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EDGE ARTICLE

NHC-catalysed, chemoselective crossed-acyloin reactions†

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It has been shown for the first time that relatively electron deficient triazolium pre-catalysts promote (at low loadings in the presence of base) highly chemoselective crossed acyloin condensation reactions between aldehydes and α-ketoesters to afford densely functionalized products incorporating a quaternary stereocentre of considerable synthetic potential. Hydroacylation pathways which have hitherto been dominant in these reactions can be completely avoided. The scope of the process is extraordinarily broad with respect to both coupling partners, and a preliminary study has established the principle that a high degree of stereochemical control over the reaction can also be exercised *via* the use of a chiral NHC precursor. It has also been shown for the first time that coupling of benzyl α-ketoesters with aldehydes followed by acylation and simple hydrogenolysis furnishes a product formally derived from the chemoselective 1 : 1 coupling of two different aliphatic aldehydes in high yield with absolute control over which coupling partner behaves as the acyl-anion equivalent.

Introduction

α-Hydroxy-β-ketoacid derivatives incorporating a quaternary stereogenic centre in the α-position (*i.e.* **1**, Fig. 1) are structural features in a range of natural products.[1] In addition, they are densely functionalised, highly synthetically-pliable molecules which can serve as useful precursors to the α-hydroxy acid/α-hydroxy ketone motifs remarkably common in naturally occurring biomolecules,[2] tetracycline/glycylcycline antibiotics,[3] artificial β-amino acids/alcohols and α,β-dihydroxylated acids (in addition to a plethora of other useful building blocks). The undoubted synthetic utility of these materials is curtailed by the synthetic routes to these compounds – which are based in the main on often functional-group sensitive α-oxidation methods (*e.g.* **2** → **1**, Fig. 1).[4,5]

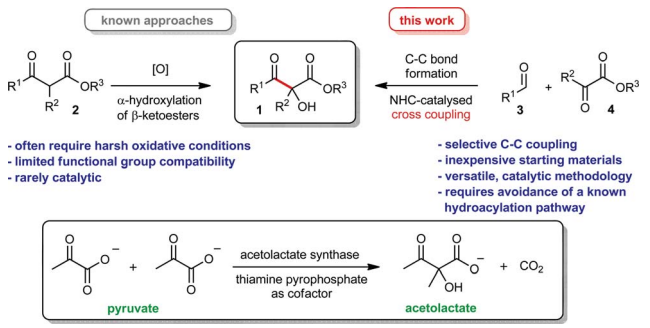

Fig. 1 α-Hydroxy-β-ketoacid derivatives: known approaches and a proposed direct catalytic C–C bond forming route.

Inspired by the mode of action of the thiamine pyrophosphate-dependent enzyme acetolactate synthase, which catalyses the coupling of two molecules of pyruvate to generate acetolactate (a precursor to valine, leucine and isoleucine, Fig. 1),[6,7] we envisaged the possibility of developing an analogous route to **1** from the direct *N*-heterocyclic carbene (NHC)-catalysed coupling of an aldehyde **3** with an α-ketoester **4** in a chemoselective crossed acyloin condensation (AC) reaction (Fig. 1, right).

While such a coupling process would obviously represent a considerable advance over literature methods (which often require the use of excess of one coupling partner) in terms of greater synthetic flexibility, two major barriers (outlined in Fig. 2) to its development were identified. First, in previous studies involving the NHC-catalysed reaction of aldehydes and α-ketoesters,[8,9] upon reaction of carbene **5** with the aldehyde **3**, *hydride transfer* to form the hydroacylation product **8** *via* the coupling of the initially formed alcohol **6** and acyl-heterazolium ion **7** was observed. We noted that these hydroacylation reactions[8–10] were promoted by relatively electron-rich NHCs (*e.g.* **NHC-2**, Fig. 2).[11,12] This led to the proposal that the use of a carbene incorporating a powerful inductive electron withdrawing substituent (*i.e.* **NHC-1**) would destabilise developing positive charge in the transition state leading to acyl-triazolium

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. See DOI: 10.1039/c2sc00622g

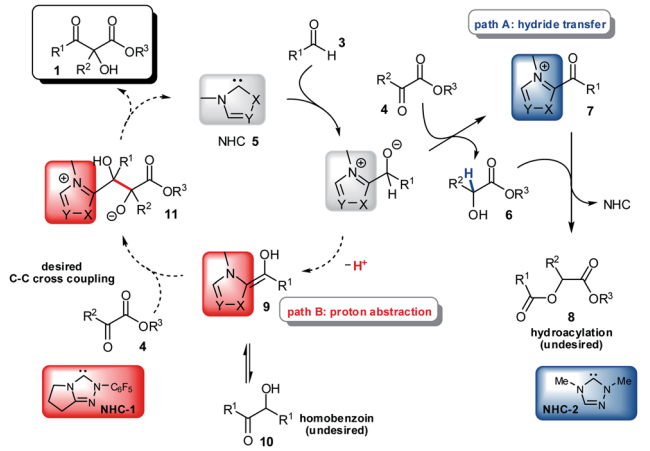


Fig. 2 Three possible pathways involving the reaction of **3** and **4** in the presence of either electron-rich or electron deficient carbenes.

