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Authors: Jared E. M. Fernando, Yuji Nakano, Changhe Zhang, and David W Lupton

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NHC catalysis

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Enantioselective N-heterocyclic carbene catalysis exploiting imine umpolung.**

*Jared E. M. Fernando, Yuji Nakano, Changhe Zhang, and David W. Lupton**

***Abstract**: The catalytic umpolung of imines remains an underdeveloped approach to reaction discovery. Herein we report an enantioselective aza-Stetter reaction that proceeds via imine umpolung using N-heterocyclic carbene catalysis. The reaction proceeds with high levels of enantioselectivity (all ≥96:4 er) and good generality (21 examples). Mechanistic studies consistent with turnover limiting addition of the NHC to the immune are reported.*

N-Heterocyclic carbenes (NHC, i.e. **1**) provide access to normal and reverse polarity intermediates integral to many reactions.[1] While a wide range of reactive intermediates are accessible, they are almost invariably formed via the Breslow intermediate (**2**), itself derived from aldehyde substrates (i.e. **3**). Alternate substrates for NHC-catalysis are known, such as esters,[2] ketones,[3] and conjugate acceptors,[4] however these remain less commonly examined, with a number of functional groups largely overlooked.

Imines are easily prepared electrophiles that would appear well suited to polarity inversion catalysis. Surprisingly enantioselective reactions of such substrates, under any type of catalysis, have only recently been reported, with access to 2-aza-anion intermediates enabling various alkylations.[5,6] NHC catalysis with imines has been known since the early 2000s, however these studies demonstrate that while they are viable as electrophilic partners, they do not undergo polarity inversion.[7,8] For example in 2005 Bode coupled cinnamaldehydes with sulfonate-imine **4** to give pyrolidinone **5** (eq. 1) in a reaction that proceeds via the homoenolate, not the imine umpolung (aza-Breslow).[8b] Independent work of Hou[9a] and Chi[9b] has demonstrated that related Ts-imines can serve as precursor to the sulfinate anion, presumably through fragmentation of the aza-Breslow intermediate. However, it wasn't until 2017 that Biju reported cycloisomerization of imine **6** to indole **7** (eq. 2) in the first NHC catalyzed reaction involving imine umpolung.[10a] Subsequently, the aza-Breslow has been invoked in the oxidation of imines to amides,[10b] and a quinolone synthesis.[10c] While these reports demonstrate the viability of the aza-Breslow in reaction discovery key challenges remain–perhaps most notably regarding enantioselectivity. As part of our interest in NHC catalysis with unconventional substrates we commenced studies on this topic. In addition to

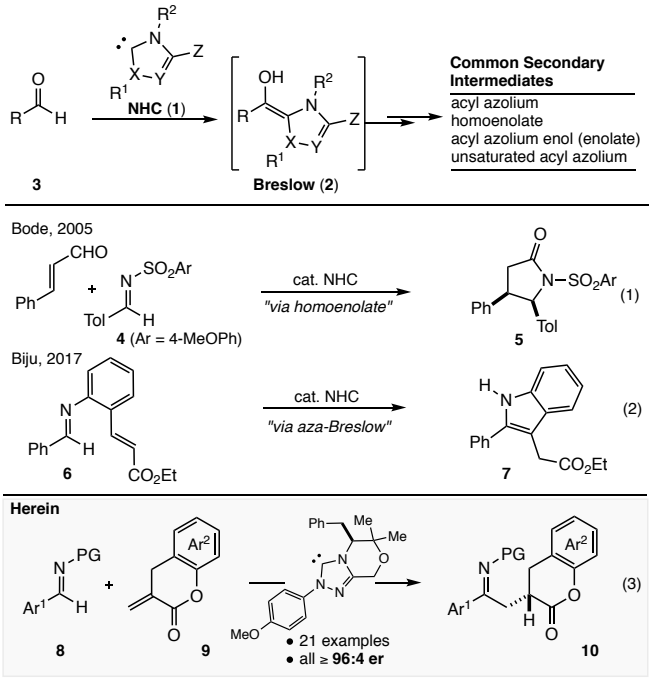

Figure 1.

