NHC Catalysis

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Enantioselective N-Heterocyclic Carbene Catalysis by the Umpolung of α,β-Unsaturated Ketones

*Yuji Nakano and David W. Lupton**

Abstract: *N-Heterocyclic carbene-catalyzed formation of β-anionic intermediates from enones has been employed in the enantioselective synthesis of 2-aryl propionates. The reaction was achievable using a homochiral 4-MeOC$_6$H$_4$ morpholinone catalyst allowing the first example of enantioselective catalysis by umpolung of α,β-unsaturated ketones. The reaction is high yielding, and shows robustness with reasonable generality. A mechanism is proposed in which the enantiodetermining protonation is achieved using either hexafluoroisopropanol or the formed naphthol product.*

Central to many N-heterocyclic carbene (NHC)-catalyzed[1] reactions are the homoenolate (**1**)[2] or α,β-unsaturated acyl azolium (**2**; Figure 1).[3] These form through initial 1,2-addition to an α,β-unsaturated carbonyl, and have allowed a wealth of chemical transformations to be discovered. In contrast, β-azolium ylide **3**, a species afforded through 1,4-addition to α,β-unsaturated carbonyls followed by tautomerization,[4] as reported by Fu in 2006,[5] has been largely overlooked in synthesis. While many nucleophilic catalysts undergo 1,4-addition to conjugate acceptors, this usually triggers reactions by the resultant enolate (**4**).[6] Tautomerization to reveal a β-anion is rare and, to our knowledge, unique to NHC catalysis. Although β-anion **3** was introduced nearly a decade ago, its utility remains unclear with limited studies reported to date. Notably Matsuoka[7a,c–g] and Glorius[7b] have introduced tail-to-tail dimerization of enolates, while Chen has examined polymerization catalysis via intermediates **3** and **4**.[8] Presumably, the paucity of studies on this intermediate, compared to the plethora on the aforementioned intermediates **1** and **2**, is related to challenges in achieving reaction discovery without triggering reactions of enolate **4**, which are known with NHCs.[6a–d]

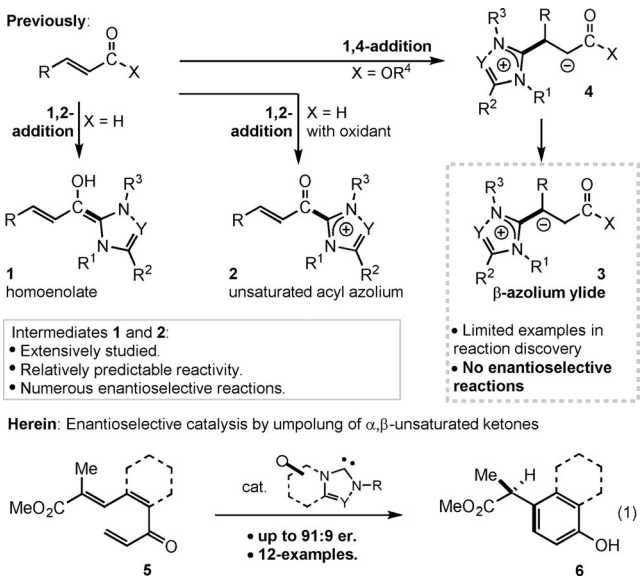

Figure 1. Overview of NHC reactions.

