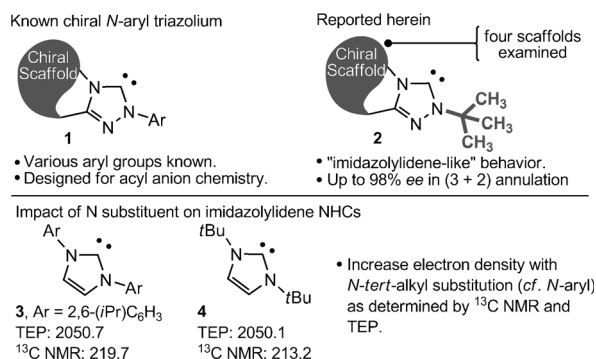


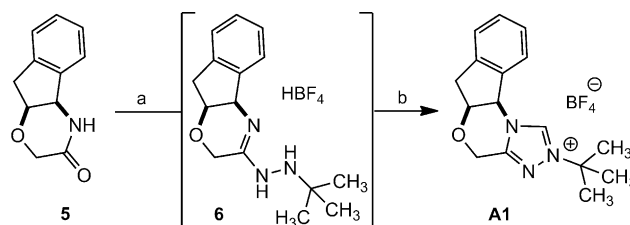
N-tert-Butyl Triazolyldienes: Catalysts for the Enantioselective (3+2) Annulation of α,β -Unsaturated Acyl Azoliums**

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In 1996 the triazolyldiene-catalyzed benzoin reaction was reported by Enders et al.^[1] Following this seminal report triazolyldienes (i.e. **1**) have emerged as the N-heterocyclic carbene (NHC) organocatalyst of choice in many contexts.^[2] In 2008 we began studies on NHC catalysis using substrates at the ester oxidation state.^[3] Pivotal to the success of these studies was the use of electron-rich imidazolyldiene NHCs (i.e., **3** or **4**), with triazolyldienes generally proving unsatisfactory. Partly as a consequence of this limitation, enantioselective variants of these reactions have been difficult to realize.^[3a] To address this, access to chiral triazolyldiene NHCs, with imidazolyldiene-like reactivity was deemed valuable.



The electronic nature of the triazolyldiene can be modulated, to enhance reactivity and/or selectivity, through selection of the N substituents.^[4–6] In this context N-aryl^[4] and N-benzyl^[5] groups have been studied. Surprisingly, tertiary or secondary alkyl N-substituted triazolyldiene NHCs have yet to be examined in enantioselective catalysis, even though these groups significantly increase the electron density of NHCs (for example see: **3** versus **4**).^[6] Herein we introduce electron-rich homochiral N-tert-butyl triazolyldiene catalysts



Scheme 1. a) (CH₃)₃OBF₄, CH₂Cl₂, 12 h, then tBuNHNH₂, 16 h; b) HC(OEt)₃, PhCl, 120 °C, 12 h. Yield 37% (two steps).

(**2**), which have enabled the development of an enantioselective all carbon (3+2) annulation.

Studies commenced with the synthesis of the N-tert-butyl variant of the Rovis triazolium precatalyst, namely **A1** (Scheme 1). This triazolium was prepared using methods originally reported by Knight and Leeper, and later modified by others.^[7] Although **A1** was accessible in this way, other N-tert-butyl triazolium tetrafluoroborates prepared for this study were generally synthesized as the HCl salt,^[4d,7] then converted into the tetrafluoroborate (see the Supporting Information).

With **A1** in hand its utility was examined in the enantioselective (3+2) annulation between donor-acceptor cyclopropane ($\pm$)-**7a** and α,β -unsaturated acyl fluoride **8a** (Table 1). This reaction proceeds with high yield and diastereoselectivity, although it is yet to be achieved with enantioselectivity.^[3e] Using previously reported reaction conditions, and the known N-aryl triazolyldienes **A2**, **A3**, or **A4** the reaction failed (Table 1, entries 1–3), however **A1** afforded the desired cyclopentyl β -lactone **9aa** in 8% yield (Table 1, entries 4). Unfortunately, because of the low yield and purity of the product, it was not possible to determine the enantioselectivity.