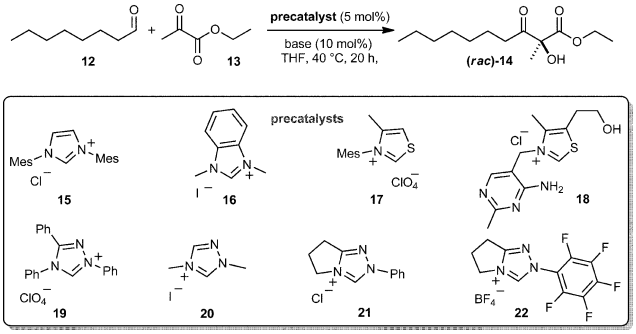
ion and hence disfavour the hydride transfer pathway in favour of a proton-transfer step leading to the nucleophilic Breslow intermediate **9**.[13]

Next, for chemoselective cross coupling to occur **9** must eschew reaction with **3** (leading to homobenzoin **10**[14,15]) and add preferentially to ketoester **4** to afford the cross-coupled product **1** *via* adduct **11**. Examples of intermolecular chemoselective crossed-acyloin reactions involving two aldehydes are very rare,[16] and to the best of our knowledge the only ketone substrates that have been shown to participate in these processes[17,18] are highly activated heterocyclic trifluoromethylketones.[19] We have previously studied the performance of **NHC-1**[20,21] in (crossed)[16e,f] acyloin condensations involving two different aldehydes and were confident – given a combination of the relatively mild reactivity of **NHC-1** and superior electrophilicity of **4** over **3** in previously reported hydroacylation studies – that if **9** could be formed selectively the crossed acyloin pathway would be dominant.[22]

Results and discussion

Our study began with the reaction between octanal (**12**) and one equivalent of the inexpensive ethyl pyruvate (**13**) in the presence of a range of azolium ions and bases (Table 1). Imidazolium, thiazolium and triazolium ions devoid of σ-withdrawing substituents (*i.e.* **15–20**), failed to mediate the formation of **14** above trace levels in the presence of K_2CO_3 (entries 1–2, 3–4 and 5–6 respectively). Use of the simple *N*-phenyl triazolium ion **21** did result in a modest amount of cross-coupling (entry 7), however, we were pleased to observe the clear superiority of the *N*-pentafluorophenyl substituted precatalyst **22**, which furnished the coupled product in excellent yield (entry 8). Exchange of the carbonate base for either sodium hydride (entry 10) or potassium *tert*-butoxide (entry 9) resulted in inefficient catalysis (entries 9 and 10), while potassium phosphate was found to be a suitable substitute (entry 11). Two tertiary amine bases were also evaluated: DBU failed to facilitate clean cross-coupling (entry 12) while excellent product yields were obtained using Hünig's base (entry 13).

Table 1 Crossed AC reactions: preliminary experiments



Entry	Precatalyst	Base	Yield[a] (%)
1	**15**	K_2CO_3	<5
2	**16**	K_2CO_3	<5
3	**17**	K_2CO_3	<5
4	**18**	K_2CO_3	<5
5	**19**	K_2CO_3	<5
6	**20**	K_2CO_3	<5
7	**21**	K_2CO_3	9
8	**22**	K_2CO_3	>95 (92)[b]
9	**22**	KO*t*-Bu	34
10	**22**	NaH	<5
11	**22**	K_3PO_4	>95
12	**22**	DBU	28
13	**22**	*i*-PrNEt$_2$	>95

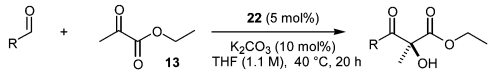
[a] Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b] Isolated yield in parenthesis.

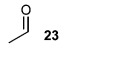
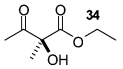
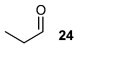
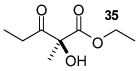
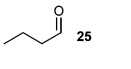
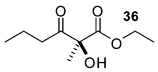
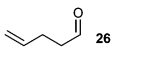
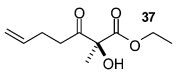
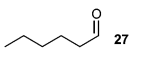
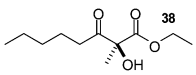
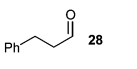
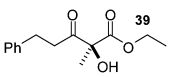
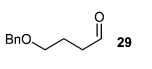
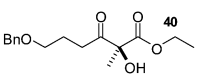
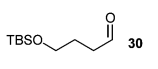
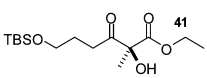
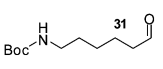
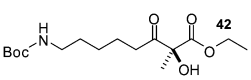
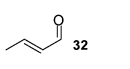
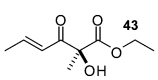
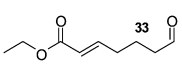
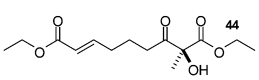
With chemoselective cross coupling established and convenient conditions identified, we next turned to a systematic examination of the reaction scope. Beginning with aliphatic aldehydes (Table 2), we were pleased to find that substrates incorporating hydrocarbon chains **23–28** were converted to the corresponding α-hydroxy-β-ketoesters **34–39** in uniformly excellent isolated yields (entries 2–6). Both protected hydroxy and amine functionality are well tolerated (*i.e.* **40**, **41** and **42** entries 7–9) as are peripheral double bonds (*i.e.* **37**, entry 4), however isolation of **43** is more problematic due to either competitive Stetter reaction or homoenolate pathways, nonetheless the highly functionalised α,β-unsaturated product can be isolated in appreciable yield (entry 10). It is noteworthy that not only are homobenzoin and hydroacylation pathways excluded here, but that a lactone-generating reaction *via* a homoenolate pathway reported by You[23] in the presence of more electron-rich carbenes, was also avoided. Of particular interest is the observation that **33** (which incorporates a less activated Michael acceptor yet which is – from a stereoelectronic perspective – well-disposed towards a 5-*exo*-trig Stetter cyclisation reaction) undergoes exclusive 1 : 1 intermolecular coupling with **13** (entry 11) in excellent yield.