The underdeveloped chemistry of β-azolium ylide **3**, specifically as it relates to enantioselective catalysis, piqued our interest in this area. To this end, we envisaged a cycloisomerization of *bis*-conjugate acceptors (**5**) to 2-aryl propionates (**6**; Eq. 1) as a method to expand knowledge of these neglected intermediates. Herein, we report the outcome of these studies, which have allowed the discovery of the first enantioselective reaction involving the β-anion **3** intermediate. The reaction provides a method to access 2-aryl propionates in up to 91:9 e.r. and good yields. Mechanistic studies, and a discussion of unsuitable substrates, provides a picture of a reaction balanced between competing side reactions, and with sensitivity to alcohol-containing additives. In addition to providing information regarding β-anion **3**, the products contain the 2-aryl propionate motifs found extensively in non-steroidal anti-inflammatory drugs (NSAIDs).[9]

Studies commenced with the preparation of diene **5a** using procedures modified from Gravel.[10] When exposed to the Enders **TPT**[11] catalyst, we were pleased to isolate 2-aryl propionate **6a** in 92% yield (Table 1, entry 1). The discovery of an enantioselective variant proved significantly more challenging, and commenced with a survey of new and known chiral catalysts. Based on previous success with morpholinone-based NHCs,[12] a screen of six catalysts bearing various N-substituents was undertaken (Table 1, entries 2–7). This approach also reflected observations of Chen who found that polymerization of acrylate derivatives was sensitive to the nature of the azolium, and the N-substitution pattern.[8,13] In this case, N-*t*-butyl (**A1**) and N-C$_6$F$_5$ (**A2**) were not viable, while N-Mes (**A3**), N-Ph (**A4**), N-4-MeOC$_6$H$_4$ (**A5**), and N-2,6-(MeO)$_2$C$_6$H$_3$ (**A6**) all gave the expected product with moderate enantioselectivity. The highest selectivity of 74:26 e.r. was obtained with N-4-MeOC$_6$H$_4$ (**A5**). Both the yield and the enantioselectivity were depressed using alternate bases (Table 1, entries 8 and 9). The decrease with KHMDS was striking, and speaks to the role of the conjugate acid (hexamethyldisilazane) in the enantiodetermining protonation (see below). Introduction of

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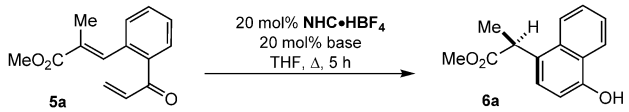
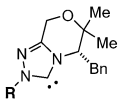
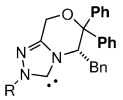
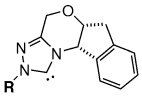
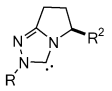
Table 1: Selected optimizations.



Entry	NHC	Base	Yield[a]	e.r.[b]
1[c]	**TPT**	KOtBu	92	–
				
2	**A1**, R = t-Bu	KOtBu	no rx	–
3	**A2**, R = C_6F_5	KOtBu	no rx	–
4	**A3**, R = Mes	KOtBu	65	31:69
5	**A4**, R = Ph	KOtBu	71	69:31
6	**A5**, *R* = 4-$MeOC_6H_4$	KOtBu	92	**74:26**
7	**A6**, *R* = 2,6-$MeO_2C_6H_3$	KOtBu	43	72:28
8	**A5**, *R* = 4-$MeOC_6H_4$	KHMDS	67	66:34
9	**A5**, *R* = 4-$MeOC_6H_4$	Cs_2CO_2	68	71:29
				
10	**B**, *R* = 4-$MeOC_6H_4$	KOtBu	no rx	–
				
11	**C1**, *R* = 4-$MeOC_6H_4$	KOtBu	48	74:26
12	**C2**, *R* = 2,6-$MeO_2C_6H_3$	KOtBu	–	–
13	**C3**, R = Ph	KOtBu	70	70:30
	 R = 4-$MeOC_6H_4$			
14	**D1**, R^2 = Bn	KOtBu	59	**76:24**
15	**D2**, R^2 = $CHPh_2$	KOtBu	69	68:32
16	**D3**, R^2 = C(OH)Ph_2	KOtBu	trace	–
	additive			
17	**A5** HFIP[d]	KOtBu	80	80:20
18[e,f]	**A5** HFIP[d]	KOtBu	80	**87:13**
19[c,f]	**A5** HFIP[d]	KOtBu	80	85:15

[a] Isolated yield following chromatography. [b] The e.r. was determined by HPLC with chiral stationary phases. [c] 10 mol% **TPT** or **A5·HBF$_4$** and base. [d] 1 equiv. [e] 30 mol% **A5·HBF$_4$** and base. [f] 40 °C.

