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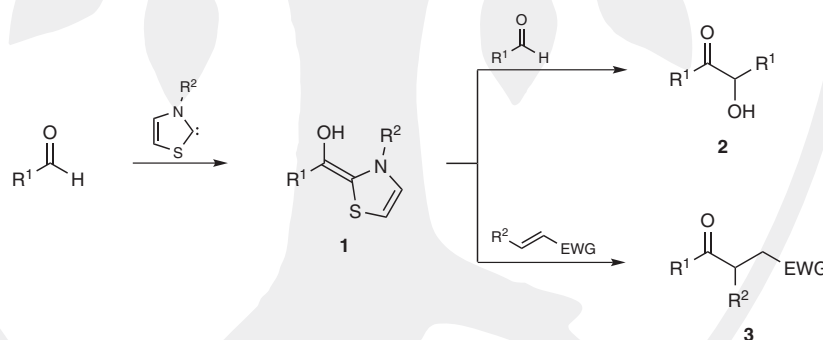
Asymmetric Benzoin and Stetter Reactions

D. A. DiRocco and T. Rovis

General Introduction

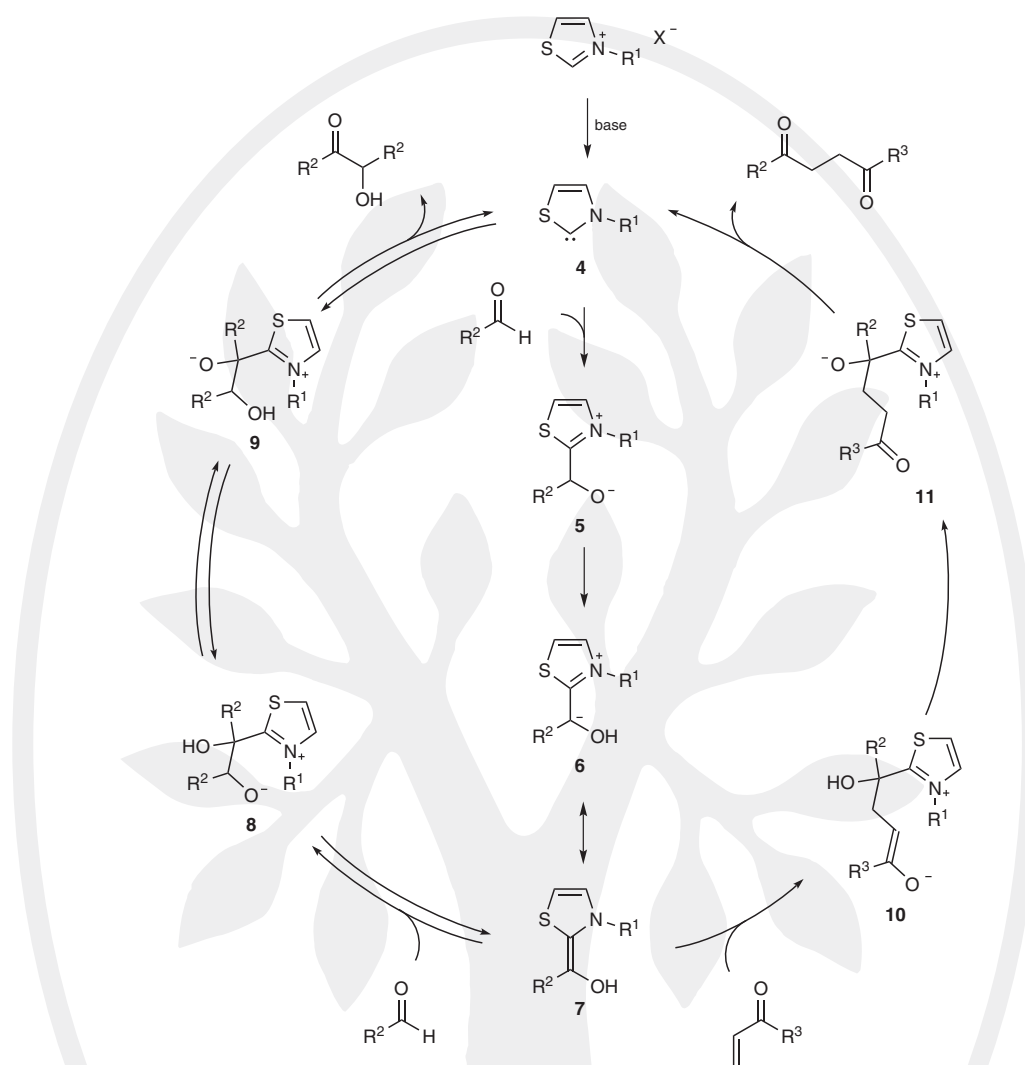
Aldehydes are important functional groups in synthetic organic chemistry and are used in a variety of bond-forming reactions, typically utilizing the electrophilic character of the carbonyl group. Reactions which reverse this normal mode of reactivity, termed “umpolung”, render the aldehyde nucleophilic, giving rise to acyl anion equivalents and complementary reactivity.^[1] Traditional methods for converting aldehydes into umpolung reagents involve the use of stoichiometric reagents such as dithianes and protected cyanohydrin derivatives.^[2,3] These methods typically require strong bases and harsh conditions that are incompatible with many functional groups, thereby limiting their utility. The development of catalytic methods for the in situ formation of acyl anion equivalents under mild conditions has been a topic of interest in the past decades. Two related reactions that utilize the umpolung reactivity of aldehydes are the benzoin and Stetter reactions (Scheme 1).^[4,5] The key component of both of these transformations is a catalytically generated acyl anion equivalent **1**, capable of forming new carbon–carbon bonds. In the benzoin reaction, the acyl anion equivalent adds to an aldehyde to provide α -hydroxy ketones **2** as products. Similarly, the conjugate addition of acyl anion equivalent **1** to a Michael acceptor affords 1,4-functionalized products **3**; this transformation is known as the Stetter reaction.

Scheme 1 The Benzoin and Stetter Reactions^[4,5]



The first benzoin reaction was described in 1832 and used cyanide as a catalyst.^[6] It was later found that thiazolium salts in the presence of base also act as suitable catalysts for the benzoin reaction.^[7] In 1903, the currently accepted mechanism of the benzoin reaction catalyzed by cyanide was proposed.^[8] Later, the mechanism of the benzoin reaction catalyzed by thiazolium salts was elucidated (Scheme 2), showing the similarities between cyanide and azolium catalysis.^[9] As there is no detailed mechanistic study of the Stetter reaction to date, we will focus on the mechanism of the benzoin reaction, which is proposed to be similar, differing largely in the choice of electrophile.

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Scheme 2 Mechanism of the Benzoin and Stetter Reactions^[9]

It is proposed that tetrahedral intermediate **5** is first generated by nucleophilic attack of the in situ generated carbene **4** to the aldehyde. Following proton transfer, an acyl anion equivalent **6** (which can also be represented as the Breslow intermediate **7**) is generated; this reacts in a 1,2-fashion with an aldehyde in the benzoin reaction or in a 1,4-fashion with a Michael acceptor in the Stetter reaction. Both reactions lead to the formation of a new carbon–carbon bond while generating a new tetrahedral intermediate **8** or **10**, respectively. After subsequent proton transfer and collapse of the resultant tetrahedral intermediate **9** or **11**, the desired product is formed while regenerating the carbene catalyst **4**.

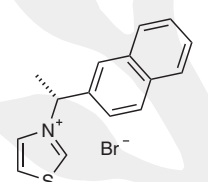
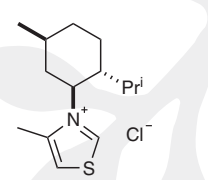
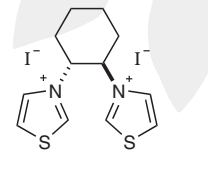
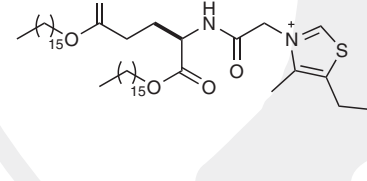
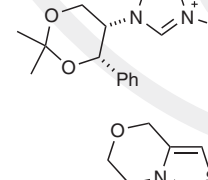
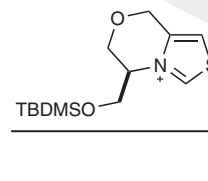
In 1966, the first example of an asymmetric benzoin reaction was reported, which showed that enantioenriched thiazolium salts can relay chiral information to the product.^[10] Since this first observation, there have been numerous groups that have worked on developing new chiral thiazolium scaffolds for the asymmetric benzoin reaction (Scheme 3), but it was not until the introduction of thiazolium salts that significant advances were made.^[11–14] The rational design and synthesis of chiral, bicyclic thiazolium salts that hypothetically would decrease the degrees of freedom in the chiral environment

leading to higher enantioselectivity was also reported.^[15-17] Although initial attempts did not lead to great improvements, the application of this hypothesis to chiral triazolium salts accomplished high enantioselectivity in the asymmetric benzoin reaction.^[18,19] The development of chiral, bicyclic triazolium salts for the asymmetric benzoin reaction was crucial to the success in catalyst design for the asymmetric Stetter reaction. Using these same principles, a series of chiral bicyclic triazolium salts have been developed, which have rendered the intramolecular and intermolecular Stetter reactions efficient and highly enantioselective.^[20]

Scheme 3 Evolution of Catalysts for the Asymmetric Benzoin Reaction^[10-19,21]



The reaction scheme shows benzaldehyde (Ph-CHO) reacting with a catalyst to form benzoin (Ph-CH(OH)-CH2-Ph).

| Catalyst | ee (%) | Yield (%) | Ref |
|---|--------|-----------|------|
|  | 51 | 6 | [21] |
|  | 35 | 20 | [11] |
|  | 27 | 11.5 | [12] |
|  | 18 | 35 | [13] |
|  | 75 | 66 | [14] |
|  | 20 | 34 | [15] |

for references see p 28

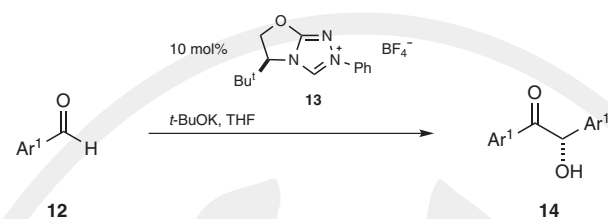
| Catalyst | ee (%) | Yield (%) | Ref |
|----------|--------|-----------|------|
| | 21 | 50 | [15] |
| | 30 | 18 | [17] |
| | 30 | 18 | [17] |
| | 80 | 45 | [18] |
| | 48 | 47 | [18] |
| | 63 | 22 | [18] |
| | 90 | 83 | [19] |

2.17.1 Asymmetric Intermolecular Benzoin Reactions of Aryl Aldehydes

Aryl aldehydes may be asymmetrically transformed into their corresponding benzoin products employing catalysis by triazolylidene or thiazolylidene carbenes, metallophosphites, and enzymes. To date, there are no efficient methods for the preparation of enantioenriched aliphatic acylolins.