To evaluate the utility of these reactions on a more synthetically relevant scale, 15 mmol of pyruvate ester **13** was coupled to a stoichiometric amount of **28**, resulting in the formation of multigram quantities of **39** in excellent yield (Scheme 1).

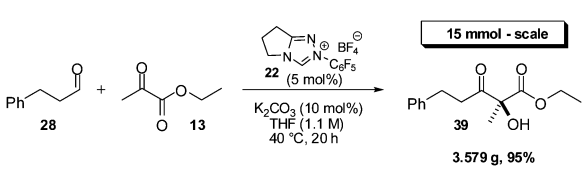
Initially, the efficiency of the corresponding coupling reactions involving aromatic aldehydes (Table 3) was disappointing – for example the crossed AC reaction between *p*-chlorobenzaldehyde (**45**)

Table 2 Coupling of aliphatic aldehydes to ethyl pyruvate



Entry	Aldehyde	Product	Yield[a] (%)
1			92[b]
2			93
3			94
4			87
5			91
6			95
7			88
8			76
9			77
10			48
11			90

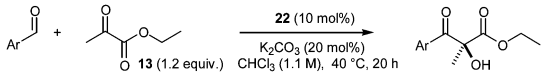
[a] Isolated yield. [b] Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard.

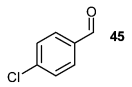
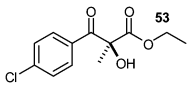


Scheme 1 A crossed AC reaction on preparative scale.

and **13** proceeded in 56% yield (entry 1). After considerable experimentation it was found that the use of chloroform as the reaction solvent allowed the circumvention of this difficulty.[24] Thus, **45** could be converted to **53** in 83% yield in the presence of catalyst **22** (10 mol%) in this solvent (entry 2). In a similar fashion, activated (*i.e.* **46**, entry 3), electron-neutral (*i.e.* **47**–**48**, entries 4 and 5) in addition to deactivated (*i.e.* **49**, entry 6) aromatic aldehydes and heteroaromatic aldehydes (*i.e.* **50**–**52**, entries 7–9)[25] could be coupled with **13** to afford **54**–**60** respectively in good isolated yields.

Table 3 Coupling of aromatic and heteroaromatic aldehydes to ethyl pyruvate



Entry	Aldehyde	Product	Yield[a] (%)
1[b]			56
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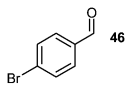
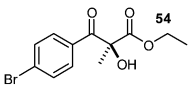
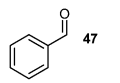
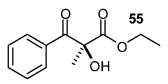
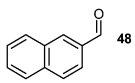
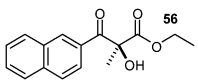
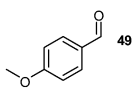
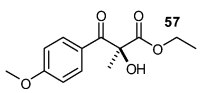
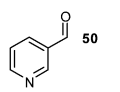
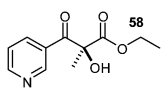
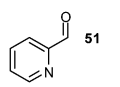
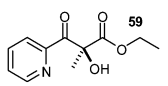
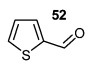
3			76
4			86
5			84
6[c]			93
7[d]			91
8[d]			92
9[d]			86

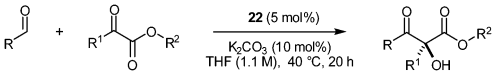
[a] Isolated yield. [b] *Reaction conditions*: **22** (10 mol%), K_2CO_3 (20 mol%), 1 equiv. of **13**, THF (1.1 M), 40 °C, 16 h. [c] Reaction time: 48 h. [d] 1.7 equiv. of **13**.

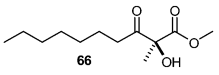
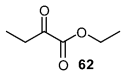
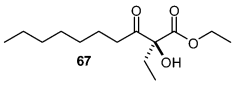
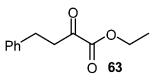
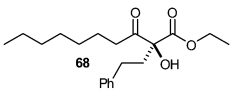
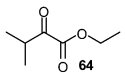
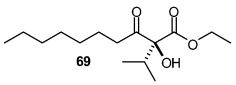
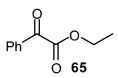
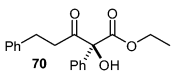
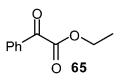
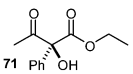
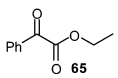
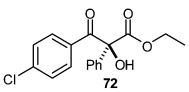
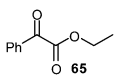
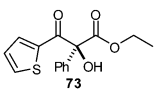
The methodology is not limited to the use of **13** and is also applicable to other α-ketoester coupling partners (Table 4). For instance, methyl pyruvate (**61**) could be coupled to **12** with excellent efficiency (entry 1), while high yields were also obtained from α-ketoesters with elongated chains (entries 2 and 3). The hindered ketone **64** reacted sluggishly under standard conditions resulting in a lower isolated yield of 40% (entry 4). Aromatic ketoesters also proved difficult substrates, however these reactions responded well to a change of solvent from THF to chloroform,[24] which allowed the formation of **70** and **71** in yields ≥80% (entries 5 and 6). Aromatic aldehydes could also be coupled to aromatic ketoesters (entries 7 and 8).

