Asymmetric Synthesis

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Simple and Efficient Asymmetric α-Alkylation and α,α-Bisalkylation of Acyclic Ketones by Using Chiral N-Amino Cyclic Carbamate Hydrazones

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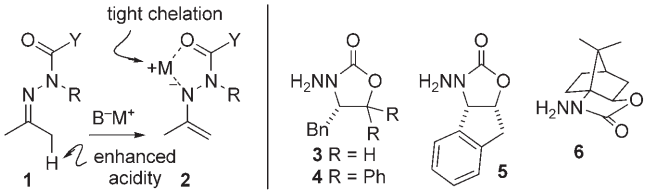
Ketone α-alkylation is fundamental to organic synthesis. Remarkably, however, only one effective asymmetric version of this transformation applicable to acyclic systems is available.[1–3] Introduced over 25 years ago, this method is based on the alkylation of metalated SAMP/RAMP hydrazones, and has enabled numerous total syntheses.[1] Unfortunately, its further development has been impeded as a result of certain inherent limitations. For instance, the dialkyl hydrazones used are only weakly acidic, so azaenolate formation requires exposure to lithium diisopropylamide (LDA) for 2–10 h.[1a] Alkylation must then be conducted at an extremely low temperature (−110 to −78 °C),[1a] making large-scale applications impractical. Moreover, removal of the costly auxiliary under recommended[1a] conditions (ozonolysis or quaternization/hydrolysis) limits functional group compatibility. The auxiliary itself is liberated in an altered form that hinders recycling.[4] Given these limitations, it is apparent that asymmetric α-alkylation of ketones remains an unsolved problem. Herein, we report a substantial advance in this field through the development of chiral N-amino cyclic carbamates (ACCs). These auxiliaries significantly diminish the drawbacks associated with the use of chiral dialkyl hydrazines, yet still provide excellent stereoselectivity. In addition, the auxiliaries exhibit a unique directing effect that overrides the inherent selectivity of LDA, thus enabling the asymmetric α,α-bisalkylation of ketones, a previously unattainable transformation.

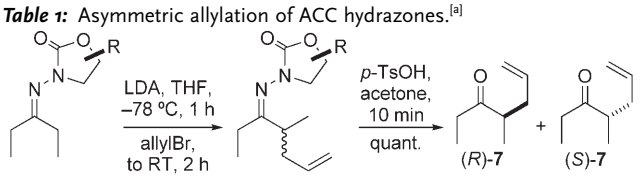
Hydrazones possessing an electron withdrawing group (**1**, Scheme 1), which we term activated hydrazones, are readily formed from the corresponding substituted hydrazines (e.g., hydrazides, sulfonyl hydrazides, etc.) and ketones under mild conditions, and are rapidly hydrolyzed under similarly mild conditions, making them excellent candidates for auxiliary-based synthetic methods. We anticipated that the enhanced acidity of these activated hydrazones would enable rapid metalation over a range of temperatures. Moreover, the substantial electron density imparted to the electron withdrawing group in the derived azaenolates (**2**) should lead to tight metal cation binding, in a manner analogous to, for example, chelation of hydroxamate anions. In the context of asymmetric transformations, this could potentially bring high facial selectivity during alkylation, even at temperatures well above −110 to −78 °C, as required of SAMP/RAMP systems. Collectively, these factors suggested that chiral hydrazines substituted with a conjugated electron-withdrawing group could provide the basis of a simple method for asymmetric ketone α-alkylation.



Scheme 1. Activated hydrazone deprotonation (**1**→**2**) and N-amino cyclic carbamates (**3**–**6**). Bn = benzyl.

We focused our initial studies along these lines on the easily accessible ACCs.[5] Thus, **3** was prepared by amination of the corresponding oxazolidinone and was then condensed with 3-pentanone to give **8** (Table 1). This activated hydrazone **8** was readily deprotonated with LDA at −78 °C and allylated in excellent yield (90%). The auxiliary was also easily removed and recovered quantitatively, giving (*R*)- and (*S*)-**7** in a 76:24 ratio. The analogous sequence with ACC **5** led to a better asymmetric induction (86:14). Suspecting that an increase in steric bulk near the amino function would result in a better selectivity, we examined ACC **4**. Indeed, alkylation of the derived hydrazone **10** gave (*R*)- and (*S*)-**7** in a ratio of 91:9. The enantiomeric ratio was further improved to 96:4 using the more conformationally rigid ACC **6**.