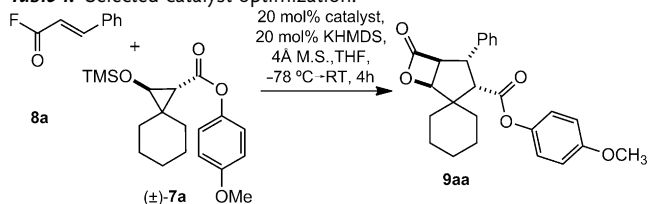
To improve conversion, less sterically hindered pyrrolidine-derived triazolium catalysts **B1–B4** were prepared.^[8] With both **B1** and **B2**, cyclopentane **9aa** formed with moderate enantioselectivity (50% and 63% ee) and yield (Table 1, entries 5 and 6). When using the more hindered bis(tert-butyl) catalyst **B3**, or the tert-butyl variant of the pyrrolidine catalyst^[9] (**B4**), the reaction failed (Table 1, entries 7 and 8). Attention was next directed to the morpholine-derived triazolium^[10] **C1**. It was hoped that this catalyst would display the advantageous features of **B2**, but enhance the enantioselectivity through conformational restriction of the benzyl group. This proved to be the case with cyclopentyl β -lactone **9aa** formed as a single diastereoisomer in 88% ee and 75% yield (Table 1, entry 9). Finally, reducing the catalyst loading to 10 mol % of **C1** had little effect on the yield, but

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Table 1: Selected catalyst optimization.



Entry	Catalyst	^{13}C NMR δ [ppm] ^[a]	Yield [%] ^[b]	<i>ee</i> ^[c]
1	A2 , R = C ₆ F ₅	—	no reaction	—
2	A3 , R = Mes	—	no reaction	—
3	A4 , R = Ph	—	no reaction	—
4	A1 , R = <i>t</i> Bu	—	8	n.d.
5	B1 , R = <i>i</i> Pr	—	51	50
6	B2 , R = Bn	—	40	63
7	B3 , R = <i>t</i> Bu	—	no reaction	—
8	B4 , R = C(OH)Ph ₂	—	no reaction	—
9	C1 , R = <i>t</i> Bu	206.9	75	88
10 ^[d]	C1 , R = <i>t</i> Bu	206.9	72	90
11	C2 , R = <i>i</i> Pr	207.0	23	69
12	C3 , R = 4-CH ₃ OC ₆ H ₄	209.3	53	79
13	C4 , R = Ph	211.0	26	77
14	C5 , R = Mes	212.8	18	67
15	C6 , R = 2,6-(CH ₃ O) ₂ C ₆ H ₃	214.0	no reaction	—
16	C7 , R = C ₆ F ₅	217.4	no reaction	—

[a] ^{13}C NMR shift of the carbenic carbon atom (C5) in C₆D₆; see the Supporting Information. [b] Yield of the product isolated after flash column chromatography. [c] Determined by HPLC using Daicel AD-H stationary phases. [d] Reaction performed with both 10 mol% **C1** and KHMDS. n.d. = not determined. M.S. = molecular sieves, KHMDS = potassium hexamethyldisilazide, THF = tetrahydrofuran, TMS = trimethylsilyl.

cyclopentane **9aa** was isolated with 90% *ee* (Table 1, entry 10).