providing a new enantioselective transformation, we felt that such studies could facilitate access to secondary intermediates analogous to those derived from the Breslow intermediate (Figure 1). Herein, we report the enantioselective intermolecular aza-Stetter reaction (eq. 3).[11] The reaction proceeds with excellent enantioselectivity allowing imines (i.e. **8**) to couple with 3-methylene-chroman-2-ones (i.e. **9**) to provide highly enantioenriched γ–imino lactones (**10**). While the enantioselective reaction requires 3-methylene-chroman-2-ones, achiral catalysts allow use of simpler acrylates.

We postulated that the imine protecting group would be most influential on aza-Breslow formation, and hence reaction viability. Thus, studies commenced by screening a number of protected aldimines (**8a-e**) using achiral catalyst **A1** (Table 1, entries 1 and 2). When heated in THF at reflux imines **8a-d** gave no coupled products, with **8a**, **b** and **d** isolated unchanged, while **8c** gave the product of sulfinate addition.[9c] In contrast benzoyl imine **8e** gave enone **12e** in 82% isolated yield. The unique viability of this imine we believe is due to a combination of its electron-withdrawing capacity, combined with enhanced stability compared to **8c**. Formation of **12e** is consistent with either the polarity inverted conjugate acceptor,[4] or the imine, followed by isomerization. Various mechanistic studies support the later (*vide infra*). Attention was now directed the enantioselective variant. While catalysts **A2-4**

[*] Mr. Jared E. M. Fernando, Dr Yuji Nakano, Dr Changhe Zhang and Professor David W. Lupton*
School of Chemistry, Monash University
Clayton 3800, Victoria, AUSTRALIA
Fax: (+) 61 3 9905 4597
E-mail: david.lupton@monash.edu

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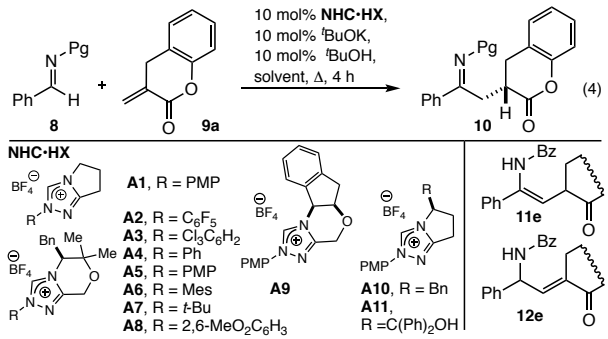
and **A7** gave no coupled material (Table 1, entry 3) the more nucleophilic[12] **A5** (R = 4-$MeOC_6H_4$)[13] and **A8** (R = 2,6-$MeO_2C_6H_3$)[14] gave enamine **11e**, and isomeric enone **12e**, in comparable yields (Table 1, entry 6). Shorter reaction times, in higher boiling dioxane, somewhat suppressed isomerization allowing γ–imino ester **10e** to be isolated in 50% yield with excellent enantiopurity (98:2 er) (Table 1, entry 7). A similar outcome was achieved with indanol **A9**, while pyrrolidine **A10** exclusively gave enone **12e**, and catalyst **A11** gave no coupled products (Table 1, entries 8-10). With catalyst **A5**, the outcome was improved in lower boiling THF (Table 1, entry 11), while an equivalent of ^{t}BuOH[15a] gave **10e** in 77% yield and 99:1 enantiomeric ratio (Table 2, entry 12).

Table 1. Discovery of the enantioselective aza-Stetter.