With the scope of the process systematically explored, we were ready to examine the possibility of carrying out asymmetric variants of these reactions.

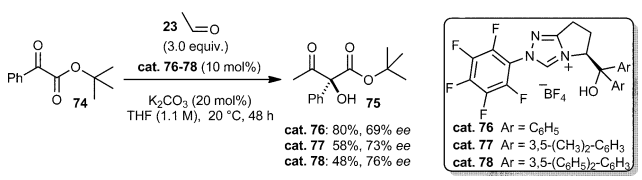
We were gratified to find that augmentation of the steric requirement of the α-ketoester derivative resulted in improved levels of product enantiomeric excess relative to that obtained using ethyl pyruvate. For instance, protection of the acid functionality as the easily removed *tert*-butyl ester (*i.e.* **74**, Scheme 2) allowed coupling with acetaldehyde[26] to occur in 58–80% yield

Table 4 Coupling of aliphatic and aromatic aldehydes with various α-ketoesters



Entry	α-Ketoester	Product	Yield[a] (%)
1			90
2			90
3[b]			70
4			40
5[c]			80
6[d]			82
7[e]			64
8[e]			66

[a] Isolated yield. [b] Using **22** (8 mol%) and K_2CO_3 (15 mol%). [c] Using **28** as the aldehyde partner. *Reaction conditions*: **22** (10 mol%), K_2CO_3 (20 mol%), $CHCl_3$ (1.1 M), 40 °C, 20 h, rt. [d] Using **23** as the aldehyde partner. *Reaction conditions*: **22** (10 mol%), K_2CO_3 (20 mol%), $CHCl_3$ (1.1 M), 40 °C, 20 h. [e] *Reaction conditions*: **65** (3.0 equiv.), **22** (10 mol%), K_2CO_3 (20 mol%), $CHCl_3$ (1.1 M), 45 °C, 20 h.



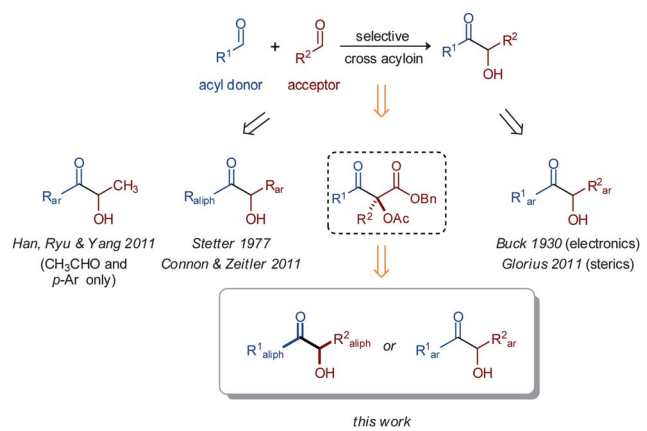
Scheme 2 Asymmetric crossed AC using chiral precatalysts.

and 69–76% *ee* using the chiral precatalysts **76–78**. While the level of asymmetric induction is not yet optimal, it is of interest that using the novel precatalyst **78** a high degree of stereochemical control is exercisable over the process.[27] We are currently designing new catalysts to perfect this quaternary stereocentre-generating reaction from an enantioselectivity standpoint.

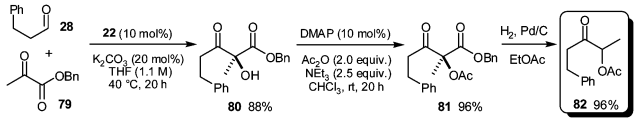
Finally, while the potential utility of such densely functionalised adducts as synthetic building blocks is reasonably obvious, we were also interested in investigating the use of the pyruvate unit as a 'masked aldehyde' in crossed acyloin reactions which are currently not possible to carry out in a completely chemoselective fashion using NHC catalysis (Scheme 3) – most importantly, those between two different aliphatic and two different aromatic aldehydes. While there has been a recent surge in interest in the investigation of the factors which influence the outcome of crossed acyloin reactions,[16–19] in all cases where useful selectivity was observed the system consisted of the reaction between one aliphatic aldehyde and one aromatic aldehyde – where the inherent differences in electrophilicity and steric bulk of the two substrates can be exploited to bring about a measure of selective (although rarely completely chemoselective) coupling. However, no examples of chemoselective crossed acyloin reactions between two *aliphatic* aldehydes catalysed by an NHC catalyst are known.