2.17.1.1 Homodimerization of Aryl Aldehydes Catalyzed by N-Heterocyclic Carbenes

The homodimerization of aryl aldehydes **12** in the benzoin reaction gives benzoin **14** in moderate to good yields and high enantiomeric excess using chiral triazolium salt **13** as precatalyst in the presence of potassium *tert*-butoxide (Scheme 4).^[19] Benzaldehyde and electron-deficient analogues give excellent results whereas more electron-rich aldehydes (e.g., **12**, Ar¹ = 4-MeOC₆H₄) result in lower yields, albeit with excellent enantioselectivity.

Scheme 4 Asymmetric Homodimerization of Aryl Aldehydes^[19]

| Ar ¹ | Temp (°C) | ee ^a (%) | Yield ^b (%) | Ref |
|------------------------------------|-----------|---------------------|------------------------|------|
| Ph | 18 | 90 | 83 | [19] |
| 4-FC ₆ H ₄ | 18 | 83 | 81 | [19] |
| 4-FC ₆ H ₄ | 0 | 91 | 61 | [19] |
| 4-BrC ₆ H ₄ | 0 | 91 | 59 | [19] |
| 3-ClC ₆ H ₄ | 0 | 86 | 85 | [19] |
| 3-Tol | 18 | 86 | 70 | [19] |
| 4-MeOC ₆ H ₄ | 18 | 95 | 8 | [19] |
| 2-furyl | -78 | 88 | 41 | [19] |
| 2-naphthyl | 18 | 80 | 69 | [19] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

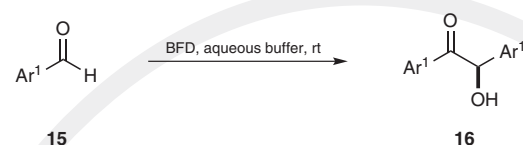
(S)-1,2-Diaryl-2-hydroxyethanones **14**; General Procedure:^[19]

The aromatic aldehyde **12** (10 mmol) was added to a soln of triazole **13** (331 mg, 1 mmol) in abs THF (0.7 mL·mmol⁻¹) at rt. The mixture was tempered for 5 min, and then *t*-BuOK (112 mg, 1 mmol) in abs THF (0.4 mL·mmol⁻¹) was added dropwise. The mixture was stirred for 16 h and then poured into H₂O, the resultant mixture was extracted with CH₂Cl₂ (2 ×), and the extracts were dried (MgSO₄). The solvent was evaporated and the residue was purified by column chromatography (silica gel, Et₂O/pentane 1:1) or by crystallization to give the aromatic acyloins as colorless, crystalline solids or pale yellow oils.

2.17.1.2 Homodimerization of Aryl Aldehydes by Enzyme Catalysis

Aryl aldehydes **15** can be transformed into the corresponding benzoin **16** in good yield and excellent enantioselectivity using benzoyl formate decarboxylase (BFD) in an aqueous potassium phosphate (KPi) buffer system (Scheme 5).^[22] Yields are generally high with the exception of 3- or 4-substituted benzaldehydes; however, enantioselectivities are always excellent.

for references see p 28

Scheme 5 Benzoyl Formate Decarboxylase Catalyzed Asymmetric Benzoin Synthesis^[22]

| Ar ¹ | ee ^a (%) | Yield ^b (%) | Ref |
|------------------------------------|---------------------|------------------------|------|
| Ph | >99 | 70 | [22] |
| 3-MeOC ₆ H ₄ | >99 | 18 | [22] |
| 4-MeOC ₆ H ₄ | >99 | 12 | [22] |
| 4-Tol | >99 | 69 | [22] |
| 2-FC ₆ H ₄ | >99 | 68 | [22] |
| 4-FC ₆ H ₄ | >99 | 25 | [22] |
| 4-ClC ₆ H ₄ | >99 | 17 | [22] |
| 4-BrC ₆ H ₄ | >99 | 13 | [22] |
| 2-furyl | 94 ^c | 62 | [22] |
| | 96 | 50 | [22] |
| 2-thienyl | 95 | 65 | [22] |
| 2-BrC ₆ H ₄ | n.d. | <2 | [22] |
| 2-NCC ₆ H ₄ | – | 0 | [22] |
| 2-MeOC ₆ H ₄ | n.d. | <2 | [22] |

^a Determined by HPLC analysis using a chiral stationary phase; n.d. = not determined.

^b Isolated yields after chromatography.

^c Determined immediately after work-up.

(R)-Benzoin (16, Ar¹ = Ph); Typical Procedure:^[22]

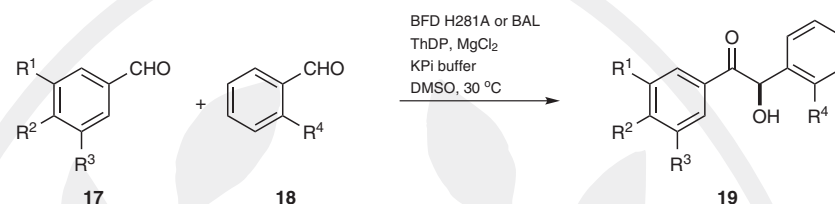
Benzaldehyde (**15**, Ar¹ = Ph; 318 mg, 3 mmol) was dissolved in a mixture of DMSO (30 mL) and 50 mM KPi buffer [100 mL, pH 7.0, containing MgSO₄ (2.5 mM) and thiamine diphosphate (ThDP; 0.15 mM)]. After addition of BFD (450 U relative to decarboxylation of benzoyl formate), the mixture was allowed to stand at rt for 48 h (the reaction was monitored by GCMS and HPLC). The mixture was extracted with CH₂Cl₂ (250 mL) and the organic layer was washed with H₂O (25 mL) and brine (25 mL) and then dried (Na₂SO₄). The solvent was evaporated and the crude product was purified by column chromatography (silica gel, CH₂Cl₂); yield: 223 mg (70%); >99% ee.

2.17.1.3 Heterodimerization of Aryl Aldehydes by Enzyme Catalysis

The synthesis of enantioenriched benzoin **19** by enzyme catalysis [benzoyl formate decarboxylase (BFD) or benzaldehyde lyase (BAL) in the presence of thiamine diphosphate (ThDP) and a potassium phosphate buffer (KPi)] has been extended to heterodimerization of aryl aldehydes **17** and **18**, leading to a more versatile method with a broader scope (Scheme 6).^[23] Selectivity in these substrates is obtained by a donor–acceptor concept which is determined by the substitution on the aryl aldehydes. A wide range of substitu-

tion is tolerated on the aldehyde, but this reaction is still limited to electron-deficient aryl aldehydes.

Scheme 6 Chemoselective, Asymmetric Synthesis of Mixed Benzoin^[23]



| R ¹ | R ² | R ³ | R ⁴ | Enzyme | Selectivity ^a (%) | ee ^b (%) | Conversion (%) | Ref |
|--------------------|-----------------|----------------|----------------|-----------|------------------------------|---------------------|----------------|------|
| CN | H | H | Cl | BFD H281A | >99 | 90 | >99 | [23] |
| H | Br | H | Cl | BFD H281A | 95 | 95 | 90 | [23] |
| H | CF ₃ | H | Cl | BFD H281A | >99 | 93 | 75 | [23] |
| OCH ₂ O | H | Cl | BAL | 83 | >99 | 98 | [23] | |
| OMe | OMe | OMe | Cl | BAL | 97 | >99 | 82 | [23] |
| OMe | OMe | H | Cl | BAL | 95 | >99 | >99 | [23] |

^a The selectivity is defined as the percent ratio of product in relation to the sum of all benzoin products obtained.

^b Determined by HPLC analysis using a chiral stationary phase.

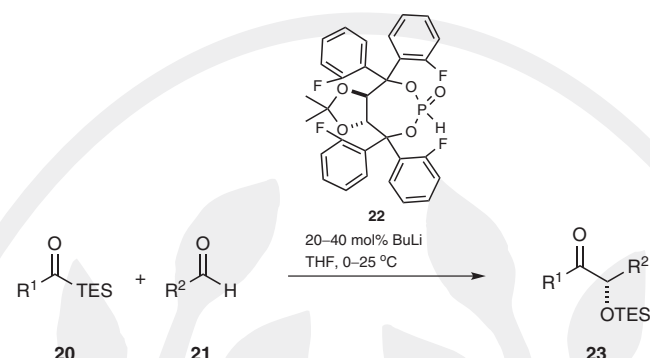
(R)-1-(4-Bromophenyl)-2-(2-chlorophenyl)-2-hydroxyethanone (19, R¹ = R³ = H; R² = Br; R⁴ = Cl); Typical Procedure:^[23]

To a suspension of 2-chlorobenzaldehyde (**18**, R⁴ = Cl; 563 mg, 5.0 mmol), 4-bromobenzaldehyde (**17**, R¹ = R³ = H; R² = Br; 925 mg, 5.0 mmol), and DMSO (40 mL) in 50 mM KPi buffer (150 mL, pH 7.0, ThDP 0.5 mM, MgCl₂ 2.5 mM) was added BFD H281A (1000 U), dissolved in KPi buffer (10 mL). This suspension was stirred at 30 °C until conversion was complete (48 h). The aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were concentrated and the crude product was dissolved in Et₂O (10 mL) before H₂O (2 mL) was added to extract remnants of DMSO. The organic layer was dried (Na₂SO₄) and the solvent was removed under reduced pressure to obtain a yellow solid; yield: 1.22 g (82%, as reported); 95% ee.