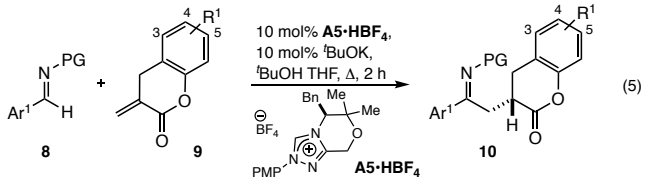
entry	NHC	Imine	solvent	**10**:**11**:**12**[a]	yield[b]	er[c]
1	**A1**	**8a** (Boc), **8b** (Ac), **8c** (Ts), **8d** ($P(O)Ph_2$)	THF	-	0	-
2	**A1**	**8e** (Bz)	THF	-	82 (**12e**)	-
3	**A2-4, A7**	**8e** (Bz)	THF	-	0	-
4	**A5**	**8e** (Bz)	THF	0:5:2	49 (**11e**)	-
5	**A6**	**8e** (Bz)	THF	-	*trace*	-
6	**A8**	**8e** (Bz)	THF	0:0:1	46 (**12e**)	-
7[d]	**A5**	**8e** (Bz)	Dioxane	5:0:3	50	98:2
8[d]	**A9**	**8e** (Bz)	Dioxane	2:1:0	43	98:2
9[d]	**A10**	**8e** (Bz)	Dioxane	0:0:1	80 (**12e**)	ND[e]
10[d]	**A11**	**8e** (Bz)	Dioxane	-	0	-
11[d]	**A5**	**8e** (Bz)	THF	7:1:0	65	98:2
12[df]	**A5**	**8e** (Bz)	THF	8:1:0	77	99:1

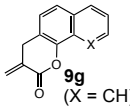
[a] Ratio by ^{1}H NMR analysis [b] Isolated yield [c] By HPLC with a chiral stationary phase. [d] 2h [e] ND = not determined. [f] 100 mol% ^{t}BuOH

Having achieved a highly enantioselective reaction, generality was examined with twelves aryl and heteroaryl aldimines and seven chromanones (Table 2). Aldimines bearing electron-donating, withdrawing, and heteroaromatic Ar^1 substituents all coupled to lactone **9a** to give aza-Stetter products **10e-i** with high enantiopurity (all ≥98:2 er), and highest yields using electron rich imines (Table 2, entries 1-5). Unfortunately, aliphatic imines bearing acidic α–protons, such as the imine of *iso*-butyraldehyde, underwent facile isomerization to the enamine, a common limitation in imine based catalysis.[16] Next, the imine protection was modified, with 4-MeOBz and 4-ClBz protected aldimines reacting to give the four products **10j-m** with 59-73% yield and ≥98:2 er (Table 2, entries 6-9).

Next we examined a series of chromanone derivatives bearing alkyl (i.e. **9b**, **d** and **e**), electron-releasing (i.e. **9c**), or electron-withdrawing groups (i.e. **9f**) at the 3-, 4-, and 5- positions. All gave aza-Stetter products (**10n-t**) with excellent enantioselectivity (≥96:4 er). Yields suggest a sensitivity to

Table 2. Scope of the enantioselective aza-Stetter.



entry	Ar^1	PG	**9** (R^1)	Product **10**	Yield **10**[a]	er[b]
1	Ph	Bz	**9a** (H)	**e**	77	99:1
2	4-$MeOC_6H_4$	"	"	**f**	67	98:2
3	3-$MeOC_6H_4$	"	"	**g**	80	99:1
4	4-BrC_6H_4	"	"	**h**	52	98:2
5	2-thiophenyl	"	"	**i**	88	99:1
6	Ph	(4-MeO)Bz	"	**j**	73	98:2
7	4-BrC_6H_4	"	"	**k**	61	98:2
8	4-$MeOC_6H_4$	"	"	**l**	59	99:1
9	Ph	(4-Cl)Bz	"	**m**[c]	60	98:2
10	4-MeC_6H_4	(4-MeO)Bz	**9b** (4-Me)	**n**	78	99:1
11	2-thiophenyl	Bz	"	**o**	79	99:1
12	4-MeC_6H_4	Bz	"	**p**	61	99:1
13	Ph	(4-MeO)Bz	**9c** (4-MeO)	**q**	45	98:2
14	4-$MeOC_6H_4$	Bz	**9d** (4-Et)	**r**	64	97:3
15	Ph	(4-MeO)Bz	**9e** (3,5-Me_2)	**s**	75	98:2
16	"	"	**9f** (4-Br)	**t**	49	96:4
17	"	"	 **9g** (X = CH)	**u**	63	96:4
18	2-thiophenyl	Bz		**v**	81	98:2
19	3-$MeOC_6H_4$	"		**w**	68	>99:1
20	2-thiophenyl	"	**9h** (X = N)	**x**	47	98:2
21	3-$MeOC_6H_4$	"		**y**	44	96:4