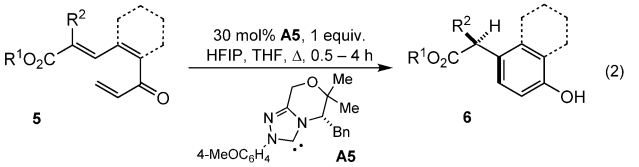
a diphenyl group in the morpholinone scaffold (**B**) caused the reaction to fail (Table 1, entry 10), while switching to the indanol NHCs (**C1–3**) with the three most promising N-substituents did not improve the enantioselectivity or yield (Table 1, entries 11–13). Pyrrolidinone NHCs **D1–3** were examined, with benzyl-substituted catalyst **D1** giving the product with improved enantioselectivity, but modest yield (Table 1, entry 14), while catalyst **D2** decreased selectivity, and **D3** failed to provide **6a** (Table 1, entries 15 and 16).

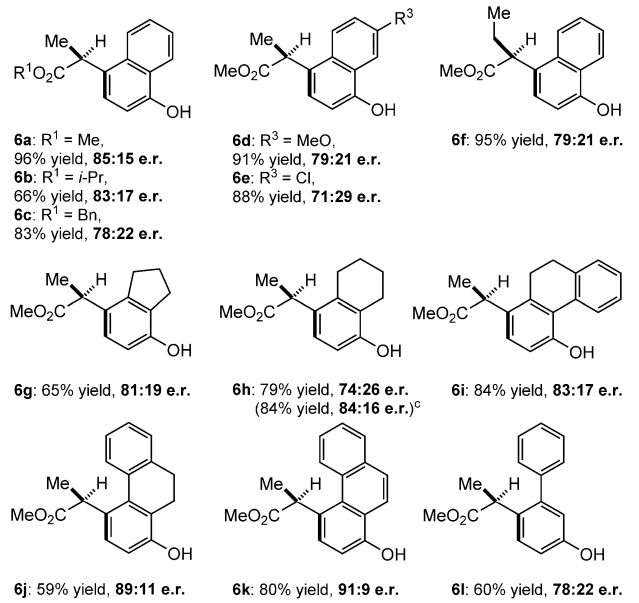
As detailed above the reaction showed significant sensitivity to proton sources. Thus, alcoholic additives were examined (results not shown),[14] with hexafluoroisopropanol (HFIP) found to give the greatest improvement in enantioselectivity (Table 1, compare entries 6 and 17).[14h] Further improvement to 87:13 e.r. was achieved by conducting the reaction at slightly lower temperatures and with 30 mol% **A5** (Table 1, entry 18). The reaction could also be achieved with similar levels of enantioselectivity using 10 mol% catalyst at 40 °C (Table 1, entry 19).

The generality of the reaction was examined initially by modifying the ester functionality (Table 2). Use of *i*-Pr and benzyl esters led to moderate decreases in enantioselectivity. Similarly, perturbing the electronics of the aryl scaffold with electron-releasing or -donating substituents decreased the enantioselectivity (MeO, 79:21 e.r.; Cl, 71:29 e.r.). Extending the alkyl side chain gave naphthol **6f** in 79:21 e.r., while the use of non-aryl tethers was tolerated with the cyclopentane derivative **6g** forming in good yield and 81:19 e.r., while the cyclohexyl variant **6h** formed in a 74:26 e.r. The latter result could be improved to 84:16 e.r. using naphthol **6a** as an additive rather than HFIP. Synthesis of partially saturated anthracenyl propionate **6i** was achieved in 83:17 e.r., while isomeric **6j** formed in 89:11 e.r. This could be improved to 91:9 e.r.[15] when preparing anthracene **6k**, while biaryl **6l** was formed with reasonable enantioselectivity and good yield.