2.17.1.4 Heterodimerization of Aryl Aldehydes Catalyzed by Metallophosphites

Metallophosphites have been shown to be competent umpolung catalysts in the cross silyl benzoin reaction.^[24] Treatment of a variety of acylsilanes **20** with aryl aldehydes **21** in the presence of the chiral metallophosphite derived from **22** results in good yields and enantioselectivities of the corresponding silylated crossed-benzoin products **23** (Scheme 7). Both electron-deficient and electron-rich aryl acylsilanes and aryl aldehydes are well tolerated, but alkyl substitution on either substrate leads to poor enantioselectivity. The triethylsilyl group in compounds **23** is removed under acidic conditions to give the 2-hydroxyethanones **24**.

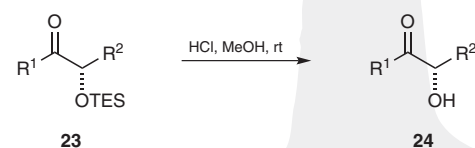
for references see p 28

Scheme 7 Asymmetric Catalytic Cross Silyl Benzoin Reaction^[24]

| R ¹ | R ² | 22 (mol%) | ee ^a (%) | Yield ^b (%) | Ref |
|--|--|------------------|---------------------|------------------------|------|
| Ph | Ph | 7.5 | 82 | 84 | [24] |
| Ph | 4-ClC ₆ H ₄ | 7.5 | 82 | 75 | [24] |
| 4-ClC ₆ H ₄ | Ph | 7.5 | 87 | 82 | [24] |
| Ph | 4-MeOC ₆ H ₄ | 5 | 91 | 87 | [24] |
| 4-MeOC ₆ H ₄ | Ph | 7.5 | 88 | 83 | [24] |
| 4-ClC ₆ H ₄ | 4-MeOC ₆ H ₄ | 7.5 | 90 | 83 | [24] |
| 4-MeOC ₆ H ₄ | 4-ClC ₆ H ₄ | 10 | 83 | 79 | [24] |
| Ph | 4-Me ₂ NC ₆ H ₄ | 5 | 81 | 80 | [24] |
| 4-Me ₂ NC ₆ H ₄ | Ph | 12.5 | 86 | 86 | [24] |
| Ph | 2-furyl | 7.5 | 85 | 65 | [24] |
| Ph | iPr | 15 | 73 | 78 | [24] |
| Ph | (CH ₂) ₅ Me | 20 | 41 | 88 | [24] |
| (CH ₂) ₅ Me | Ph | 20 | 67 | 72 | [24] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.



(S)-(-)-1,2-Diaryl-2-(triethylsiloxy)ethanones 23; General Procedure:^[24]

A flame-dried, round-bottomed flask with a magnetic stirrer bar was charged with acylsilane **20** (0.5 mmol), aldehyde **21** (1.5 equiv), and phosphite **22** (0.05–0.2 equiv) in a drybox. The flask was sealed with a septum and was brought out of the drybox. Under argon, THF (8 mL) was added via syringe. BuLi (0.2–0.4 equiv) was added at 0 °C dropwise via syringe. The ice bath was removed and the mixture was stirred under argon for 0.5 h (monitored by TLC). The solvent was removed with a rotary evaporator and the crude product was purified by flash chromatography.

(S)-(-)-1,2-Diaryl-2-hydroxyethanones 24; General Procedure:^[24]

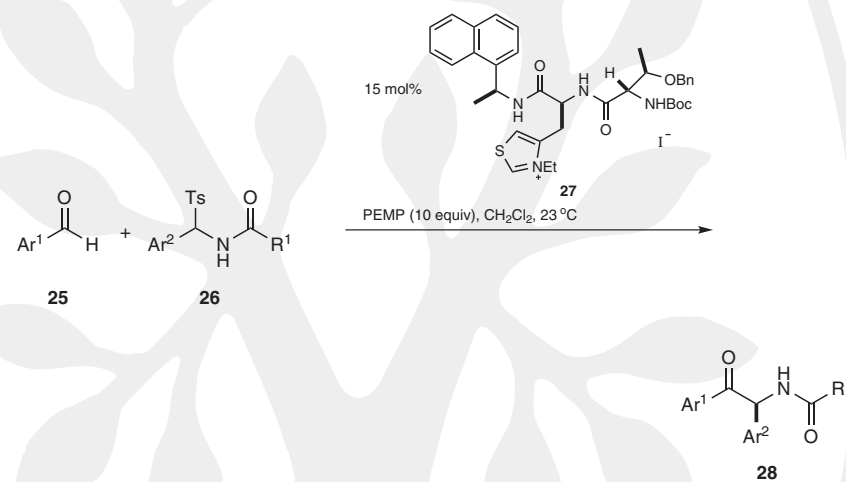
A round-bottomed flask with a magnetic stirrer bar was charged with the pure siloxy ketone **23** (0.2 mmol). MeOH (10 mL) and 1 M aq HCl (10 mL) were added and the mixture was

stirred for 10 min at 25 °C before Et₂O (15 mL) was added to the flask. The organic layer was separated and the aqueous layer was extracted with Et₂O (2 × 15 mL). The organic extracts were combined and dried (MgSO₄), and the solvent was removed with a rotary evaporator. The product was purified by flash chromatography.

2.17.1.5 Aldehyde–Imine Cross Coupling Catalyzed by N-Heterocyclic Carbenes

In a transformation related to the benzoin reaction, treatment of aryl aldehydes **25** with acyl imines, generated in situ from tosyl-substituted amides **26**, in the presence of chiral thiazolium salt **27** and the base 1,2,2,6,6-pentamethylpiperidine (PEMP), produces α -amido ketones **28** in good yield and good enantioselectivity (Scheme 8).^[25] The scope is limited to electron-deficient aryl aldehydes and electron-rich amide precursors. Many of the products can be recrystallized to enantiomeric excesses greater than 98%.

Scheme 8 Thiazolium-Catalyzed Asymmetric Aldehyde–Imine Coupling^[25]



| Ar ¹ | Ar ² | R ¹ | Time | ee ^a (%) | Yield ^b (%) | Ref |
|---|--|----------------|--------|-----------------------|------------------------|------|
| 4-ClC ₆ H ₄ | Ph | Ph | 1 h | 81 | 57 | [25] |
| 4-ClC ₆ H ₄ | Ph | Ph | 2 h | 76 (>98) ^c | 100 (60) ^c | [25] |
| 4-ClC ₆ H ₄ | 4-MeOC ₆ H ₄ | Ph | 2 h | 85 (98) ^c | 91 (72) ^c | [25] |
| 3-O ₂ NC ₆ H ₄ | 4-MeOC ₆ H ₄ | Ph | 15 min | 82 | 77 | [25] |
| 3-O ₂ NC ₆ H ₄ | 4-MeOC ₆ H ₄ | iPr | 15 min | 79 | 63 | [25] |
| 4-ClC ₆ H ₄ | Ph | iPr | 2 h | 75 (>98) ^c | 97 (48) ^c | [25] |
| 4-ClC ₆ H ₄ | 3,4-(MeO) ₂ C ₆ H ₃ | Ph | 1 h | 81 | 80 | [25] |
| Ph | Ph | Ph | 2 h | 83 | 15 | [25] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

^c Results in parentheses are those obtained after recrystallization.

(S)-N-[2-(4-Chlorophenyl)-2-oxo-1-phenylethyl]benzamide (**28**, Ar¹ = 4-ClC₆H₄; R¹ = Ar² = Ph); Typical Procedure:^[25]

Into a 10-mL, round-bottomed flask containing a stirrer bar was added *N*-[phenyl-(tosyl)methyl]benzamide (**26**, R¹ = Ar² = Ph; 23.7 mg, 0.0650 mmol) and 4-chlorobenzaldehyde (**25**, Ar¹ = 4-ClC₆H₄; 46.0 mg, 0.325 mmol). The flask was sealed with a rubber septum and purged with anhyd N₂ for 1 h. An aliquot of a soln of catalyst **27** in CH₂Cl₂ (650 μ L,

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0.00980 mmol) was added in one portion to the mixture at 23 °C, followed by addition of 1,2,2,6,6-pentamethylpiperidine (117 μ L, 0.650 mmol) via syringe. The resulting mixture was allowed to stir at 23 °C for 1 h, after which it was diluted with CH_2Cl_2 (10 mL) and washed with 10% w/v aq citric acid (10 mL), followed by extraction of the aqueous layer with CH_2Cl_2 (3 \times 5 mL). The resulting organic layer was dried (Na_2SO_4), concentrated onto silica gel, and immediately purified by chromatography (silica gel, hexane /EtOAc 9:1); yield: 12.9 mg (57%); 81% ee.

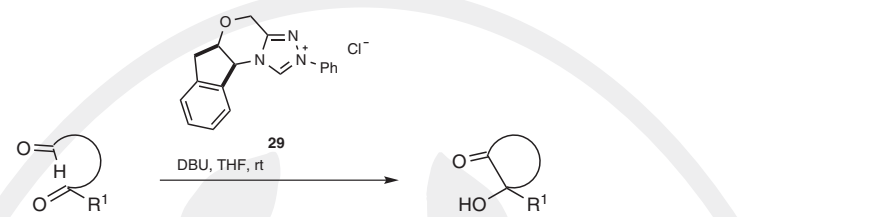
The same procedure was repeated on larger scale with a reaction time of 2 h using *N*-[phenyl(tosyl)methyl]benzamide (**26**, $\text{R}^1 = \text{Ar}^2 = \text{Ph}$; 95.0 mg, 0.260 mmol), 4-chlorobenzaldehyde (**25**, $\text{Ar}^1 = 4\text{-ClC}_6\text{H}_4$; 181 mg, 1.30 mmol), catalyst **27** (30.0 mg, 0.039 mmol), 1,2,2,6,6-pentamethylpiperidine (0.470 mL, 2.60 mmol), and CH_2Cl_2 (2.6 mL); yield: 91.4 mg (100%); 76% ee. The enantiopurity of the product was enhanced by crystallization (EtOAc/hexanes) to give racemic material, which was removed by filtration, and yielded, in the mother liquor, **28** ($\text{Ar}^1 = 4\text{-ClC}_6\text{H}_4$; $\text{R}^1 = \text{Ar}^2 = \text{Ph}$); yield: 55.0 mg (60%); >98% ee; $[\alpha]_{\text{D}}^{26.6} +188.4$ (*c* 1.0, CHCl_3).

