Highly Chemoselective Direct Crossed Aliphatic-Aromatic Acyloin Condensations with Triazolium-Derived Carbene Catalysts

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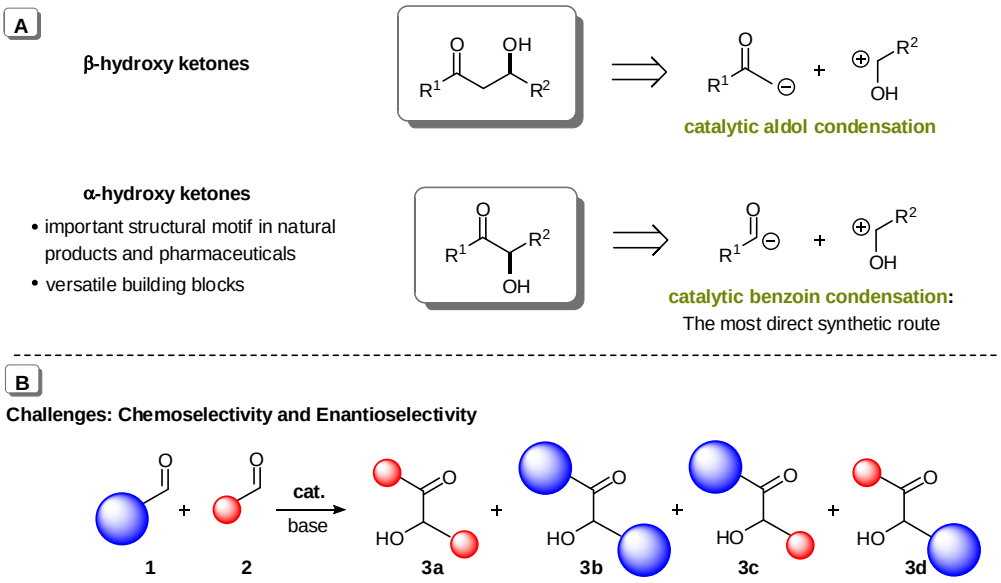
Abstract: It has been shown for the first time that triazolium pre-catalysts promote (in the presence of base) highly chemoselective crossed acyloin condensation reactions between aliphatic and *ortho*-substituted aromatic aldehydes. An *o*-bromine atom can serve as a temporary directing group to ensure high chemoselectivity (regardless of the nature of the other substituents on the aromatic ring) which then can be conveniently removed. The process is of broad scope and is operationally simple as it does not require the pre-activation of any of the coupling partners to ensure selectivtiy. Preliminary data indicates that highly enantioselective variants of the reaction are feasible using chiral pre-catalysts.

α-Hydroxy ketones are highly useful building blocks for the synthesis of heterocycles, natural products, agrochemicals and (inter alia[1]) pharmaceuticals.[2] In addition, the unsymmetrical nature of the building block allows for access to other important synthetic precursors, such as chiral 1,2-diols and amino alcohols.[3] As a consequence, the development of routes to these compounds *via* metal-catalysed heteroatom transfer[4] and organocatalytic α-oxidation chemistry[5] have been extensively investigated

recently.[6] While these methods are undoubtedly useful, if one considers the power and utility of the aldol reaction[7] as a C-C bonding forming process for the generation of β-hydroxy aldehydes/ketones, it is apparent that the organocatalytic direct coupling of two different aldehydes (if chemoselective) potentially offers a more modular and direct approach to the preparation of acyloins than α-functionalization chemistry (Scheme 1A).

Scheme 1. Comparison of Aldol Reactions with Acyloin/Benzoin Condensations and the Challenges associated with Direct Crossed Acyloin Condensations.