While the reaction was robust with substrates in which the Michael acceptors were linked by annulation, the reaction was not possible when this functionality was removed. For

Table 2: Scope of the reaction.[a,b]





[a] Isolated yield following chromatography. [b] The e.r. was determined by HPLC with chiral stationary phases. [c] Without HFIP, with 1 equiv **6a**.

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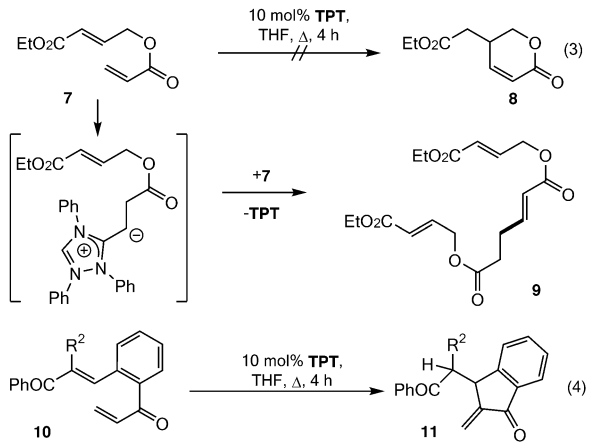
example bis-Michael acceptor **7**, rather than undergoing cyclization, provided dimer **9**, presumably through a reaction analogous to those of Glorius and Matsuoka (Scheme 1, eq. 3).[7] In addition, increasing the electrophilicity of the second Michael acceptor, as in ketone **10**, diverted the reaction, with the competing Rauhaut–Currier product **11** being formed (eq. 4).

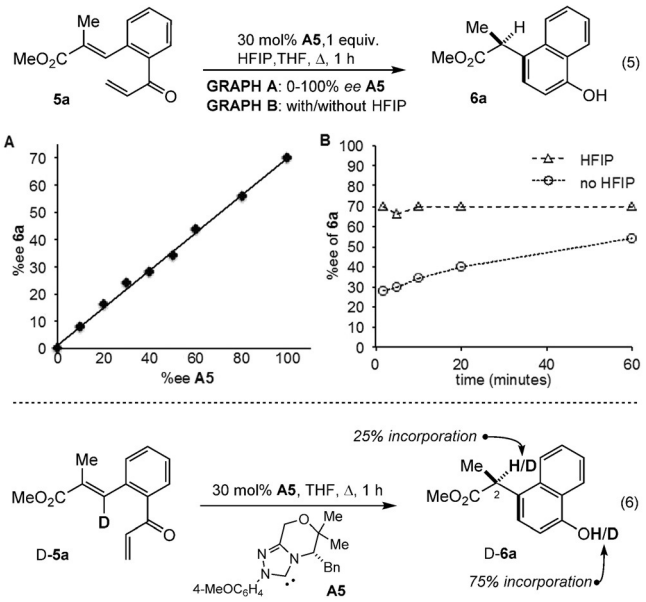
The sensitivity of the reaction to catalyst loading prompted an examination of non-linear effects (NLE). In this case, no NLE was observed (Scheme 2 A), implicating a single equivalent of catalyst **A5** in the enantiodetermining event. An alternate explanation for the sensitivity to catalyst loading would involve the phenolic product **6** participating in the enantiodetermining step, and thus the catalyst to substrate ratio would impact the enantioselectivity. Support for this scenario can be gleaned from the enhanced enantioselectivity (84:16 vs. 74:16 e.r.) observed in the formation of **6h** using naphthol **6a** as an additive (Table 2, footnote c). Furthermore, in the absence of HFIP, the *ee* of naphthol **6a** progressively increased from 28% after two minutes, to 54% at reaction completion (Scheme 2 B). Reintroduction of HFIP gave a reaction that proceeded at 70% *ee* for its duration. Finally, support for this scenario was obtained when the cycloisomerization was performed with deuterated substrate **D-5a**. In addition to deuteration of the phenolic hydrogen, around 25% deuterium incorporation was observed at the 2-position (eq. 6). To determine whether proton transfer between these positions occurs following reaction completion, racemic **6a** and enantioenriched **6a** were subjected to catalyst **A5** and **TPT** respectively. In both cases, no change in the optical purity was observed.[16] Thus, a plausible mechanism (Scheme 3) for this reaction commences with NHC addition to the terminal olefin to afford enolate **I** which, following tautomerization, provides the key β-azolium ylide **II**. Conjugate addition proceeds through intermediate **II**, with a *trans* arrangement between the azolium and the acceptor, and the azolium positioned to minimize steric interactions between the benzyl group and the phenyl linker, to afford enolate **III**. Diastereoselective protonation of **III** then affords **IV**, which, following E1cB reaction and tautomerization, affords propionate **6a**. An alternate explanation would involve E1cB prior to protonation, a mechanistic scenario difficult to distinguish. When the reaction was monitored by NMR, the only azolium-type structure was the free NHC, indicating that this is likely the resting state of the catalyst.