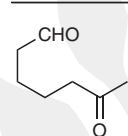
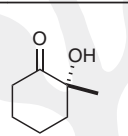
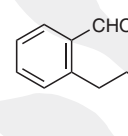
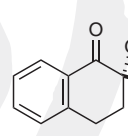
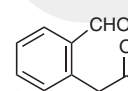
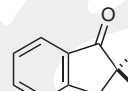
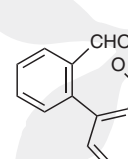
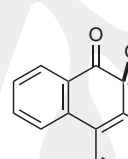
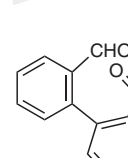
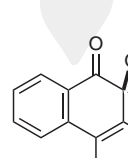
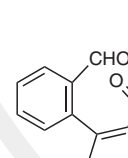
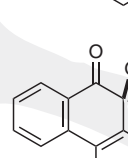
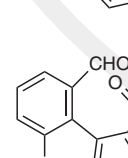
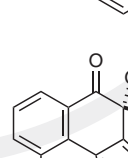
2.17.2 Asymmetric Intramolecular Benzoin Reactions

Aldehyde substrates containing a pendant ketone functional group can be cyclized to the corresponding cyclic α -hydroxy ketones efficiently with high enantioselectivity under triazolylidene carbene catalysis.

2.17.2.1 Aldehyde–Ketone Crossed Benzoin Reactions Catalyzed by *N*-Heterocyclic Carbenes

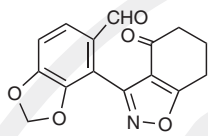
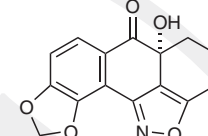
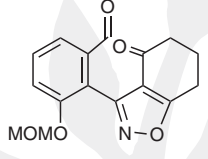
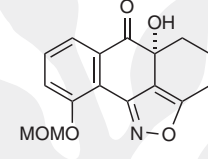
Cyclic α -hydroxy ketones (e.g., **31**, **34**, and **37**) can be synthesized efficiently and highly enantioselectively using chiral triazolium salts (e.g., **29**, **32**, and **36**) (Tables 1 and 2, and Scheme 9).^[26–28] Cyclization of aryl or alkyl aldehydes (e.g., **30**, **33**, and **35**) to form six-membered rings occurs in good yield and excellent enantioselectivity; however, formation of five-membered rings remains a challenge in this area.

Table 1 Formation of Carbocycles by Catalytic Asymmetric Intramolecular Crossed Benzoïn Reactions^[26]


| Substrate | 29 (mol%) | DBU (mol%) | Product | ee ^a (%) | Yield ^b (%) | Ref |
|---|---------------------|---------------|--|------------------------|---------------------------|------|
|  | 20 | 20 |  | 96 | 44 | [26] |
|  | 20 | 20 |  | 96 | 70 | [26] |
|  | 25 | 20 |  | 60 | 69 | [26] |
|  | 10 | 20 |  | 39 | 73 | [26] |
|  | 20 | 20 |  | 90 | 47 | [26] |
|  | 20 | 20 |  | 85 | 74 | [26] |
|  | 10 | 20 |  | 98 | 91 | [26] |

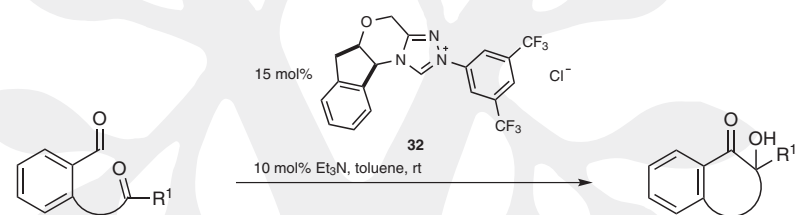
for references see p 28

Table 1 (cont.)

| Substrate | 29 (mol%) | DBU (mol%) | Product | ee ^a (%) | Yield ^b (%) | Ref |
|---|---------------------|---------------|--|------------------------|---------------------------|------|
|  | 40 | 40 |  | 99 | 73 | [26] |
|  | 10 | 10 |  | 99 | 92 | [26] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

Table 2 Formation of Carbo- and Heterocycles by Catalytic Asymmetric Intramolecular Crossed Benzoïn Reactions^[27]

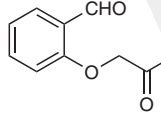
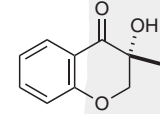
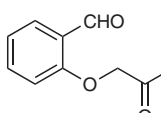
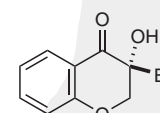
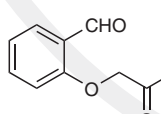
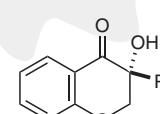
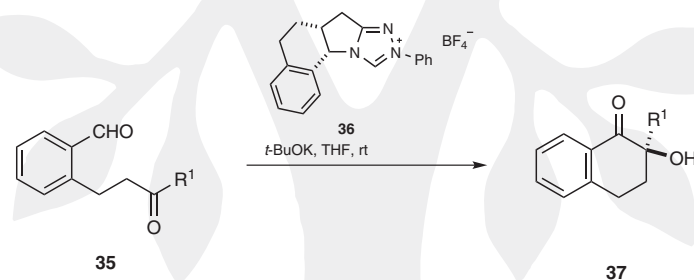
| Substrate | Product | ee ^a (%) | Yield ^b (%) | Ref |
|---|---|---------------------|------------------------|------|
|  |  | 94 | 90 | [27] |
|  |  | 94 | 87 | [27] |
|  |  | 90 | 61 | [27] |

Table 2 (cont.)

| Substrate | Product | ee ^a (%) | Yield ^b (%) | Ref |
|-----------|---------|---------------------|------------------------|------|
| | | 78 | 95 | [27] |
| | | 96 | 92 | [27] |
| | | 60 | 90 | [27] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

Scheme 9 Catalytic Asymmetric Intramolecular Crossed Benzoin Reactions^[28]

| R ¹ | Catalyst (mol%) | Base (mol%) | ee ^a (%) | Config | Yield ^b (%) | Ref |
|----------------|-----------------|-------------|---------------------|--------|------------------------|------|
| Me | 10 | 9 | 94 | S | 93 | [28] |
| Et | 20 | 19 | 95 | S | 90 | [28] |
| Bu | 10 | 9 | 98 | S | 85 | [28] |
| iBu | 20 | 19 | 98 | R | 91 | [28] |
| Bn | 20 | 19 | 93 | R | 43 | [28] |

^a Determined by HPLC analysis on a chiral stationary phase.

^b Isolated yields after chromatography.

(5aR)-5a-Hydroxy-10-(methoxymethoxy)-4,4,5,5a-tetrahydro-6H-anthra[9,1-cd]isoxazol-6-one (31); Typical Procedure:^[26]

A mixture of dicarbonyl compound **30** (934 mg, 3.1 mmol) and triazolium salt **29** (101 mg, 0.31 mmol) in anhyd THF (8.75 mL) was degassed by three freeze–pump–thaw cycles. To the mixture was added degassed 0.40 M DBU in THF (0.78 mL, 0.31 mmol) dropwise at rt under a N₂ atmosphere. After stirring at this temperature for 12 h, the mixture was cooled to 0 °C, and H₂O was added. The products were extracted with CH₂Cl₂ (30 mL) and EtOAc

for references see p 28

(2 × 30 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/CH₂Cl₂/hexane 3:4:3) to give a yellow solid; yield: 92%; 99% ee. Recrystallization (EtOAc) gave enantiomerically pure colorless needles; yield: 75%; >99% ee.

(R)-3-Benzyl-3-hydroxy-2,3-dihydro-1-benzopyran-4-one (34); Typical Procedure:^[27]

A mixture of dicarbonyl compound **33** (83.5 mg, 0.330 mmol) and triazolium salt **32** (22.8 mg, 0.049 mmol) in toluene (1.1 mL) was degassed by two freeze–pump–thaw cycles. To the mixture was added Et₃N (4.6 μL, 0.033 mmol) at rt under a N₂ atmosphere. After stirring at this temperature for 5 h, the mixture was cooled to 0 °C, and H₂O was added. The products were extracted with EtOAc (3 ×). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/CH₂Cl₂/hexane 1:1:3) to give a colorless oil; yield: 72.6 mg (87%); 94% ee.

(R)-2-Hydroxy-2-isobutyl-3,4-dihydronaphthalen-1(2H)-one (37; R¹ = iBu);

Typical Procedure:^[28]

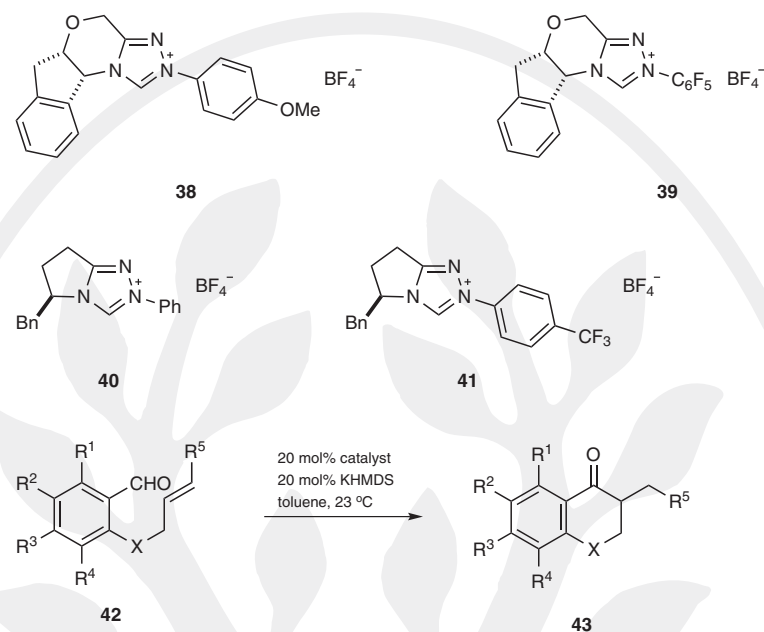
Precatalyst **36** (20.6 mg, 0.055 mmol) was suspended in anhyd THF (1.7 mL) in a Schlenk tube under argon at rt. A soln of freshly sublimed *t*-BuOK (5.9 mg, 0.052 mmol) in anhyd THF (0.6 mL) was added slowly, and the soln was stirred for 5 min. Dicarbonyl compound **35** (R¹ = iBu; 60 mg, 0.275 mmol) was dissolved in anhyd THF (0.5 mL) and added to the carbene soln. The mixture was stirred for 48 h, diluted with CH₂Cl₂, quenched with H₂O, extracted with CH₂Cl₂ (2 ×), and dried (MgSO₄). The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, CH₂Cl₂/pentane 2:1) to yield a colorless liquid; yield: 54 mg (91%); 98% ee.