Given that the AC reactions detailed above (Tables 1–4) are 100% chemoselective, we reasoned that coupling of an α-ketobenzyl ester with an aliphatic aldehyde would, on hydrogenolysis of the benzyl group, result in *in situ* decarboxylation to give a product formally derived from the chemoselective coupling of two aliphatic aldehydes. This hypothesis was validated as follows: aldehyde **28** was coupled with benzyl pyruvate (**79**) in the presence of **22** (5 mol%) in excellent yield (Scheme 4). After acylation of the tertiary alcohol, hydrogenolysis of **81** in the presence of Pd/C led to the clean formation of **82** - which is formally derived from the completely chemoselective crossed AC reaction between **28** and one equivalent of acetaldehyde (**23**).[28] Thus by utilising an α-ketoester partner with the requisite α-substituent followed by a simple acylation/hydrogenolysis protocol it is now conceivable to generate the acylated product derived from the AC reaction between any two aliphatic aldehydes (within the substrate scope outlined in Tables 2–4) with complete control over which aldehyde formally acts as the acyl-anion synthon.[29]

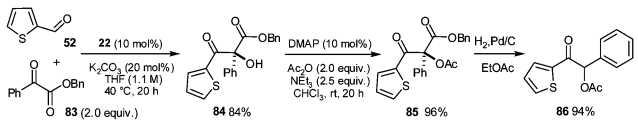
Apart from the selective formation of crossed aliphatic acyloins derived from two different *aliphatic* aldehydes, this acetylation/decarboxylation approach can easily be extended to generate other crossed acyloin products which are difficult to synthesize using other methodologies. While – as outlined in Scheme 3 – *partial* solutions are available for the selective coupling of aliphatic and aromatic aldehydes, a general



Scheme 3 An α-ketoester as a masked aldehyde for the synthesis of selective AC reaction products.



Scheme 4 An aliphatic α-ketoester as a masked aldehyde in an AC reaction for the synthesis of crossed aliphatic acyloins.



Scheme 5 Chemoselective crossed AC followed by acetylation/decarboxylation to generate a benzoin acetate formally derived from the chemoselective coupling of thiophene carbaldehyde and benzaldehyde.

NHC-mediated method for accessing crossed aromatic benzoins (*i.e.* between two different aromatic aldehydes) has remained elusive until now. We have now brought this new methodology to bear on this long-term problem. Heteroaromatic aldehydes also proved to be suitable substrates (Scheme 5). Thiophene aldehyde **52** could be coupled with ketoester **83** to allow access to the crossed aromatic acyloin acetate **86**, which is formally derived from a selective AC reaction between two aromatic aldehydes of very similar steric and electronic properties.

In summary, we have developed the first chemoselective,[30] intermolecular crossed AC reactions between aldehydes and inexpensive α-ketoesters catalysed by an NHC catalyst. Through the selection of a more electron-deficient carbene promoter the hitherto dominant hydroacylation pathways can be completely avoided. In contrast with the majority of previous attempts to effect such transformations in the literature, in this reaction the two partners can react in a 1 : 1 ratio to furnish densely functionalised products containing a quaternary stereocentre of high potential synthetic utility in good to excellent yields. The scope of the process is extraordinarily broad: both aliphatic and aromatic aldehydes are well tolerated, while also both aromatic and aliphatic substituents at the α-carbon (in addition to various ester functionalities) are accommodated in the α-ketoester electrophile. A preliminary study has established that a high degree of stereochemical control over the reaction can also be exercised *via* the use of a chiral NHC precursor. In addition, a benzyl α-ketoester can be utilised as a masked aldehyde equivalent – thus practitioners can synthesise (*via* a chemoselective AC reaction) acylated AC products formally derived from the 1 : 1 coupling of two aldehydes (even if they have very similar steric/electronic characteristics) with absolute control over which partner will behave as the acyl anion equivalent and which will serve as the electrophile. Investigations to further develop the utility/enantioselectivity of these reactions are underway.

Acknowledgements

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Notes and references

1 For examples, see: (*a*) W. Herz and S. V. Bhat, *J. Org. Chem.*, 1970, **35**, 2605; (*b*) L. Quljano, E. J. Oliweh and N. H. Fischer, *Phytochemistry*, 1980, **19**, 1485; (*c*) S. Schulz, *Liebigs Ann. Chem.*, 1992, 829; (*d*) T. Tanaka, I. Koundo and G.-I. Nonaka, *Chem. Pharm. Bull.*, 1996, **44**, 34; (*e*) J. Zhu, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron Lett.*, 1994, **35**, 2787; (*f*) Y. Shikishima, Y. Takaishi, G. Honda, M. Ito, Y. Takeda, M. Tori, S. Takaoka, O. K. Kodzhimato and O. Ashurmetov, *J. Nat. Prod.*, 2002, **65**, 1897.

2 (*a*) G. Olack and H. Morrison, *J. Org. Chem.*, 1991, **56**, 4969; (*b*) F. A. Davis, C. Clark, A. Kumar and B.-C. Chen, *J. Org. Chem.*, 1994, **59**, 1184; (*c*) K. Tamaki, J. B. Shotwell, R. D. White, I. Drutu, D. T. Petsch, T. V. Nheu, H. He, Y. Hirokawa, H. Maruta and J. L. Wood, *Org. Lett.*, 2001, **3**, 1689; (*d*) F. Neuser, H. Zorn and R. G. Berger, *J. Agric. Food Chem.*, 2000, **48**, 6191.