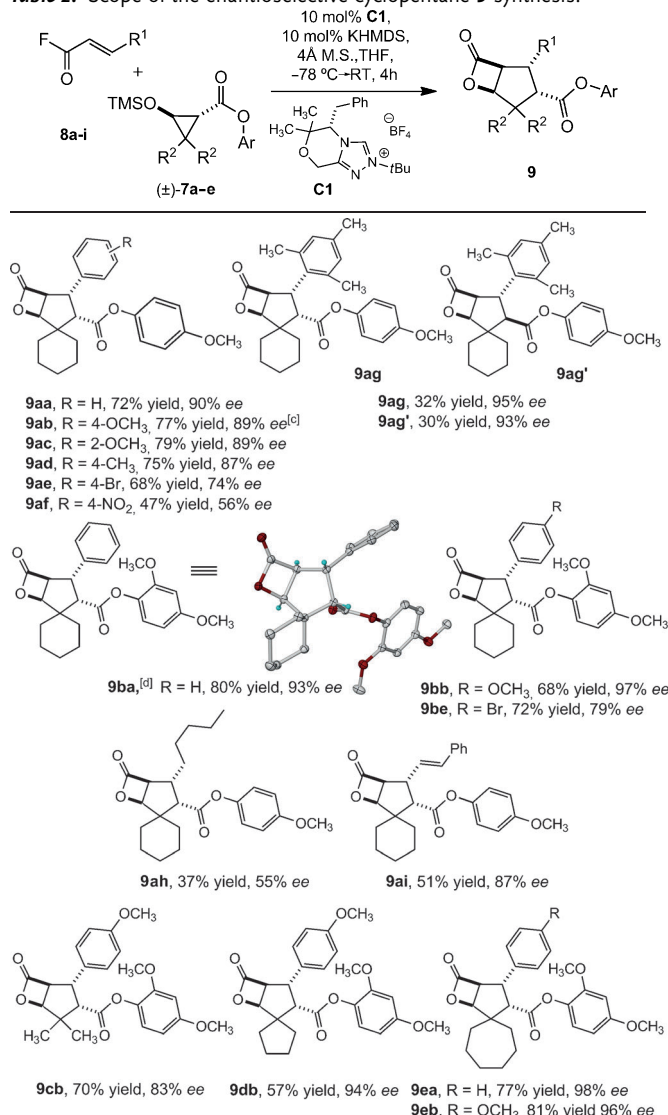
To examine in more detail the impact of catalyst electronics on the reaction, seven triazoliums (**C1–C7**) were prepared using this chiral scaffold by varying the N substituent. In addition to assessing their utility in the synthesis of cyclopentane **9aa** the ^{13}C NMR spectrum of the free carbene was determined to provide a measure of electron density at the carbenic carbon atom.^[11] ^{13}C NMR analyses of the NHCs derived from **C1–C7** indicate that the *tert*-butyl NHC (Table 1, entry 9) is most electron rich, followed by *i*Pr (Table 1, entry 11) and then the aryl NHCs ranging from *p*-CH₃OC₆H₄ through to C₆F₅ (Table 1, entries 12–16). The *ortho*-disubstituted NHCs (Table 1, entries 14 and 15) are less

electron rich than might be expected, a situation arising as a consequence of a twisted arrangement between the triazolylidene and the *N*-aryl group. In terms of catalytic activity the least electron-rich NHCs were inactive (Table 1, entries 15 and 16) or moderately active (Table 1, entries 13 and 14), whereas the more-electron-rich *N*-alkyl and aryl catalysts (**C1–C3**) gave the expected cyclopentane **9aa** in reasonable yields (Table 1, entries 9–12). When the yield is modest the product is accompanied by ring-opened cyclopropane,^[12] presumably its formation is kinetically viable as the desired reaction slows. While catalysts **C2–C5** achieved similar enantioinduction (67–79% *ee*), the most sterically encumbered^[13] and electron-rich catalyst **C1** gave the highest enantioselectivity (Table 1, entry 10). Although a qualitative connection between NHC electronics and reaction outcome has been established, quantitative studies are ongoing.