2.17.3 Asymmetric Intramolecular Stetter Reactions Catalyzed by N-Heterocyclic Carbenes

The development of chiral triazolium salts for the asymmetric Stetter reaction has been largely influenced by the work of many individuals in the asymmetric benzoin reaction. Chiral bicyclic triazolium salts have been the most efficient scaffolds in this area. Further elaboration on this initial premise has led to highly efficient and selective catalysts for the catalytic asymmetric Stetter reaction.^[20] A variety of aldehyde substrates can be cyclized to form the corresponding ketones in high yield and excellent enantioselectivity.

2.17.3.1 Asymmetric Intramolecular Stetter Reaction of Aryl Aldehydes

Aldehydes **42** containing a pendant Michael acceptor can be cyclized to ketones **43** in good yield and excellent enantioselectivity utilizing chiral triazolylidene carbene catalysts **38–41** (Scheme 10).^[29,30] The reaction is tolerant of a variety of heteroatom linkers as well as aryl and aliphatic backbones. A variety of Michael acceptors are also well tolerated, giving similar results. Cyclization of terminally disubstituted Michael acceptors **44** leads to the formation of two contiguous stereocenters in the ketones **45** with high enantioselectivity and high diastereoselectivity (Scheme 11).^[31]

Scheme 10 Asymmetric Intramolecular Stetter Reaction of Aryl Aldehydes^[29,30]

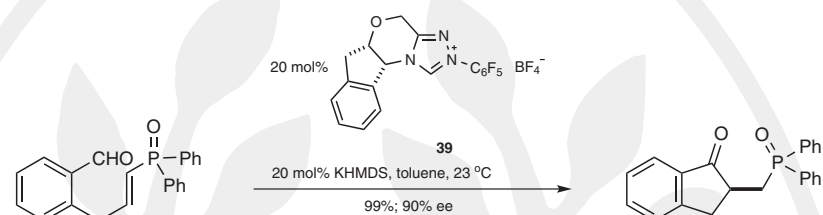
| R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X | Catalyst | ee ^a (%) | Config | Yield ^b (%) | Ref |
|----------------|----------------|------------------|----------------|--|-----------------|-----------|------------------------|--------|---------------------------|------|
| H | H | H | H | CO ₂ Et | O | 38 | 94 | R | 94 | [29] |
| H | H | H | Me | CO ₂ Et | O | 38 | 84 | R | 90 | [29] |
| H | H | H | H | Bz | O | 38 | 81 | R | 50 | [29] |
| H | H | H | H | CO ₂ Et | CH ₂ | 40 | 92 | R | 90 | [29] |
| H | H | H | H | CO ₂ Et | S | 38 | 96 | R | 63 | [29] |
| H | H | H | H | CO ₂ Et | S | 40 | 90 | S | 84 | [29] |
| H | H | H | H | CO ₂ Me | NMe | 38 | 82 | R | 64 | [29] |
| H | H | H | OMe | CO ₂ Et | O | 41 | 95 | S | 86 | [29] |
| H | OMe | H | H | CO ₂ Et | O | 41 | 93 | S | 84 | [29] |
| H | Br | H | H | CO ₂ Et | O | 41 | 92 | S | 94 | [29] |
| H | H | NEt ₂ | H | CO ₂ Et | O | 41 | 95 | S | 55 | [29] |
| H | H | H | H | CO ₂ CH ₂ CH=CH ₂ | O | 39 | 93 | R | 94 | [29] |
| H | H | H | H | CO ₂ <i>t</i> -Bu | O | 39 | 97 | R | 94 | [29] |
| H | H | H | H | C(O)Et | O | 39 | 92 | R | 94 | [29] |
| H | H | H | H | C(O)SEt | O | 39 | 70 | S | 85 | [29] |
| H | H | H | H | | O | 39 | 92 | R | 94 | [29] |
| H | H | H | H | CHO | O | 39 | 30 | R | 50 | [29] |
| H | H | H | H | P(O)Ph ₂ | O | 39 | 86 | R | 90 | [30] |
| H | Cl | H | H | P(O)Ph ₂ | O | 39 | 94 | R | 90 | [30] |
| H | H | H | OMe | P(O)Ph ₂ | O | 39 | 87 | R | 75 | [30] |
| H | H | OMe | H | P(O)Ph ₂ | O | 39 | 93 | R | 86 | [30] |

for references see p 28

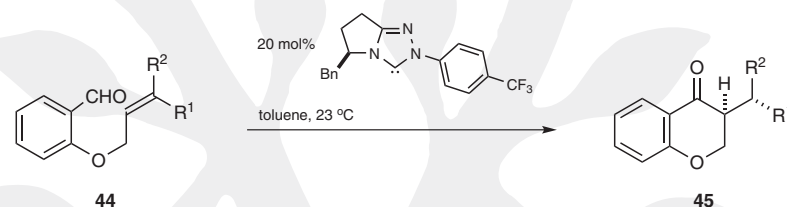
| R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X | Catalyst | ee ^a (%) | Config | Yield ^b (%) | Ref |
|----------------|----------------|----------------|----------------|------------------------|---|-----------|---------------------|--------|------------------------|------|
| H | H | H | H | P(O)Ph ₂ | S | 39 | 92 | R | 70 | [30] |
| H | H | H | H | P(O)(OEt) ₂ | O | 39 | 80 | R | 65 | [30] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.



Scheme 11 Diastereoselective Asymmetric Intramolecular Stetter Reactions of Aryl Aldehydes^[31]



| R ¹ | R ² | ee ^a (%) | dr | Yield ^b (%) | Ref |
|---------------------------------------|--------------------|---------------------|------|------------------------|------|
| Me | CO ₂ Et | 95 | 30:1 | 94 | [31] |
| Et | CO ₂ Et | 92 | 35:1 | 95 | [31] |
| Bu | CO ₂ Et | 94 | 12:1 | 53 | [31] |
| Bn | CO ₂ Et | 84 | 20:1 | 80 | [31] |
| CH ₂ CH=CH ₂ | CO ₂ Me | 83 | 13:1 | 95 | [31] |
| Me | Ac | 55 | 10:1 | 85 | [31] |
| (CH ₂) ₂ OC(O) | | 94 | 10:1 | 95 | [31] |
| (CH ₂) ₃ C(O) | | 95 | 18:1 | 80 | [31] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

Dihydronaphthalene-1-ones/2,3-Dihydro-4H-1-benzopyran-4-ones/2,3-Dihydro-4H-1-benzothiopyran-4-ones/Dihydroquinolin-4-ones 43; General Procedure:^[29]

A flame-dried, round-bottomed flask was charged with the triazolium salt (0.2 equiv) and toluene (5 mL). To this soln was added via syringe 0.5 M KHMDS (0.2 equiv) in toluene, prepared prior to use from KHMDS (0.05 g) and toluene (0.5 mL), and the soln was stirred at ambient temperature for 5 min. A soln of the substrate **42** (1 equiv, 0.12 mmol) in toluene (2 mL) was added. The resulting soln was allowed to stir at ambient temperature and monitored by TLC. The mixture was placed directly onto a column (silica gel) and was purified by flash column chromatography (hexane/EtOAc typically 4:1). Evaporation of solvent afforded analytically pure product.

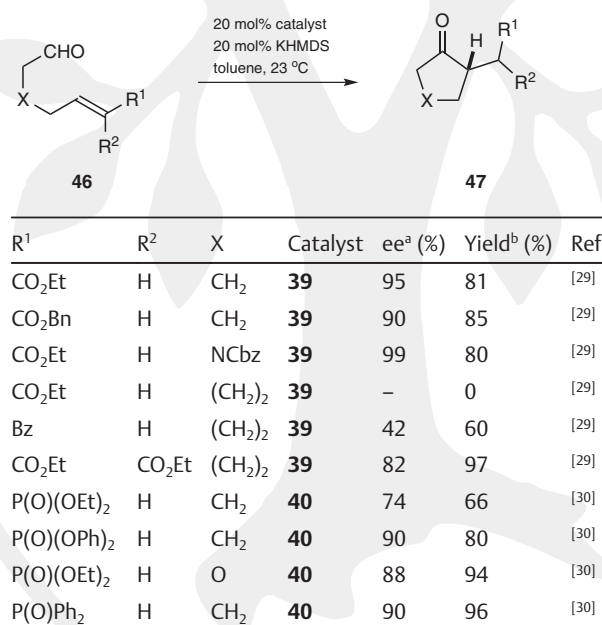
3-Substituted 2,3-Dihydro-4H-1-benzopyran-4-ones 45; General Procedure.^[31]

A flame-dried, round-bottomed flask was charged with the triazolium salt **41** (0.2 equiv) and toluene (2 mL). To this soln was added 0.5 M KHMDS in toluene (0.2 equiv) via syringe, and the soln was stirred at ambient temperature for 5 min. Toluene and hexamethyl-disilazane were removed under reduced pressure by placement under high vacuum for 1 h. Toluene (3 mL) was added, followed by a soln of the substrate **44** (1 equiv, 0.12 mmol) in toluene (2 mL). The resulting soln was allowed to stir at ambient temperature for 24 h. The reaction was quenched with AcOH/toluene (15:85; 2 mL), and the resulting soln was purified by flash column chromatography (hexane/EtOAc typically 6:1). Evaporation of the solvent afforded analytically pure product.