The kinetics of the reaction are finely balanced, with the desired cyclization (**II**→**III**) moderately faster than reaction with a second equivalent of substrate (that is, **7**→**9**, eq. 3). Furthermore, proton transfer to afford β-azolium ylide **II** is slightly faster than Rauhaut–Currier cyclization (that is, **10**→**11**, eq. 4).

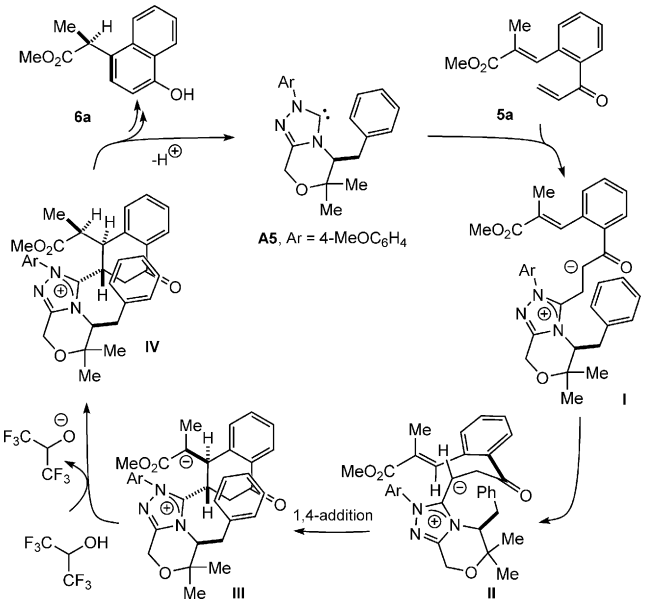
The umpolung of Michael acceptors by 1,4-addition of NHCs is an unusual activation mode, in comparison to the



Scheme 1. Competing reactions.



Scheme 2. Mechanistic studies.



Scheme 3. Plausible mechanism.

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more commonly observed 1,2-addition chemistry. Herein, a cycloisomerization reaction that exploits this reaction pathway is reported. This study has allowed the first enantioselective reaction through the β-azolium ylide to be discovered. For this transformation, electron-rich triazolium-derived NHCs were ideal, while an alcohol additive improved the enantioselectivity. Although the enantioselectivity is not exceptional, these studies provide a strong framework for catalyst and reaction design likely to inform future studies exploiting the β-azolium ylide **3**.

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[15] Single crystal X-ray analysis of anthracene **6k** was performed using CuK_α radiation for assignment of absolute stereochemistry. CCDC 1443409 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[16] This result also precludes Brønsted base-mediated chemistry as being the origin of enantioselectivity.

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