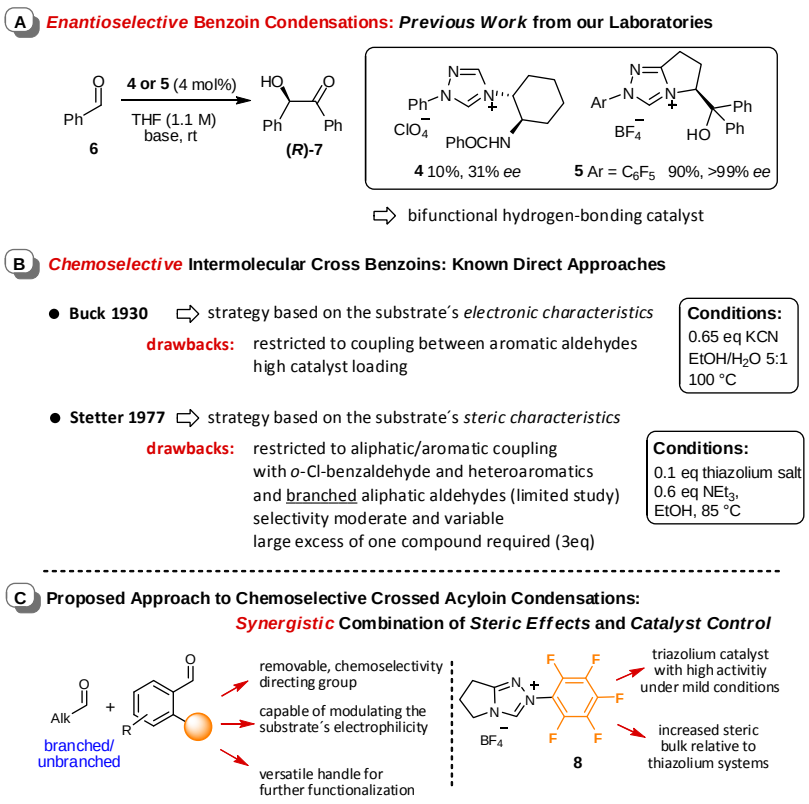


The acyloin condensation (AC) is one of the oldest carbon-carbon bond forming reactions in organic chemistry – with a rich history dating back to the pioneers Liebig and Wöhler in 1832.[8] For much of the intervening time, it has proven first an interesting mechanistic challenge[9, 10] and later a process which inspired the development of a suite of *N*-heterocyclic carbene-based catalysts capable of facilitating a remarkable array of reactions proceeding through *umpolung* intermediates.[11] While significant advances in the catalysis of the (asymmetric) carbene-catalysed homo-AC reaction have been made recently,[12,13,14,15,16] the absence of a *selective* carbene-mediated catalytic methodology capable of promoting the intermolecular reaction[17] between two different aldehydes in a chemo- and enantioselective fashion, curtails the utility of the process. The challenges associated with the development of an efficient and selective crossed acyloin condensation protocol are considerable – the

objective is to exercise control (*via* the catalyst) over the process to the extent that a single major adduct is formed from 8 possible products (4 chiral ketones **3a-d** × 2 enantiomers each, Scheme 1B) in good yield.[18]

In 1930, Buck *et al*. published a report concerning the crossed benzoin condensation of aromatic aldehyde partners of contrasting electronic character in the presence of high loadings of cyanide ion (Scheme 2). This investigation concentrated on the use of benzaldehydes of disparate electronic characteristics; aliphatic aldehydes were not employed in the study.[19,20] Over 30 years ago Stetter *et al*.,[21] in an attempt to develop efficient routes to 1,2-diketones, reported in a short, limited study that an achiral thiazolium salt-derived carbene catalysed the crossed AC between aromatic and aliphatic aldehydes: good crossed product yields could be obtained if the aliphatic aldehyde was utilised in high excess (3.0 equiv), however chemoselectivity was both highly variable and substrate dependent – which significantly detracted from the synthetic applicability of the methodology.[22,23,24]