Table 1: Asymmetric allylation of ACC hydrazones.[a]



Entry	ACC	Hydrazone	Allylated hydrazone	Yield [%]	(*R*)-**7**/(*S*)-**7**
1	**3**	**8**	**12**	90	76:24
2	**5**	**9**	**13**	82	86:14
3	**4**	**10**	**14**	93	91:9
4	**6**	**11**	**15**	96	96:4

[a] Ts = toluenesulfonyl.

Allylation by using auxiliaries **4** and **6** was studied under a variety of conditions (Table 2). Of the bases evaluated, LDA

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Table 2: Effect of reaction conditions on stereoselectivity.

Entry	Hydrazone	Base	Solvent	T [°C]	(*R*)-**7**/(*S*)-**7**
1	**11**	LDA	THF	−78 to RT	96:4
2	**11**	LDA	Et_2O	−78 to RT	96:4
3	**11**	LDA	toluene	−78 to RT	96:4
4	**11**	LiHMDS[a]	THF	−78 to RT	87:13
5	**11**	NaHMDS[a]	THF	−78 to RT	82:18
6	**11**	KHMDS[a]	THF	−78 to RT	82:18
7	**11**	LDA	THF	−110 to RT	96:4
8	**11**	LDA	THF	−60 to RT	96:4
9	**11**	LDA	THF	−40 to RT	96:4
10	**11**	LDA	THF	−20 to RT	91:9
11	**11**	LDA	THF	0 to RT	90:10
12	**10**	LDA	THF	−110 to RT	91:9
13	**10**	LDA	THF	−78 to RT	91:9
14	**10**	LDA	THF	−60 to RT	90:10
15	**10**	LDA	THF	−40 to RT	91:9
16	**10**	LDA	THF	−20 to RT	85:15
17	**10**	LDA	THF	0 to RT	86:14

[a] HDMS = hexamethyldisilazide.

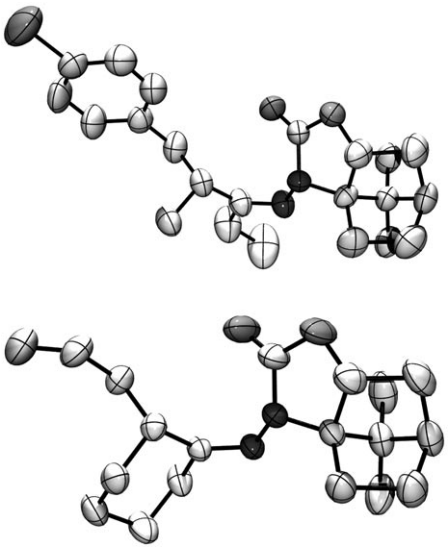


Figure 1. Structures of **23** (top) and **26** (bottom) in the solid state. C white, Br light gray, O gray, N black.

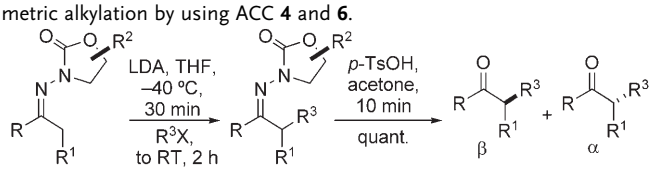
gave the highest stereoselectivity and showed no solvent dependence. The asymmetric induction proved largely independent of temperature; the same high selectivity was obtained when the alkylation was conducted up to −40 °C, with only a slight decrease at temperatures up to 0 °C.

The scope of the reaction was examined with ACC **4** and **6** (Table 3). Excellent yield and stereoselectivity resulted for each alkyl halide examined, including a secondary alkyl iodide (Table 3, entry 6). ACC **6** consistently outperformed **4** in terms of asymmetric induction, giving results comparable with literature reports, yet with considerably improved yields of isolated products.[6] Alkylation by using ACCs is also very easy to carry out: hydrazone formation and cleavage are straightforward and efficient, with no damage or loss of the auxiliary, and the azaenolate is readily formed and alkylated at temperatures up to 0 °C. Significantly, this simple method engenders the possibility of large-scale asymmetric α-alkylation of ketones. In a preliminary test, we carried out the allylation using 7.002 g of **11**, which was more than a 100-fold increase over our initial experiments. Exposure of **11** to LDA for 45 min at −40 °C, followed by addition of allyl bromide and stirring for 45 min, gave **15** in 98 % yield. Hydrolysis with *p*-TsOH·H_2O in acetone (15 min) afforded ketone **7** in 94 % yield with an unchanged enantiomeric ratio (96:4), along with acetone-derived hydrazone **38** in 98 % yield. After treatment of **38** with $HONH_2$·HCl in THF/H_2O, the ACC auxiliary **6** was recovered in 95 % yield.