[a] Isolated yield of **10** [b] By HPLC with chiral stationary phases [c] Compound **10m** contaminated by ~10% of inseparable byproduct, likely **11m** and **12m**.

electronics, with the electron rich and poor products **10q** and **t** formed in modest yields of 45 and 49% (Table 2, entries 10-16). Finally naphthalene and quinoline derived chromanones (**9g** and **9h**) coupled with various imines to give the expected products **10u-y** with excellent enantioselectivity (all ≥96:4 er), although the heterocyclic products formed with modest yields (Table 2, entries 20-21).

Attempts to expand the range of conjugate acceptors met with limited success. For example, chalcone, cyclohexan-2-one, 2-amino acrylates, and methylmethacrylate failed to couple with various imines. In these cases the acceptor was often isolated while the imine gave aza-benzoin **13** (eq. 6). In contrast to the benzoin condensation, which is often reversible,[15b] aza-benzoin **13** does not serve as an aza-Breslow precursor,[17] thereby impacting the generality of the aza-Stetter reaction. However, when the achiral catalyst **A1** was used methylacrylate, methylmethacrylate, and acrylonitrile gave aza-Stetter products **10z-ab** and the related enamine **13g** (eq. 7 and 8). These reactions suggest that alternate variants of the enantioselective aza-Stetter reactions may well be viable in the future.

