4.0 M in dioxane, 1.0 equiv) were added to a solution of 1-phenylpentane-1,4-dione (59.8 mg, 0.34 mmol, 1.0 equiv) in MeOH (0.2 M, 1.7 mL) under an atmosphere of nitrogen. The resulting mixture was stirred at 50°C for 10 h, and then cooled to room temperature and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (5% MeOH/CH_2Cl_2) to afford **30** (33.8 mg, 23% yield) as a yellow foam. m.p.: 132–133°C; $[\alpha]_D^{20}=74.14$ ($c=2.53$, MeOH); IR(KBr): $\tilde{\nu}=3030$, 2924, 1587, 1513, 1476, 1445, 1396, 1308, 1194, 756, 732, 702 cm^{-1}; ^1H NMR (500 MHz, MeOD): $\delta=7.50$ (d, $J=7.0$ Hz, 2H), 7.44 (t, $J=7.7$ Hz, 2H), 7.34 (t, $J=7.2$ Hz, 1H), 7.10 (s, 2H), 6.18 (d, $J=3.5$ Hz, 1H), 5.97 (d, $J=3.0$ Hz, 1H), 4.76 (dd, $J=14.5$, 5.5 Hz, 1H), 4.69–4.70 (m, 1H), 4.45 (dd, $J=15.0$, 10 Hz, 1H), 3.31–3.34 (m, 1H), 3.18 (ddd, $J=17.5$, 9.5, 4.7 Hz, 1H), 2.79–2.82 (m, 1H), 2.50–2.51 (m, 1H), 2.36 (s, 3H), 2.18 (s, 3H), 2.04 ppm (s, 6H); ^{13}C NMR (125 MHz, MeOD): $\delta=164.3$, 143.5, 136.3, 134.9, 134.6, 133.2, 132.4, 130.6, 130.1, 129.3, 128.5, 111.5, 109.3, 62.1, 46.9, 31.5, 22.0, 21.1, 17.4, 13.3 ppm; HRMS (ESI): m/z calcd for $C_{26}H_{29}N_4^+$: 397.2392 $[M]^+$, found: 397.2374.

Acknowledgements

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