2.17.3.2 Asymmetric Intramolecular Stetter Reaction of Aliphatic Aldehydes

Aliphatic aldehydes **46** can also be cyclized efficiently to the ketones **47** with high enantioselectivity utilizing phenylalanine-derived triazolium salts **39** or **40** (Scheme 12).^[29,30] A variety of heteroatom linkers are tolerated, leading to heterocyclic products. The Michael acceptor is also widely variable, leading to structurally diverse products. Cyclizations of trisubstituted Michael acceptors **48** proceed in a highly enantioselective and diastereoselective fashion, forming two contiguous stereocenters in the ketone products **49** (Scheme 13).^[31]

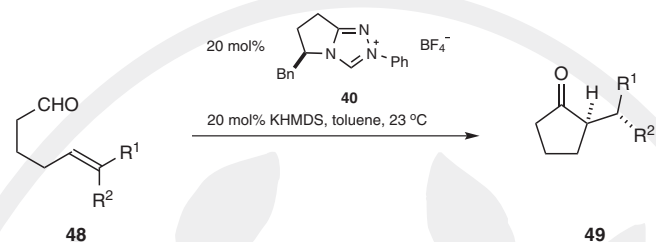
Scheme 12 Asymmetric Intramolecular Stetter Reactions of Aliphatic Aldehydes^[29,30]



^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

for references see p 28

Scheme 13 Diastereoselective Asymmetric Intramolecular Stetter Reaction of Aliphatic Aldehydes^[31]

| R ¹ | R ² | ee ^a (%) | dr | Yield ^b (%) | Ref |
|--------------------------------------|----------------|---------------------|------|------------------------|------|
| C(O)O(CH ₂) ₂ | | 99 | 50:1 | 94 | [31] |
| C(O)NPhC(O) | | 88 | 15:1 | 80 | [31] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

Cyclopentanones/Dihydrofuran-3-ones/Pyrrolidin-3-ones 47; General Procedure:^[29]

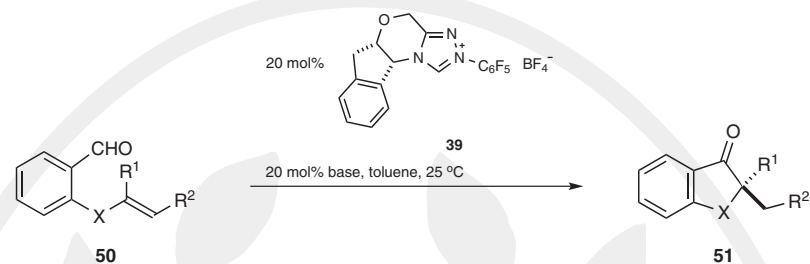
A flame-dried, round-bottomed flask was charged with triazolium salt **39** or **40** (0.2 equiv) and toluene (5 mL). To this soln was added via syringe 0.5 M KHMDS (0.2 equiv) in toluene, prepared prior to use from KHMDS (0.05 g) and toluene (0.5 mL), and the soln was stirred at ambient temperature for 5 min. A soln of the substrate **46** (0.12 mmol, 1 equiv) in toluene (2 mL) was added. The resulting soln was allowed to stir at ambient temperature and monitored by TLC. The mixture was placed directly onto a column (silica gel) and was purified by flash column chromatography (hexane/EtOAc typically 4:1). Evaporation of the solvent afforded analytically pure product.

2-Substituted Cyclopentanones 49; General Procedure:^[31]

A flame-dried, round-bottomed flask was charged with triazolium salt **40** (0.2 equiv) and toluene (2 mL). To this soln was added via syringe 0.5 M KHMDS in toluene (0.2 equiv), and the soln was stirred at ambient temperature for 5 min. Toluene and hexamethyldisilazane were removed under reduced pressure by placement under high vacuum for 1 h. Toluene (3 mL) was added, followed by a soln of the substrate **48** (0.12 mmol, 1 equiv) in toluene (2 mL); the resulting soln was allowed to stir at ambient temperature for 24 h. The reaction was quenched with AcOH/toluene (15:85; 2 mL), and the resulting soln was purified by flash column chromatography (hexane/EtOAc typically 6:1). Evaporation of the solvent afforded analytically pure product.

2.17.3.3 Formation of Quaternary Stereocenters

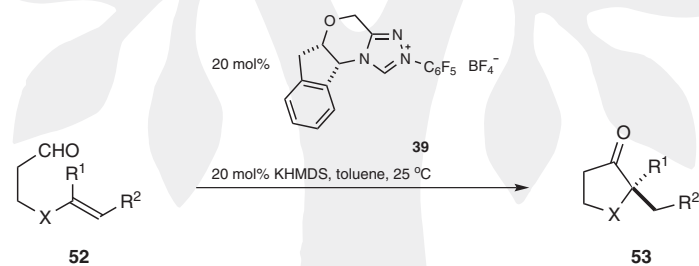
Catalysis by chiral triazolylidene carbenes also allows the highly stereoselective formation of quaternary stereocenters in the Stetter reaction. Treatment of aromatic aldehydes **50** (Scheme 14) or aliphatic aldehydes **52** (Scheme 15) containing β -substitution on the Michael acceptor with the triazolium salt **39** and base yields the corresponding ketone products (**51** and **53**, respectively) in high yields and with excellent enantioselectivities.^[32] A variety of heteroatom linkers, Michael acceptors, and substitutions are tolerated; however, the method is mainly limited to the formation of five-membered rings.

Scheme 14 Formation of Quaternary Stereocenters by Asymmetric Intramolecular Stetter Reactions of Aromatic Aldehydes^[32]

| R ¹ | R ² | X | Base | ee ^a (%) | Yield ^b (%) | Ref |
|------------------------------------|--------------------|-----------------|-------------------|---------------------|------------------------|------|
| Et | CO ₂ Me | O | Et ₃ N | 97 | 96 | [32] |
| Et | CO ₂ Me | S | <i>t</i> -BuOK | 97 | 90 | [32] |
| Pr | CO ₂ Me | S | <i>t</i> -BuOK | 98 | 83 | [32] |
| (CH ₂) ₂ Ph | CO ₂ Me | S | <i>t</i> -BuOK | 99 | 91 | [32] |
| Ph | CO ₂ Me | S | <i>t</i> -BuOK | 82 | 15 | [32] |
| Me | CO ₂ Et | CH ₂ | Et ₃ N | 99 | 95 | [32] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

Scheme 15 Formation of Quaternary Stereocenters by Asymmetric Intramolecular Stetter Reactions of Aliphatic Aldehydes^[32]

| R ¹ | R ² | X | ee ^a (%) | Yield ^b (%) | Ref |
|----------------|--------------------|-----------------|---------------------|------------------------|------|
| Pr | CO ₂ Me | S | – | 0 | [32] |
| Pr | CO ₂ Me | SO ₂ | 80 | 98 | [32] |
| Me | Ac | NAc | 95 | 65 | [32] |
| Me | | CH ₂ | 96 | 85 | [32] |
| Me | | CH ₂ | 84 | 90 | [32] |
| Me | Ac | CH ₂ | 95 | 81 | [32] |

for references see p 28

| R ¹ | R ² | X | ee ^a (%) | Yield ^b (%) | Ref |
|----------------|----------------|-----------------|---------------------|------------------------|------|
| Me | | CH ₂ | 99 | 63 | [32] |
| Bu | Bz | CH ₂ | 98 | 71 | [32] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

Indan-3-ones/Benzo[b]furan-3-ones/Benzo[b]thiophen-3-one 1,1-Dioxides 51;

General Procedure:^[32]

A flame-dried, round-bottomed flask was charged with triazolium salt **39** (0.02 mmol), evacuated for 5 min, and then filled with argon. Substrate **50** (0.1 mmol) in toluene (1 mL) was added via syringe, followed by the addition of *t*-BuOK (0.02 mmol), and the soln was stirred at ambient temperature under argon for 24 h. The mixture was then poured onto a column (silica gel) and eluted (EtOAc/hexanes) to afford analytically pure product.

Cyclopentanones/Pyrrolidin-3-ones/Dihydrothiophen-3-one Dioxides 53;

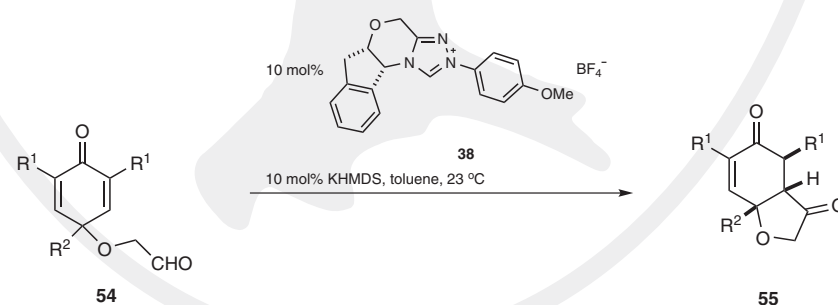
General Procedure:^[32]

A flame-dried, round-bottomed flask was charged with triazolium salt **39** (0.02 mmol) and toluene (1 mL) under argon. To this soln was added 0.5 M KHMDS in toluene (0.02 mmol) via syringe, and the soln was stirred at ambient temperature for 5 min. Substrate **52** (0.1 mmol) in toluene (1 mL) was added via syringe and the mixture was allowed to stir for 24 h at ambient temperature. The mixture was then poured onto a column (silica gel) and eluted (EtOAc/hexanes) to afford analytically pure product.

2.17.3.4 Desymmetrization of Cyclohexadienones

Cyclohexadienones are suitable substrates for asymmetric desymmetrization using the intramolecular Stetter reaction. Treatment of cyclohexadienones **54** containing a pendant aldehyde with triazolium salt **38** yields dihydrobenzofuran-3,5-dione products **55** in high yield and excellent enantioselectivity (Scheme 16).^[33] A variety of substitution patterns are tolerated, leading to a wide range of dihydrobenzofuran-3,5-dione products.