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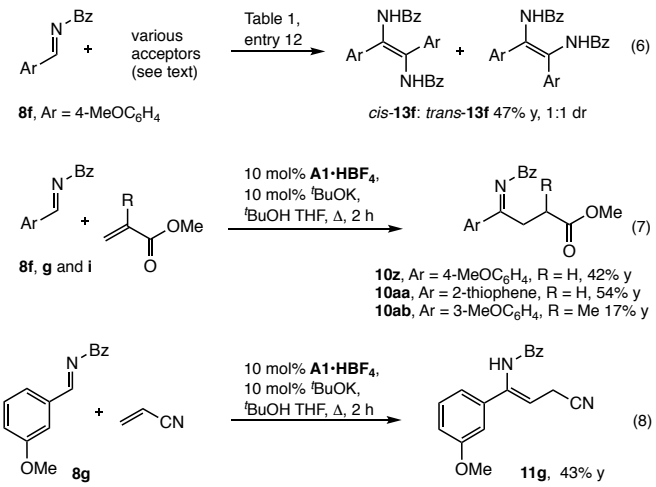
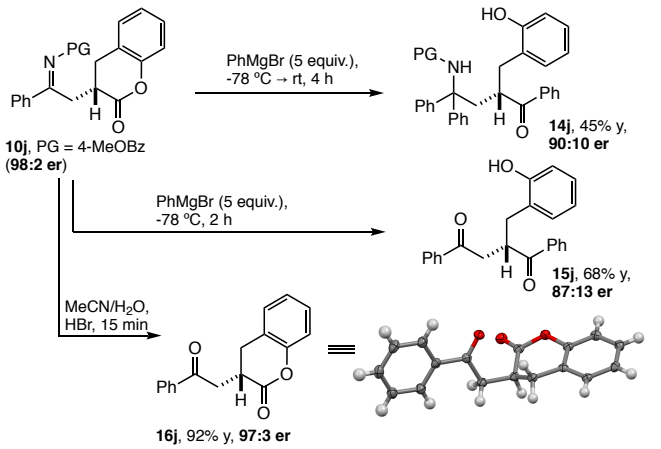
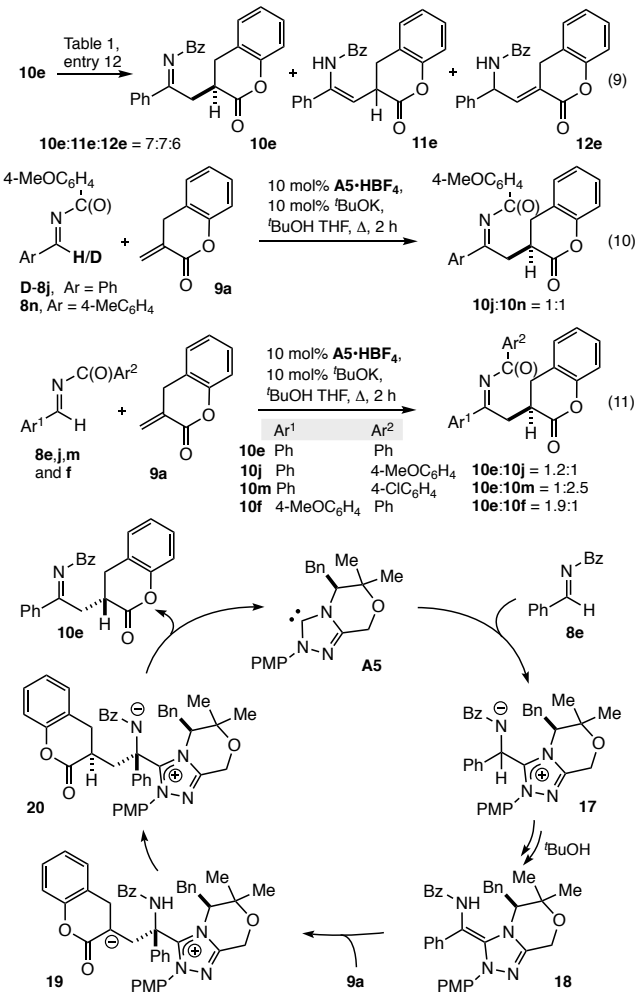


Derivatization was undertaken to examine the reactivity of the products and allow absolute configuration to be determined (Scheme 2). Exhaustive addition of PhMgBr to **10j** gave triphenyl benzamide **14j**, while at lower temperature chemoselective addition of PhMgBr gave diketone **15j**. Some erosion of enantiopurity was observed in both cases. Finally hydrolysis gave γ–keto ester **16j**, which allowed absolute configuration to be determined via x-ray crystallographic analysis.[18]



Scheme 2. Derivatization studies with aza-Stetter product **10j** and ORTEP of ketone **16j**.

From our optimization and scope studies it appears that the aza-Breslow is less reactive than the Breslow, and that catalysis requires highly nucleophilic NHCs. To gain a more detailed mechanistic picture studies commenced by examining the significance of enamine and enone formation observed during optimization. When imine **10e** was resubjected to the reaction conditions a 7:7:6 mixture of **10e**, **11e**, and **12e** formed (Scheme 3, eq. 9). In contrast, resubjection of enamine **11e**, or enone **12e** failed to produce **10e**, with **11e** and **12e** returned, along with decomposition products. These results are consistent with imine umpolung leading to **10e**, rather than homoenolate formation providing **11e** or **12e**, which isomerizes to **10e**. Next the turnover limiting step was examined. Competition between **D-8j** and **8n**, with associated controls,[19a] showed lack of a primary KIE (eq. 10), thus deprotonation is unlikely to be turnover limiting. When competition studies with electronically differentiated protecting groups (i.e. **8e** *cf.* **8j** and **8e** *cf.* **8m**) were undertaken it demonstrated that the reaction is enhanced by electron-withdrawing imine protection (eq. 11).[19b] This trend was also observed with competitions involving manipulation of the electronics of the imine Ar[1] group (**8e** *cf.* **8f**). Taken together these results are consistent with turn over limiting addition of the NHC to the imine to afford **17**. Further support for this interpretation can be derived from studies into the order of the reaction.[20] Preliminary studies show the reaction to be close to 0 in chromanone (0.30), and first order in NHC (0.74) and imine (1.12). Unfortunately, while related aza-Breslow intermediates have been isolated,[7,8] this was not possible with benzoyl imine **8**, with all attempts leading to formation of aza-Benzoin **13**. Thus we propose turn over limiting addition of the NHC to the imine, followed by ^{t}BuOH mediated tautomerization to afford aza-Breslow **18**, which undergoes 1,4-addition to chromanone **9** to provide enolate **19**. Diastereoselective protonation provides **20**[21] with elimination of the catalyst completing the cycle.