Crystal structures of the major diastereomer of **23** and **26** (Figure 1) showed that alkylation occurs *syn* to the auxiliary, relative to the C–N double bond, indicating that the azaenolate intermediate likely has the *Z* configuration about this bond (Z_{CN}). Furthermore, alkylation in each case (**11**→**23**; **18**→**26**) provided the same sense of chirality at the newly formed stereogenic center, implying that, like cyclic compound **18**, the acyclic systems react through the azaenolate with *E* configuration at the C–C bond (E_{CC}).

The regioselectivity of the alkylation was consistent with a directing effect in the deprotonation step, which could provide a convenient and general means of overriding the inherent selectivity of LDA. Moreover, this would make the direct asymmetric synthesis of optically enriched α,α-disubstituted ketones possible for the first time. To test this idea, **38** was subjected to allylation giving **39**

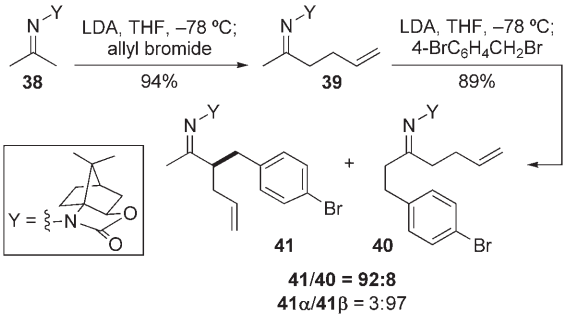
Table 3: Asymmetric alkylation by using ACC **4** and **6**.



Entry	R	R^1	ACC	Hydrazone	R^3X	Alkylated hydrazone	Yield [%]	Ketone	β/α
1	Et	Me	**6**	**11**	allylBr	**15**	96	**7**	96:4
2	Et	Me	**6**	**11**	BnBr	**19**	99	**30**	96:4
3	Et	Me	**6**	**11**	EtI	**20**	92	**31**	97:3
4	Et	Me	**6**	**11**	PrI	**21**	89	**32**	96:4
5	Et	Me	**6**	**11**	PrOTs	**21**	76	**32**	85:15
6	Et	Me	**6**	**11**	*i*PrI	**22**	77	**33**	94:6
7	Et	Me	**6**	**11**	$ArCH_2Br$[a]	**23**	93	**34**	96:4
8	Ph	Me	**6**	**16**	allylBr	**24**	91	**35**	96:4
9	*i*Pr	Me	**6**	**17**	allylBr	**25**	88	**36**	98:2
10	-$(CH_2)_4$-		**6**	**18**	allylBr	**26**	91	**37**	82:18
11	Et	Me	**4**	**10**	allylBr	**14**	93	**7**	91:9
12	Et	Me	**4**	**10**	BnBr	**27**	98	**30**	92:8
13	Et	Me	**4**	**10**	EtI	**28**	83	**31**	90:10
14	Et	Me	**4**	**10**	PrI	**29**	77	**32**	92:8

[a] Ar = 4-BrC_6H_4.

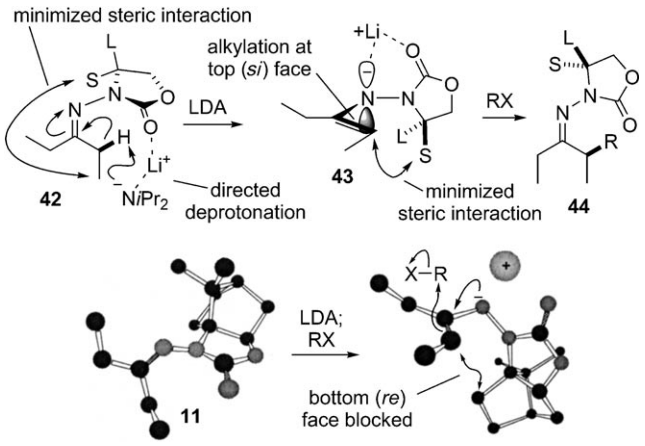
regioselectively in 94% yield as a single double-bond diastereomer. Alkylation of **39** also proceeded regioselectively to give the α,α- and the α,α′-bisalkylation products **41** (97:3 diastereomeric ratio; major shown) and **40**, respectively, in a 92:8 ratio, thus demonstrating the concept of directed deprotonation (Scheme 2). In contrast, LDA-mediated bisalkylation of ketones,[7] imines,[2] and dialkyl hydrazones[1] gives α,α′-bisalkylation products. This appears to be the first instance of not only directed deprotonation in azaenolate formation through a neutral coordinating element,[8] but also asymmetric α,α-bisalkylation of a ketone.