Scheme 16 Catalytic Asymmetric Desymmetrization of Cyclohexadienones^[33]



| R ¹ | R ² | ee ^a (%) | Yield ^b (%) | Ref |
|----------------|----------------|---------------------|------------------------|------|
| H | Me | 92 | 90 | [33] |
| H | Et | 94 | 86 | [33] |
| H | iPr | 94 | 87 | [33] |

| R ¹ | R ² | ee ^a (%) | Yield ^b (%) | Ref |
|---------------------|--|---------------------|------------------------|------|
| H | <i>t</i> -Bu | 94 | 86 | [33] |
| H | 4-BrC ₆ H ₄ | 84 | 78 | [33] |
| H | CH ₂ OAc | 83 | 86 | [33] |
| H | (CH ₂) ₂ OMe | 82 | 86 | [33] |
| H | (CH ₂) ₂ CO ₂ Me | 87 | 94 | [33] |
| H | (CH ₂) ₂ NHBoc | 64 | 28 | [33] |
| Me | Me | >99 | 86 | [33] |
| CH ₂ OMe | Me | 99 | 71 | [33] |
| <i>t</i> -Bu | Me | >99 | 80 | [33] |
| <i>t</i> -Bu | <i>t</i> -Bu | >99 | 62 | [33] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

3a,7a-Dihydrobenzofuran-3,5(2*H*,4*H*)-diones 55; General Procedure:^[33]

A flame-dried, 25-mL, round-bottomed flask was charged with triazolium salt **38** (4.9 mg, 0.012 mmol). The flask was purged under vacuum for 5 min and then refilled with argon and toluene (12 mL). Argon was bubbled through the soln for 5 min, then 0.5 M KHMDS (24 μ L, 0.012 mmol) was added, and the soln was allowed to stir at ambient temperature for 15 min. The substrate **54** (0.12 mmol) was dissolved in toluene (3 mL) and then added via syringe, and the mixture was allowed to stir at ambient temperature. After the reaction was complete (monitored by TLC), usually in 5 min, the mixture was directly purified by flash column chromatography.

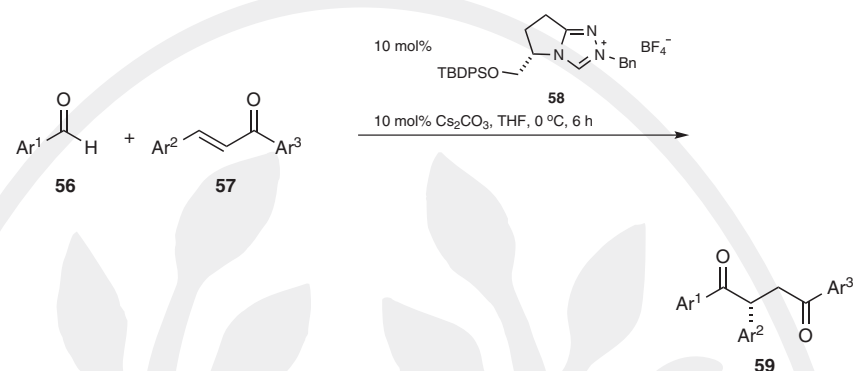
2.17.4 Asymmetric Intermolecular Stetter Reactions Catalyzed by *N*-Heterocyclic Carbenes

The asymmetric intermolecular Stetter reaction has only recently, with the development of chiral triazolium salt catalyst precursors, become a synthetically useful method. Although the intermolecular version has its limitations, a variety of aldehydes and Michael acceptors can be coupled to give ketone products in good yields and good enantioselectivities. The intermolecular reaction has the ability to expand the scope dramatically by not limiting the substrates to tethered Michael acceptors.

2.17.4.1 Reactions of Aryl Aldehydes with 1,3-Diarylprop-2-en-1-ones

Aryl aldehydes **56** may be coupled with 1,3-diarylprop-2-en-1-ones **57** (chalcones) utilizing chiral triazolium salt **58** to afford the corresponding α -aryl ketones **59** in good yields and moderate enantioselectivity (Scheme 17).^[34] These products may be recrystallized to enantioselectivities greater than 99% at the expense of yield.

for references see p 28

Scheme 17 Catalytic Asymmetric Intermolecular Stetter Reaction of Aryl Aldehydes with 1,3-Diarylprop-2-en-1-ones^[34]

| Ar ¹ | Ar ² | Ar ³ | ee ^a (%) | Yield ^b (%) | Ref |
|-----------------------------------|-----------------------------------|-----------------|-----------------------|------------------------|------|
| Ph | Ph | Ph | 66 (>99) ^c | 65 (40) ^c | [34] |
| 4-Tol | Ph | Ph | 78 (>99) ^c | 43 (31) ^c | [34] |
| 3-Tol | Ph | Ph | 70 (98) ^c | 50 (32) ^c | [34] |
| 4-ClC ₆ H ₄ | Ph | Ph | 67 | 55 | [34] |
| 4-BrC ₆ H ₄ | Ph | Ph | 56 | 68 | [34] |
| 2-naphthyl | Ph | Ph | 70 (90) ^c | 65 (41) ^c | [34] |
| 2-furyl | Ph | Ph | 56 | 98 | [34] |
| Ph | 4-Tol | Ph | 64 | 55 | [34] |
| Ph | 4-ClC ₆ H ₄ | Ph | 56 (94) ^c | 57 (21) ^c | [34] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

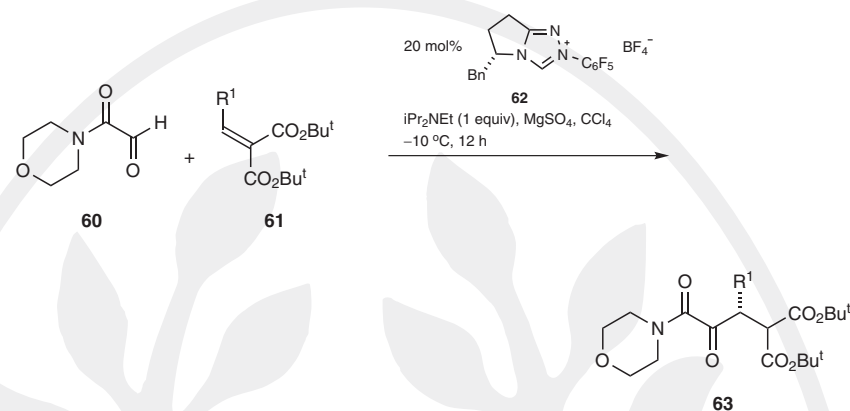
^c Results in parentheses are those obtained after recrystallization.

(R)-1,2,4-Triphenylbutane-1,4-dione (59, Ar¹ = Ar² = Ar³ = Ph); Typical Procedure:^[34]

In a dry, argon-flushed Schlenk tube the precatalyst **58** (27 mg, 0.05 mmol), anhyd Cs₂CO₃ (16 mg, 0.05 mmol), and 1,3-diphenylprop-2-en-1-one (**57**, Ar² = Ar³ = Ph; 104 mg, 0.5 mmol) were dissolved in abs THF (1 mL). The mixture was cooled to 0 °C and then benzaldehyde (**56**, Ar¹ = Ph; 64 mg, 0.60 mmol) was added dropwise. After stirring for 8 h, the mixture was directly purified by flash chromatography (silica gel, pentane/Et₂O 9:1) to give a colorless solid; yield: 102 mg (65%). Recrystallization (Et₂O) afforded the enantiomerically pure product as colorless needles; yield: 62 mg (40%); >99% ee.

2.17.4.2 Reactions of Glyoxamides with Alkylidenemalonates

Morpholine-based glyoxamides (e.g. **60**) can be coupled with alkylidenemalonates **61** using chiral triazolium salt **62** to give the α-oxo amides **63** in good yield and high enantioselectivity (Scheme 18).^[35] The aldehyde is limited to the glyoxamide functional group; however, the scope of the alkylidenemalonate is quite broad. Primary and secondary alkyl substitution is tolerated as well as a variety of pendant functional groups.

Scheme 18 Catalytic Asymmetric Intermolecular Stetter Reaction of a Glyoxamide with Alkylidenemalonates^[35]

| R ¹ | ee ^a (%) | Yield ^b (%) | Ref |
|--|---------------------|------------------------|------|
| Me | 87 | 68 | [35] |
| Et | 90 | 84 | [35] |
| Pr | 90 | 83 | [35] |
| Bu | 90 | 70 | [35] |
| (CH ₂) ₂ Ph | 88 | 81 | [35] |
| iBu | 91 | 51 | [35] |
| (CH ₂) ₂ OBn | 80 | 91 | [35] |
| (CH ₂) ₃ Cl | 81 | 84 | [35] |
| | 84 | 88 | [35] |
| (CH ₂) ₂ CH=CH ₂ | 89 | 97 | [35] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

(R)-Di-tert-butyl 2-(1-Morpholino-1,2-dioxohexan-3-yl)malonate (63, R¹ = Pr);

Typical Procedure:^[35]

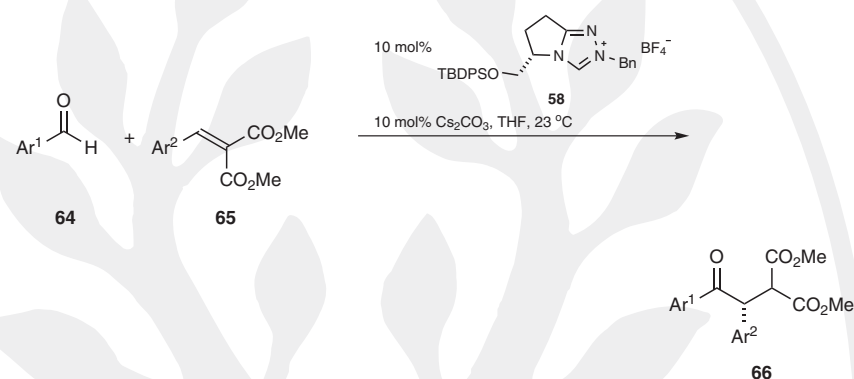
A flame-dried, 5-mL test tube was charged with triazolium salt **62** (14.5 mg, 0.032 mmol), Michael acceptor **61** (R¹ = Pr; 82 mg, 0.32 mmol), and MgSO_4 (20 mg, 0.16 mmol). The test tube was purged under vacuum and then refilled with argon (3 ×). Glyoxamide **60** (23 mg, 0.16 mmol) was then added followed by redistilled CCl_4 (0.5 mL) (**CAUTION: toxic**). The test tube was placed in a -12°C bath (temperature of reaction in test tube was -10°C) and $i\text{Pr}_2\text{NEt}$ (28 μL , 0.16 mmol) was added dropwise to the mixture. The mixture was allowed to stir at -10°C for 12 h, and then quenched with AcOH (0.1 mL) and directly purified by flash column chromatography (EtOAc/hexane 1:2); yield: 83%; 90% ee.

for references see p 28

2.17.4.3 Reactions of Hetaryl Aldehydes with Arylmethylenemalonates

Hetaryl aldehydes **64** undergo smooth addition to arylmethylenemalonates **65** in the presence of chiral triazolium salt **58** (Scheme 19).^[36] This method yields the corresponding ketones **66** in high yield and moderate enantioselectivity. The products can be recrystallized to enantioselectivities of >90%. This method is limited to the use of furfural and electron-deficient arylmethylenemalonates.