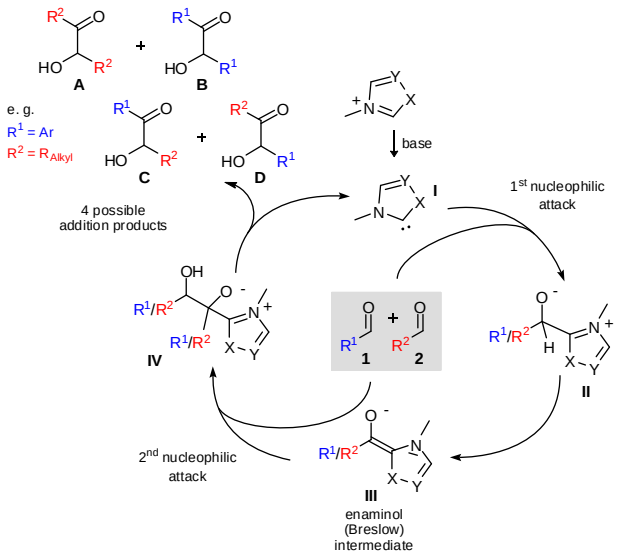
Scheme 2. Previous Approaches and the Proposed Strategy Detailed in this Work



As part of a target oriented study of *intramolecular* crossed AC reactions, Miller *et al*. carried out one *intermolecular* AC reaction reported to be selective involving *o*-tolualdehyde and hexanal in the presence of stoichiometric loadings of a triazolium ion precatalyst, however the yield of the only isolable product was low (16%).[25] A number of significant approaches to the catalytic synthesis of products (formally) derived from intermolecular AC reactions have been developed, including the use of enzyme catalysts[26] and polymer bound aldehydes,[27] in addition to indirect methods where chemoselectivity is derived from the pre-formation of an *umpolung* reagent, such as acyl-silanes,[28] acyl-phosphonates[29] and aldehyde-thiazolium carbene adducts.[30] Enders recently disclosed that aromatic aldehydes could be coupled to α,α,α-trifluoroacetophenone in good to excellent yields under the influence of triazolium carbene catalysis,[31] however, *to the best of our knowledge a general carbene-catalysed process capable of promoting the direct, chemoselective*[32] *(and enantioselective) crossed AC reaction between two different aldehydes remains elusive*.[33]

In approaching this problem, we considered what we regarded as the key question: the aldehyde is the electrophile in both the Breslow intermediate (BI, Scheme 3: **III**)- and stereocentre-forming steps, so if, for instance, aldehyde **2** is the superior electrophile in the BI-formation step (Scheme 3: **I→III**), on what basis (using traditional catalyst design strategies) can we expect **2** not to be the superior electrophile in the subsequent stereocentre-forming step (Scheme 3: **III→IV**) – leading to the homodimer **3a** instead of cross product **3d** (Scheme 1B and Scheme 3: **A** resp. **D**)?

Scheme 3. General Mechanism for NHC-catalyzed Benzoin/Acyloin Condensations



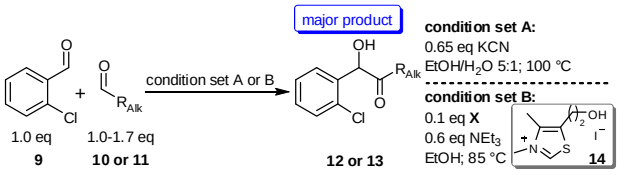
Recently we reported that hydrogen bonding could be utilised as a control element in enantioselective homo-benzoin condensation reactions.[34, 35] The pentafluorophenyl-substituted triazolium precatalyst **5** (which followed our first generation system **4**) could promote the formation of benzoin (**7**) from benzaldehyde (**6**) with excellent efficiency and stereocontrol (Scheme 2A). We postulated that the rigid, hindered nature of **5**, coupled with the presence of a catalyst hydrogen bond-donating group,[36] would allow the catalyst to potentially distinguish between the *two* aldehyde electrophiles based on the recognition of *two different substrate properties* – steric bulk and Brønsted basicity. In addition to catalyst control, we envisaged that a degree of synergistic substrate control could be brought to bear on the process in the form of a removable chemoselectivity-enhancing substituent in the *ortho* position of the aromatic aldehyde. Stetter *et al*.[21] had reported that *o*-chloro-substituted benzaldehydes participated in more selective crossed AC reactions than their unsubstituted counterparts. Thus we proposed that a halogen atom could be used in this capacity, which could later be either easily removed by hydrogenolysis or utilised as a functional handle in further structural elaboration of the product (Scheme 2C).