The scope of the reaction was initially examined with the annulation of a series of cinnamoyl fluorides **8a–i** with cyclopropane ($\pm$)-**7a** (Table 2). While electron-rich *ortho*- or *para*-substituted cinnamoyls routinely gave high enantioselectivity (**9ab**, **ac**, **ad**), electron-poor substrates resulted in decreased enantioselectivity (**9ae**, **af**). The reaction was sensitive to *ortho*-disubstitution, with the mesityl cinnamoyl fluoride **8g**, providing the expected product **9ag** along with the diastereomeric **9ag'**, both with excellent enantioselectivity.^[14] The electronic nature of the aryl ester has an impact on enantioselectivity, thus the 2,6-dimethoxy phenol cyclopropane ($\pm$)-**7b** derived products are more enantioenriched than ($\pm$)-**7a**-derived products, with **9ba** forming in 93% *ee* (**9aa**; 90% *ee*), **9bb** forming in 97% *ee* (**9ab**; 89% *ee*), and **9be** with 79% *ee* (**9ae**; 74% *ee*). In the case of **9ba** single-crystal X-ray analysis was used to determine the absolute configuration of the cyclopentanes.^[15] The reaction tolerated β -alkyl α,β -unsaturated acyl fluorides, however both yield and enantioselectivity were eroded (**9ah**; Table 2). In contrast $\alpha,\beta,\gamma,\delta$ -unsaturated acyl fluorides reacted smoothly and with high enantioselectivity to provide styrenyl cyclopentane **9ai** with 87% *ee*. Finally variation in the cyclopropane was investigated, providing dimethyl cyclopentane **9cb** (83% *ee*), bicyclopentane **9db** (94% *ee*), and cycloheptane-containing **9ea** and **9eb** (98% *ee* and 96% *ee*) smoothly.

Derivatization of the β -lactone-containing products was investigated under a number of reaction conditions. Partial reduction of **9aa** using LiAlH₄ provided diol **10** (Scheme 2). Ring opening with alcohols proved to be more challenging, and led to mixtures of products, except when the reaction was performed in the presence of NaBH₄. Finally ring opening with benzyl amine gave amide ester **12** in 93% yield. In all cases the enantiopurity was maintained.