Scheme 2. Regioselective asymmetric α,α-bisalkylation of **38**.

A stereochemical model consistent with the above observations is shown in Scheme 3. Deprotonation of **42** gives azaenolate **43** that is then alkylated from its less-hindered face to form **44**. The E_{CC} configuration of **43** originates from minimization of steric interactions between the *syn* β-methyl group and the auxiliary in **42**, and directed deprotonation through coordination of the carbonyl oxygen and LDA sets the Z_{CN} configuration. In this form, the bottom (*re*) face of the azaenolate is blocked, causing the electrophile to approach from the top (*si*) face.

In conclusion, we have developed a convenient method for asymmetric α-alkylation and α,α-bisalkylation of ketones by using ACC chiral auxiliaries. In contrast to other methods, the auxiliaries are both easily introduced into and removed from ketones with near quantitative recovery. Furthermore, deprotonation is rapid, and alkylation does not require extremely low temperature, yet proceeds with excellent stereoselectivity and substantially higher yields. Collectively, these traits render the prospect of large-scale asymmetric ketone α-alkylation, which has previously not been possible. Furthermore, the ACC auxiliaries exhibit a unique directing effect that overrides the inherent selectivity of LDA, enabling for the first time the asymmetric α,α-bisalkylation of ketones. Further studies of this directing effect and the mechanistic details, scope, and synthetic utility of this reaction are underway.



Scheme 3. Stereochemistry of azaenolate formation and alkylation. L = large substituent, S = small substituent.

Experimental Section

General procedure for oxazolidinone N-amination: *n*BuLi (2.5 M in hexanes, 11.4 mL, 28.6 mmol) was added dropwise over ca. 10 min to a stirred and cooled (−78 °C) suspension of 7,7-dimethylnorbornane-(1*S*,2*R*)-oxazolidinone[9] (4.321 g, 23.9 mmol) in THF (350 mL) under an argon atmosphere. $Ph_2P(O)ONH_2$ (6.674 g, 28.6 mmol) was then added and the mixture was removed from the cold bath, stirred for 12 h, filtered, and evaporated under reduced pressure to give a yellow solid. Flash chromatography over silica gel using EtOAc/hexanes (25:75) gave **6** (4.407 g, 94%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 4.16$ (dd, $J = 8.2$, 4.1 Hz, 1H), 3.91 (s, 2H), 2.30–2.10 (m, 2H), 2.05–1.70 (m, 3H), 1.36–1.24 (m, 1H), 1.18 (s, 3H), 1.0 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 160.2$, 83.2, 72.1, 47.3, 42.7, 35.1, 25.8, 25.4, 20.7, 19.5 ppm; ESI-MS: m/z $[M+H]^+$ calcd for $C_{10}H_{17}N_2O_2$: 197.26, found 197.1.

General procedure for hydrazone formation: *p*-TsOH·H_2O (0.96 g, 5.05 mmol) was added to a stirred solution of **6** (6.144 g, 31.31 mmol) and 3-pentanone (3.95 mL, 37.28 mmol) in CH_2Cl_2 (300 mL) under an argon atmosphere). The mixture was refluxed for 18 h, cooled to room temperature, and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using EtOAc/hexanes (10:90) gave **11** (7.645 g, 92%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 4.25$ (dd, $J = 8.2$, 4.1 Hz, 1H), 2.50–2.20 (m, 4H), 2.10–1.80 (m, 4H), 1.76 (t, $J = 4.4$ Hz, 1H), 1.32–1.24 (m, 1H), 1.23 (s, 3H), 1.15 (s, 3H), 1.13 (t, $J = 7.4$ Hz, 3H), 1.07 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 181.6$, 155.3, 82.9, 73.3, 47.9, 42.9, 35.5, 29.1, 26.6, 25.8, 21.4, 19.3, 10.7, 10.5 ppm; ESI-MS: m/z $[M+H]^+$ calcd for $C_{15}H_{25}N_2O_2$: 265.37, found 265.1.