3 (*a*) P. E. Sum and P. Petersen, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1459; (*b*) W. E. Rose and M. J. Rybak, *Pharmacotherapy*, 2006, **26**, 1099.

4 Selected recent references: (*a*) F. A. Davis, H. Liu, B.-C. Chen and P. Zhou, *Tetrahedron*, 1998, **54**, 10481; (*b*) J. Christoffers, *J. Org. Chem.*, 1999, **64**, 7668; (*c*) T. Watanabe and T. Ishikawa, *Tetrahedron Lett.*, 1999, **40**, 7795; (*d*) X. Baucherel, E. Levoirier, J. Uziel and S. Juge, *Tetrahedron Lett.*, 2000, **41**, 1385; (*e*) J. Christoffers, T. Werner, S. Unger and W. Frey, *Eur. J. Org. Chem.*, 2003, 425; (*f*) S. V. Ley, T. D. Sheppard, R. M. Myers and M. S. Chorghade, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 1451; (*g*) Y. Monguchi, T. Takahashi, Y. Iida, Y. Fujiwara, Y. Inagaki, T. Maegawa and H. Sajiki, *Synlett*, 2008, 2291; (*h*) P. Gans, O. Hamelin, R. Sounier, I. Ayala, M. A. Durá, C. D. Amero, M. Noirclerc-Savoye, B. Franzetti, M. J. Plevin and J. Boisbouvier, *Angew. Chem., Int. Ed.*, 2010, **49**, 1958; (*i*) A. M. R. Smith, H. S. Rzepa, A. J. P. White, D. Billen and K. K. Hii, *J. Org. Chem.*, 2010, **75**, 3085.

5 See also: D. H. G. Crout and D. L. Rathbone, *J. Chem. Soc., Chem. Commun.*, 1987, 290.

6 (*a*) J. V. Schloss, D. E. Van Dyk, J. F. Vasta and R. M. Kutny, *Biochemistry*, 1985, **24**, 4952; (*b*) R. S. Chaleff and C. J. Mauvais, *Science*, 1984, **224**, 1443.

7 (*a*) For a biomimetic (stoichiometric) artificialprocess, see: D. H. G. Crout, E. R. Lee and D. P. J. Pearson, *J. Chem. Soc., Chem. Commun.*, 1990, 331; (*b*) for the enzymatic C–C bond formation using diketo substrates, see: P. P. Giovannini, P. Pedrinia, V. Venturia, G. Fantin and A. Medicia, *J. Mol. Catal. B: Enzym.*, 2010, **64**, 113.

8 For the seminal work in this area, see: (*a*) A. Chan and K. A. Scheidt, *J. Am. Chem. Soc.*, 2006, **128**, 4558; (*b*) for an interesting study detailing how NHC catalysis (including the formation of acylazolium ions) can be influenced by the solvent, see: B. E. Maki, E. V. Patterson, C. J. Cramer and K. A. Scheidt, *Org. Lett.*, 2009, **11**, 3942.

9 (*a*) M. Sreenivasulu, K. A. Kumar, K. S. Reddy, K. S. Kumar, P. R. Kumar, K. B. Chandrasekhar and M. Pal, *Tetrahedron Lett.*, 2011, **52**, 727; (*b*) D. Du, Y. Lu, J. Jin, W. Tang and T. Lu, *Tetrahedron*, 2011, **67**, 7557.

10 For related NHC catalysed, but mechanistically distinct hydroacylations, see: (*a*) K. Hirano, A. T. Biju, I. Piel and F. Glorius, *J. Am. Chem. Soc.*, 2009, **131**, 14190; (*b*) A. T. Biju, N. E. Wurz and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 5970; (*c*) A. T. Biju and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 9761; for an enantioselective version, see: (*d*) I. Piel, M. Steinmetz, K. Hirano, R. Fröhlich, S. Grimme and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 4983.

11 For an exceptional hydroacylation in the presence of a relatively electron-deficient NHC catalyst, see: (*a*) M. T. Molina, C. Navarro, A. Moreno and A. G. Csáky, *J. Org. Chem.*, 2009, **74**, 9573; (*b*) for additional tested catalysts for this reaction, see ref. 12. Due to the thermodynamically favoured formation of an aromatic product this naphthoquinone hydroacylation (which is also likely to occur *via* an 1,4- and not an 1,2-addition reaction) can be considered to be

a special case. Our previous work (*cf.* ref. 21*a*) also suggests that the combinations of the base evaluated (NMM and NEt_3) and more electron-rich carbene precursor are not sufficient to ensure the generation of effectual amounts of free carbene to promote the benzoin reaction.

12 For a recent, insightful study on steric and electronic effects of *N*-mesityl substituents in carbene-catalyzed reactions, see: J. Mahatthananchai and J. W. Bode, *Chem. Sci.*, 2012, **3**, 192.

13 We thank a reviewer for suggesting an alternative hydroacylation pathway where the acylazolium may be generated from intermediate **11** upon proton transfer followed by retro-aldol reaction of the alkoxide. This alkoxide competitively can also release the carbene catalyst **5** to generate the product **1**; this process should also be favoured for electron-deficient heterazolium species.