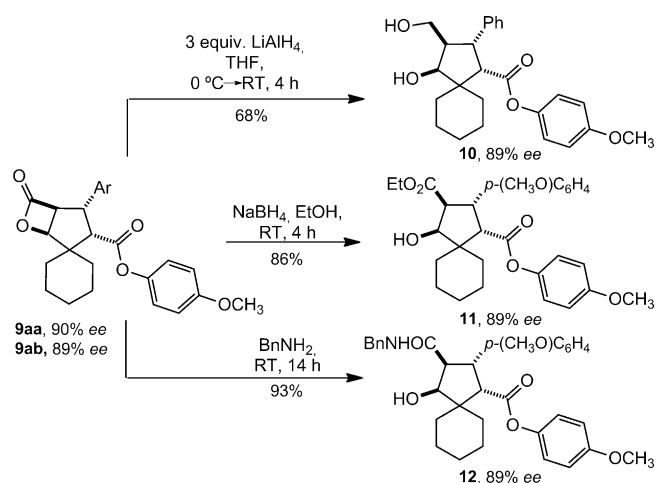
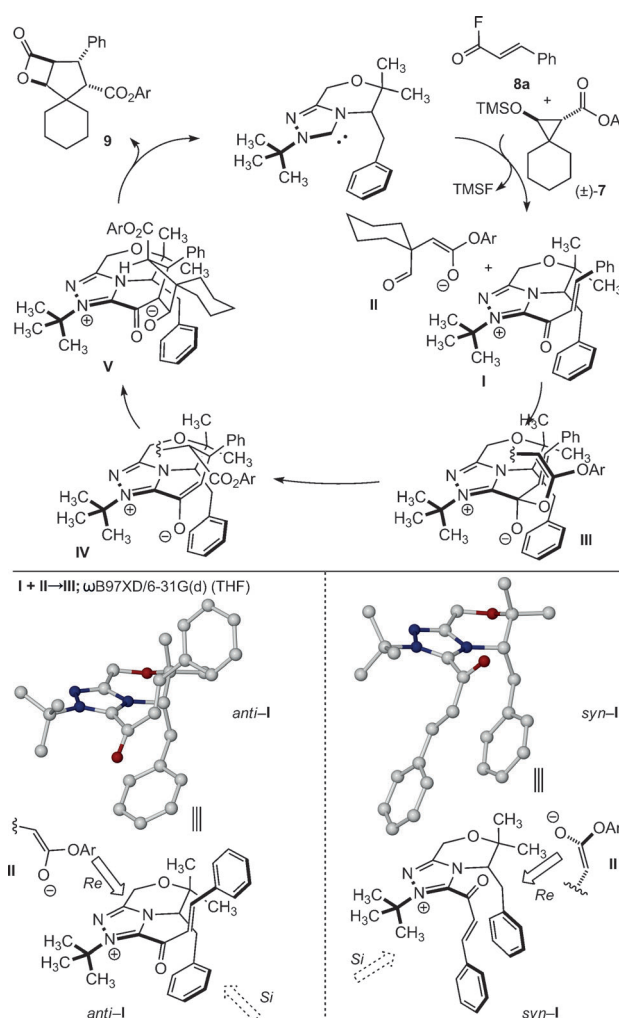
Mechanistically, the reaction likely commences with formation of the α,β -unsaturated acyl azolium **I** and ester enolate **II** from acyl fluoride **8** and cyclopropane ($\pm$)-**7** (Scheme 3).^[16] The union of **I** and **II** then occurs either via 1,2 adduct **III** with subsequent ester enolate Claisen rearrangement to afford **IV**, a process resembling pathways proposed by Bode and co-workers.^[17] Or alternatively a diastereoselective and enantioselective Michael addition allows the direct conversion of **I** and **II** into **IV**. The latter pathway is preferred by Studer, Mayr and co-workers,^[18] while computational

Table 2: Scope of the enantioselective cyclopentane **9** synthesis.^[a,b]


[a] Yield of product isolated after flash column chromatography. [b] The ee value was determined by HPLC analysis using AD-H or OD-H stationary phases. [c] Enantiomeric excess determined by analysis of diester **11**. [d] For X-ray data^[15].

studies by Schoenebeck and co-workers highlight challenges discriminating between these mechanisms.^[19] After formation of **IV**, rotation and aldol cyclization provides the cyclopentyl alkoxide **V**, which undergoes β -lactonization to provide the cyclopentane **9** and regenerate the catalyst. Modeling of azolium **I** indicates that the carbonyl group is rotated out of conjugation with the azolium, with two low-energy rotamers, *anti-I* and *syn-I*, identified with very similar energies.^[20] In both, the *Re* face appears more open than the *Si* face, thus allowing enolate approach which ultimately provides the stereochemistry observed in cyclopentane **9aa**.

NHC catalysis has grown into a vibrant and diverse aspect of organocatalysis. This growth has been achieved using a small family of chiral catalysts which display exquisite flexibility. In this report *N-tert*-butyl triazolyldiene catalysts, which combine the chiral environments of known triazolyli-


Scheme 2. Derivatization of cyclopentanes **9aa** and **9ab**.

Scheme 3. Plausible mechanism and computational modeling.

denes, with the electron-rich behavior of imidazolyldiene NHCs, are introduced. Through ¹³C NMR analysis it is clear that the electronics of the catalyst play a significant role in their success. We believe that these electron-rich triazolyli-

dene NHCs will be useful for a range of NHC-catalyzed reactions which are poorly suited to conventional triazolylidene catalysts.

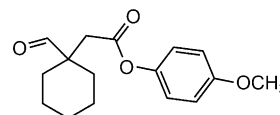
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13

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