Scheme 3. Mechanistic studies.

A wealth of reactions exploit the Breslow intermediate *en route* to diverse secondary intermediates. While our studies suggest that the aza-Breslow is less reactive than the Breslow, we expect related, as well as unique, enantioselective reactions designs to be possible via analogous secondary intermediates. Certain studies on this topic are ongoing.

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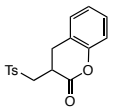

10c

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[16] See (a) J. L. G. Ruano, J. Alemán, M. B. Cid, A. Parra, *Org. Lett.* **2005**, *7*, 179; (b) J. Vesely, R. Rios *Chem. Soc. Rev.* **2014**, *43*, 611 and references therein for imine to enamine isomerization with electron-poor imines.

[17] Subjection of **13f** to the reaction conditions with acceptor **9a** failed to provide imine **10f**.

[18] Single crystal X-ray analysis of g-ketoester **18j** using CuK radiation for absolute stereochemistry (CCDC 1862310). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[19] (a) Competition between **8j** and **n** was performed and the ratio **10j**:**10n** determined as background for eq. 9. (b) To assess whether the product ratio in the competition relates to kinetics or stability of the product, the competition between **8n** and **8j** was monitored by ^{1}H-NMR, see SI. The product ratio is constant over the entire reaction, consistent with a kinetic interpretation.

[20] See SI for details. While these results are consistent with the proposed mechanism to enhance the accuracy work is ongoing.

[21] For enantiodeterming protonation in a related reaction of the Breslow intermediate see: (a) F. Liu, X. Bugaut, M. Schedler, R. Fröhlich, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 12626-12630. (b) R. Kuniyil, R. B. Sunoj, *Org. Lett.* **2013**, *15*, 5040-5043.

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NHC Catalysis

Jared E. M. Fernando, Yuji Nakano, Changhe Zhang and David W. Lupton*

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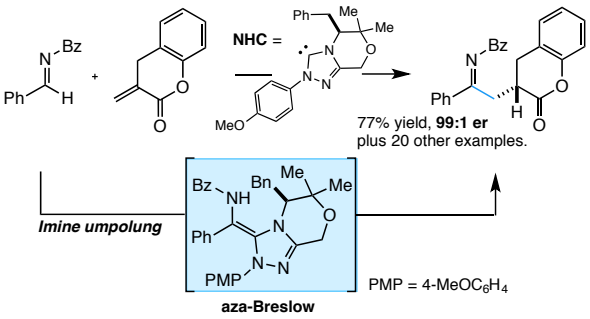
Enantioselective N-heterocyclic carbene catalysis exploiting imine umpolung.



Imine umpolung is an underdeveloped area of enantioselective catalysis despite providing a new entry to nitrogenous compounds of potential utility. Herein, we report the use of NHCs, to catalyze an enantioselective aza-Stetter reaction. In contrast to the chemistry of acyl umpolung with NHCs this reaction requires highly nucleophilic catalysts. The reaction is highly enantioselective (all ≥96:4 er) with various imines and 3-methylenechroman-2-ones coupled to give γ–imino lactones.