14 Recent reviews concerning various aspects of NHC organocatalysis: (*a*) H. U. Vora and T. Rovis, *Aldrichim. Acta*, 2011, **44**, 3; (*b*) A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res.*, 2011, DOI: 10.1021/ar2000716; (*c*) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paula, A. Josea and V. Sreekumar, *Chem. Soc. Rev.*, 2011, **40**, 5336; (*d*) P.-C. Chiang and J. W. Bode, *RSC Catal. Ser.*, 2010, **6**, 399; (*e*) C. D. Campbell, K. B. Ling and A. D. Smith, *Catal. Met. Complexes*, 2010, **32**, 263; (*f*) J. L. Moore and T. Rovis, *Top. Curr. Chem.*, 2009, **291**, 77; (*g*) E. M. Phillips, A. Chan and K. A. Scheidt, *Aldrichim. Acta*, 2009, **42**, 55; (*h*) T. Rovis, *Chem. Lett.*, 2008, **37**, 1; (*i*) K. Zeitler, *E. Schering Found. Symp. Proc.*, 2007, **2**, 183; (*j*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5506; (*k*) N. Marion, S. Diez-Gonzalez and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988; (*l*) K. Zeitler, *Angew. Chem., Int. Ed.*, 2005, **44**, 7506.

15 For kinetic studies of thiazolylidene-catalyzed benzoin reaction, see: M. J. White and F. J. Leeper, *J. Org. Chem.*, 2001, **66**, 5124.

16 (*a*) H. Stetter and G. Dämbkes, *Synthesis*, 1977, 403; (*b*) H. Stetter and G. Dämbkes, *Synthesis*, 1980, 309; (*c*) R. Heck, A. P. Henderson, B. Köhler, J. Rétey and B. T. Golding, *Eur. J. Org. Chem.*, 2001, 2623; (*d*) S. M. Mennen and S. J. Miller, *J. Org. Chem.*, 2007, **72**, 5260; (*e*) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler and S. J. Connon, *J. Org. Chem.*, 2011, **76**, 347; (*f*) C. A. Rose, S. Gundala, S. J. Connon and K. Zeitler, *Synthesis*, 2011, 190; (*g*) X. L. Huang and S. Ye, *Chinese Sci. Bull.*, 2010, **55**, 1753; (*h*) N. Kuhl and F. Glorius, *Chem. Commun.*, 2011, **47**, 573; (*i*) M. Y. Jin, S. M. Kim, H. Han, D. H. Ryu and J. W. Yang, *Org. Lett.*, 2011, **13**, 880; (*j*) I. Piel, M. D. Pawelczyk, K. Hirano, R. Fröhlich and F. Glorius, *Eur. J. Org. Chem.*, 2011, 5475.

17 For representative examples of intramolecular variants, see: (*a*) Y. Hachisu, J. W. Bode and K. Suzuki, *J. Am. Chem. Soc.*, 2003, **125**, 8432; (*b*) Y. Hachisu, J. W. Bode and K. Suzuki, *Adv. Synth. Catal.*, 2004, **346**, 1097; (*c*) D. Enders and O. Niemeier, *Synlett*, 2004, 2111; (*d*) D. Enders, O. Niemeier and T. Balensiefer, *Angew. Chem., Int. Ed.*, 2006, **45**, 1463; (*e*) H. Takikawa, Y. Hachisu, J. W. Bode and K. Suzuki, *Angew. Chem., Int. Ed.*, 2006, **45**, 3492; (*f*) D. Enders, O. Niemeier and G. Raabe, *Synlett*, 2006, 2431; (*g*) Y. Li, Z. Feng and S.-L. You, *Chem. Commun.*, 2008, 2263; (*h*) T. Ema, Y. Oue, K. Akihara, Y. Miyazaki and T. Sakai, *Org. Lett.*, 2009, **11**, 4866; for sterically controlled examples in the context of a multicatalytic cascade sequences, see: (*i*) S. P. Lathrop and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 13628; (*j*) D. Enders, A. Grossmann, H. Huang and G. Raabe, *Eur. J. Org. Chem.*, 2011, 4298; (*k*) K. E. Ozboya and T. Rovis, *Chem. Sci.*, 2011, **2**, 1835; for a recent application in natural product synthesis: (*l*) A. Takada, Y. Hashimoto, H. Takikawa, K. Hikita and K. Suzuki, *Angew. Chem., Int. Ed.*, 2011, **50**, 2297.

18 While this paper was under review, a related synthesis of α-hydroxy-1,3-ketoesters *via* the cross-coupling of aliphatic diketones with 3 equiv. of α-ketoesters using thiamine hydrochloride/Et_3N as the catalytic system was described by Fantin, Massi and co-workers: O. Bortolini, G. Fantin, M. Fogagnolo, P. P. Giovannini, V. Venturi, S. Pacifico and A. Massi, *Tetrahedron*, 2011, **67**, 8110.