Scheme 19 Catalytic Asymmetric Intermolecular Stetter Reaction of Hetaryl Aldehydes with Arylmethylenemalonates^[36]



| Ar ¹ | Ar ² | ee ^a (%) | Yield ^b (%) | Ref |
|-----------------|-----------------------------------|----------------------|------------------------|------|
| 2-furyl | Ph | 78 (99) ^c | 90 (53) ^c | [36] |
| 2-furyl | 4-ClC ₆ H ₄ | 62 (95) ^c | 92 (50) ^c | [36] |
| 2-furyl | 3-ClC ₆ H ₄ | 68 (94) ^c | 85 (45) ^c | [36] |
| 2-furyl | 4-BrC ₆ H ₄ | 70 (99) ^c | 88 (42) ^c | [36] |
| 2-furyl | 4-Tol | 72 (90) ^c | 84 (60) ^c | [36] |
| 2-pyridyl | Ph | 30 | 94 | [36] |
| 2-furyl | 2-pyridyl | 40 | 98 | [36] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

^c Results in parentheses are those obtained after recrystallization.

(R)-Dimethyl 2-[2-(2-Furyl)-2-oxo-1-phenylethyl]malonate (66, Ar¹ = 2-Furyl; Ar² = Ph);

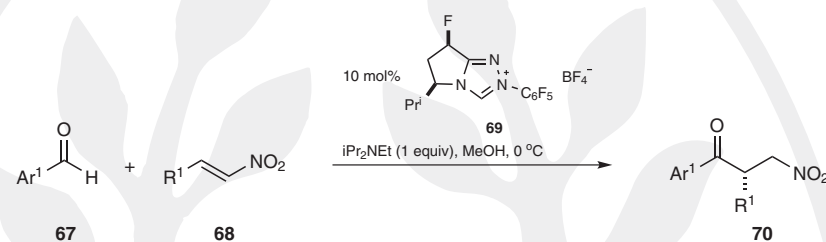
Typical Procedure:^[36]

A dry, argon-flushed Schlenk tube was charged with precatalyst **58** (27 mg, 0.05 mmol, 10 mol%), anhyd Cs₂CO₃ (16 mg, 0.05 mmol), and malonate **65** (Ar² = Ph; 110 mg, 0.5 mmol). After the addition of abs THF (1 mL) at rt, 2-furaldehyde (**64**, Ar¹ = 2-furyl; 58 mg, 0.6 mmol) was added, and the mixture was stirred for 6 h. The solvent was evaporated and the residue was directly purified by flash chromatography (silica gel, pentane/Et₂O 2:1) to give a colorless solid; yield: 127 mg (90%). Recrystallization (Et₂O) afforded a flocky, colorless solid; yield: 75 mg (53%); 99% ee.

2.17.4.4 Reactions of Hetaryl Aldehydes with Nitroalkenes

Hetaryl aldehydes **67** can be coupled with alkyl-substituted nitroalkenes **68** in the presence of chiral triazolium salt **69** to give the corresponding β -nitro ketones **70** in high yield and high enantioselectivity (Scheme 20).^[37] A variety of hetaryl aldehydes are tolerated as well as primary and secondary alkyl substitution on the nitroalkene.

Scheme 20 Catalytic Asymmetric Intermolecular Stetter Reaction of Hetaryl Aldehydes with Nitroalkenes^[37]



| Ar ¹ | R ¹ | ee ^a (%) | Yield ^b (%) | Ref |
|-----------------|----------------|---------------------|------------------------|------|
| 2-pyridyl | Cy | 95 | 95 | [37] |
| | Cy | 96 | 99 | [37] |
| | Cy | 94 | 88 | [37] |
| | Cy | 96 | 70 | [37] |
| 2-furyl | Cy | 87 | 75 | [37] |
| | Cy | 86 | 76 | [37] |
| 2-pyridyl | cyclopentyl | 90 | 98 | [37] |
| 2-pyridyl | cyclopropyl | 87 | 72 | [37] |
| 2-pyridyl | iPr | 95 | 85 | [37] |
| 2-pyridyl | iBu | 83 | 99 | [37] |
| 2-pyridyl | Pr | 83 | 82 | [37] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

2-Alkyl-1-aryl-3-nitropropan-1-ones 70; General Procedure:^[37]

To a dry 4-mL vial, with a magnetic stirrer bar, was added triazolium salt **69** (16 mg, 0.037 mmol), aldehyde **67** (0.371 mmol), nitroalkene **68** (0.556 mmol), and MeOH (1 mL). The vial was then cooled to 0 °C in an ice-water bath with stirring. *i*Pr₂NEt (64 μ L, 0.37 mmol) was added dropwise and the mixture was stirred at 0 °C for 2 h. AcOH

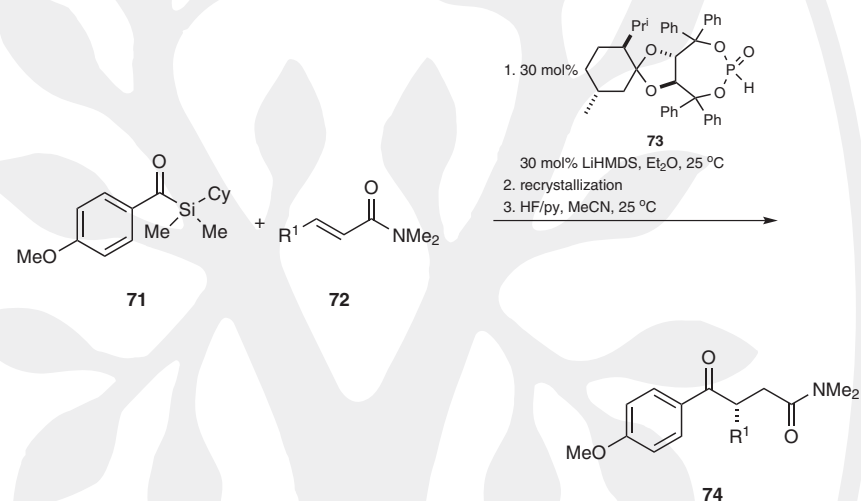
for references see p 28

(0.1 mL) was then added to quench the reaction and the mixture was concentrated under reduced pressure. Column chromatography (hexanes/Et₂O) of the resulting dark red residue gave the desired nitro ketone.

2.17.5 Asymmetric Intermolecular Acylation of α,β -Unsaturated Amides Catalyzed by Metallophosphites

In a transformation related to the Stetter reaction, α,β -unsaturated amides **72** can be acylated asymmetrically with acylsilane **71** in the presence of a chiral metallophosphite generated from phosphite **73** (Scheme 21).^[38] A variety of aryl and alkyl substituted α,β -unsaturated amides participate in this reaction to give a range of products **74**. The scope of the acylsilane is more limited, with only one example reported.

Scheme 21 Asymmetric Intermolecular Acylation of α,β -Unsaturated Amides Catalyzed by Metallophosphites^[38]



| R ¹ | ee ^a (%) | Yield ^b (%) | Ref |
|---|----------------------|------------------------|------|
| Ph | 90 (99) ^c | 68 | [38] |
| 4-MeOC ₆ H ₄ | 92 | 63 | [38] |
| 4-Tol | 90 | 78 | [38] |
| 3-Tol | 93 (99) ^c | 67 | [38] |
| 2-furyl | 24 | 15 | [38] |
| 4-ClC ₆ H ₄ | 95 (98) ^c | 66 | [38] |
| | 97 | 60 | [38] |
| 4-CF ₃ C ₆ H ₄ | 90 | 80 | [38] |

| R ¹ | ee ^a (%) | Yield ^b (%) | Ref |
|----------------|----------------------|------------------------|------|
| 2-naphthyl | 89 (97) ^c | 66 | [38] |
| Me | 86 | 56 | [38] |
| Et | 71 | 82 | [38] |

^a Determined by HPLC analysis using a chiral stationary phase.

^b Isolated yields after chromatography.

^c Results in parentheses are those obtained after recrystallization.

3-Substituted 4-(4-Methoxyphenyl)-4-oxoamides **74**; General Procedure:^[38]

In a glovebox, acylsilane **71** (0.42 mmol) was added to a dry, 20-mL scintillation vial, while phosphite **73** (0.083 mmol), LiHMDS (0.083 mmol), and amide **72** (0.63 mmol) were added to a second dry, 20-mL scintillation vial. Et₂O (4 mL) was added to the metallophosphite mixture to dissolve the contents of the vial completely. Et₂O (2 mL) was added to the acylsilane, and both vials were placed in the freezer at -35 °C. After 0.5 h, the vials were removed from the freezer and the acylsilane soln was added to the metallophosphite mixture slowly (1 drop · s⁻¹) via pipet and allowed to warm to rt. After the starting material had been consumed (TLC analysis), the solvent was removed under reduced pressure. The silylated intermediate was passed through a silica gel plug using EtOAc/hexanes (2:3), and concentrated. The product was transferred to a plastic vial containing a stirrer bar and was dissolved in MeCN (16 mL). HF/pyridine (3.4 mL) was added and the mixture was stirred. After the silylated material had been consumed (TLC analysis), the reaction was quenched with sat. aq Na₂CO₃, and CH₂Cl₂ was added to give a biphasic mixture. The organic layer was washed with H₂O (2 × 10 mL) and the combined aqueous washes were back-extracted with CH₂Cl₂ (2 × 10 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes 1:1).

for references see p 28

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