General procedure for hydrazone alkylation: *n*BuLi (2.5 M in hexanes, 11.65 mL, 29.13 mmol) was added dropwise over ca. 2 min to a stirred and cooled (−78 °C) solution of diisopropylamine (4.45 mL, 31.77 mmol) in THF (60 mL) under an argon atmosphere. The mixture was transferred to an ice bath, stirred for 30 min, and then cooled to −40 °C. A solution of **11** (7.002 g, 26.48 mmol) in THF (260 mL) was added by cannula, with additional THF (2 × 2.0 mL) as a rinse, and the mixture was stirred for 45 min. Allyl bromide (2.52 mL, 29.13 mmol) was then added and stirring was continued for 5 min. The cold bath was removed and the mixture was stirred for an additional 40 min and then partitioned between Et_2O and H_2O. The aqueous phase was extracted with Et_2O (2 × 500 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a yellow oil. Flash chromatography over silica gel using EtOAc/hexanes (10:90) gave **15** (7.899 g, 98%) as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 5.90$–5.70 (m, 1H), 5.18–4.94 (m, 2H), 4.25 (dd, $J = 8.1$, 4.1 Hz, 1H), 3.18–3.04 (m, 1H), 2.50–2.24 (m, 4H), 2.14–1.80 (m, 4H), 1.76 (t, $J = 4.4$ Hz, 1H), 1.26–1.32 (m, 2H), 1.23 (s, 3H), 1.16 (s, 3H), 1.13 (t, $J = 7.2$ Hz, 3H), 0.94 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR

($CDCl_3$, 100 MHz): $\delta = 184.4, 155.5, 136.6, 116.7, 82.9, 73.4, 47.9, 43.1, 37.6, 35.6, 35.1, 26.7, 25.8, 24.8, 21.5, 19.3, 17.3, 10.4$ ppm; ESI-MS: m/z $[M+H]^+$ calcd for $C_{18}H_{29}N_2O_2$: 305.44, found 305.1.

General procedure for hydrazone hydrolysis and ACC recovery: *p*-TsOH·H_2O (9.424 g; 49.54 mmol) was added to a stirred solution of **15** (7.541 g, 24.77 mmol) in acetone (100 mL). The mixture was stirred for 15 min and then partitioned between Et_2O and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O (2 × 250 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a colorless oil that was used directly for GC analysis.[11] Analysis was conducted under conditions (50 °C; 15 psi) that gave baseline separation of the enantiomers of an independently prepared racemic mixture of **7**. Flash chromatography of the remaining crude reaction mixture over silica gel using Et_2O/pentane (5:95) gave **7** (2.933 g, 94 %) as a colorless oil. Spectroscopic data was identical to that reported previously.[10] Continued flash chromatography using EtOAc/hexanes (25:75) gave **38** (5.737 g, 98 %) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 4.25$ (dd, $J = 8.1$, 4.1 Hz, 1H), 3.40–2.26 (m, 1H), 2.08 (s, 3H), 2.06–1.96 (m, 2H), 1.95 (s, 3H), 1.90–1.70 (m, 2H), 1.34–1.24 (m, 1H), 1.23 (s, 3H), 1.20–1.16 (m, 1H), 1.14 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.3, 155.1, 83.1, 73.2, 48.1, 42.9, 35.5, 26.8, 25.8, 25.5, 21.4, 20.1, 19.3$ ppm; ESI-MS: m/z $[M+H]^+$ calcd for $C_{13}H_{21}N_2O_2$: 237.32, found 237.1. **38** (5.729 g; 24.24 mmol) was then combined with $HONH_2$·HCl (6.731 g; 96.86 mmol) in THF/H_2O (4:1, 250 mL) and stirred for 6 h. The resulting solution was concentrated and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (2 × 300 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated to give a light-yellow solid. Flash chromatography over silica gel using EtOAc/hexanes (25:75) gave **6** (4.519 g, 95 %) as a white solid.

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