19 (*a*) D. Enders and A. Henseler, *Adv. Synth. Catal.*, 2009, **351**, 1749; (*b*) D. Enders, A. Grossmann, J. Fronert and G. Raabe, *Chem. Commun.*, 2010, **46**, 6282; for cascade sequences involving an asymmetric intermolecular aldehyde–ketone crossed benzoin reaction, see: (*c*) P.-C. Chiang, J. Kaeobamrung and J. W. Bode, *J. Am. Chem. Soc.*, 2007, **129**, 3520; (*d*) J. Ma, Y. Huang and R. Chen, *Org. Biomol. Chem.*, 2011, **9**, 1791; (*e*) for an example *via* an enzymatic carboligation reaction, see: P. Lehwald, M. Richter, C. Röhr, H.-W. Liu and M. Müller, *Angew. Chem., Int. Ed.*, 2010, **49**, 2389.

20 (*a*) M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Org. Chem.*, 2005, **70**, 5725; (*b*) H. U. Vora, S. P. Lathrop, N. T. Reynolds, M. S. Kerr, J. Read de Alaniz and T. Rovis, *Org. Synth.*, 2010, **87**, 350; (*c*) the pK_a of catalyst **22** (H_2O) has been determined to be 17.7: C. D. Campbell, N. Duguet, K. A. Gallagher, J. E. Thomson, A. G. Lindsay, A. C. O'Donoghue and A. D. Smith, *Chem. Commun*, 2008, 3528.

21 (*a*) L. Baragwanath, C. A. Rose, K. Zeitler and S. J. Connon, *J. Org. Chem.*, 2009, **74**, 9214; (*b*) S. E. O'Toole and S. J. Connon, *Org. Biomol. Chem.*, 2009, **7**, 3584.

22 Importantly, mild conditions are required, as aldol reactions as a third undesired pathway also must be avoided: (*a*) H. Takikawa and K. Suzuki, *Org. Lett.*, 2007, **9**, 2713; for selected NHC/aldol cascade reactions, see: (*b*) E. Sánchez-Larios, J. M. Holmes, C. L. Daschner and M. Gravel, *Org. Lett.*, 2010, **12**, 5772; (*c*) F.-G. Sun, X.-L. Huang and S. Ye, *J. Org. Chem.*, 2010, **75**, 273.

23 Y. Li, Z.-A. Zhao, H. He and S.-L. You, *Adv. Synth. Catal.*, 2008, **350**, 1885.

24 $CHCl_3$ as solvent allows for preferential cross-benzoin formation.

25 For the use of thiophene-2-carbaldehyde as acyl donor also see Table 4, entry 8.

26 Acetaldehyde is used in excess due to its high volatility – with heavier aldehyde partners stoichiometric loadings could be employed.

27 It is noteworthy that test reactions with Rovis' highly versatile indanol-derived *N*-pentafluorophenyl triazolium precatalyst (*cf.* ref. 20) did not lead to any conversion.

28 Acylation is necessary to prevent the formation of two regioisomeric α-hydroxyketone products *via* keto–enol tautomerism during decarboxylation. Thus it is unlikely that – under the (at least slightly) basic conditions of NHC-catalysed AC processes – a high-yielding direct NHC-catalysed cross-coupling reaction between two aliphatic aldehydes of similar characteristics (*i.e.* where the formation of one isomer would not be preferred thermodynamically over the other) will ever be possible. For a enzymatic kinetic resolution of related substrates, see: G. Scheid, W. Kuit, E. Ruijter, R. V. A. Orru, E. Henke, U. Bornscheuer and L. A. Wessjohann, *Eur. J. Org. Chem.*, 2004, 1063.

29 For representative indirect methods of preparing crossed AC products, see: *Acyl silanes*: (*a*) X. Linghu and J. S. Johnson, *Angew. Chem., Int. Ed.*, 2003, **42**, 2534; (*b*) J. C. Tarr and J. S. Johnson, *Org. Lett.*, 2009, **11**, 3870; *Acyl phosphonates*: (*c*) A. S. Demir, I. Esiringü, M. Göllü and O. Reis, *J. Org. Chem.*, 2009, **74**, 2197; (*d*) C. C. Bausch and J. S. Johnson, *Adv. Synth. Catal.*, 2005, **347**, 1207; *Aldehyde-thiazolium carbene adducts*: (*e*) A. K. Mathies, A. E. Mattson and K. A. Scheidt, *Synlett*, 2009, 377; (*f*) A. E. Mattson and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 4508; *N-Silyl oxyketene imines*: (*g*) S. E. Denmark and T. W. Wilson, *Nat. Chem.*, 2010, **2**, 937; *electron transfer using a rigid scaffold as auxiliary*: (*h*) T. J. Donohoe, A. Jahanshahi, M. J. Tucker, F. L. Bhatti, I. A. Roslan, M. Kabeshova and G. Wrigley, *Chem. Commun.*, 2011, **47**, 5849.

30 To investigate the origins of the chemoselectivity we exposed ethyl pyruvate to the homobenzoin product of benzaldehyde in the presence **22** under identical conditions to those outlined in Table 1. Less than 1% of cross-coupled product **55** was observed. In a similar fashion, the homodimer of hydrocinnamaldehyde failed to undergo retroacyloin and coupling with ethyl pyruvate under identical conditions. We would therefore suggest that the chemoselectivity observed in these processes is due to kinetic control.