Before testing this hypothesis, we wished to be certain that highly chemoselective <u>direct</u> crossed acyloin chemistry was not possible using existing technology. For instance, while Buck *et al*.[19] did not employ aliphatic aldehydes in their study and Stetter[21] utilised a large excess of one aldehyde component, we felt it prudent to first examine these two protocols to ensure that the dearth of a chemoselective protocol in the literature is not due to either a simple oversight or omission by previous researchers. Aiming for a widely applicable, practical procedure that would also allow for the implementation of higher advanced aldehyde building blocks, we focussed on conditions which would not employ a large excess of either of both coupling partners (*i.e.* aliphatic aldehyde ≤ 1.7 eq).[37]

Accordingly we carried out experiments examining the reaction between an aliphatic and an aromatic aldehyde under the influence of either cyanide (conditions defined by Buck *et al*.)[19] or thiazolium derived carbene (conditions defined by Stetter *et al*.)[21] catalysis (Table 1). In the presence of cyanide ion (65 mol%) the reaction between **9** and isobutyraldehyde (**10**) produced a poor yield of **12** as the major product, while reaction with the unbranched hydrocinnamaldehyde (**11**) failed to generate cross

product at all (entries 1-2). Utilisation of Stetter's conditions proved somewhat more successful, with the isolation of 36-38% yields of a 'major' cross product possible when 1-1.7 equivalents of the aliphatic aldehyde component were employed (entries 3-5)

Table 1. Short study on the general applicability of known direct cross acyloin procedures using branched and unbranched aliphatic aldehydes.



Entry	Condition [a]	Equivalents	'Aliphatic' Aldehyde	Yield (%)[b]
1	**A**	1.0	**10**	21 **12**
2	**A**	1.0	Ph **11**	0
3	**B**	1.0	**10**	38 **12**
4	**B**	1.7	**10**	36 **12**
5	**B**	1.0	Ph **11**	38 **13**

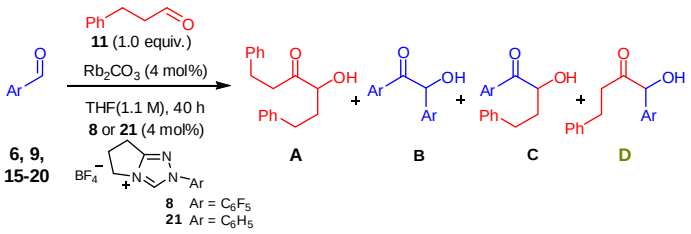
[a] For details see Supporting Information. [b] Isolated yield.

From an analysis of the results of this study, a clear picture of the limited potential of the current benchmark protocols for the direct crossed AC reaction emerged: both do not tolerate reduced amounts of the aliphatic aldehyde and also fail to produce synthetically useful amounts of cross-product if unbranched aldehydes are employed. This encouraged us to return our attention to the original proposal involving the use of triazolium salt-derived systems.

Before attempting to examine the potential of hydrogen-bonding as a control element in these reactions, we first wished to orient ourselves with respect to the natural bias (if any) a triazolium-derived carbene devoid of protic substituents would display towards one of the coupling partners in a crossed AC reaction. As a model process we chose the AC reaction between a range of substituted benzaldeyhdes **9** and **15-20** (of variable steric and electronic characteristics) and the relatively

unhindered hydrocinnamaldehyde (**11**) in the presence of the achiral precatalysts **8** or **21** and base. The results of these experiments are outlined in Table 2.

Table 2. Crossed AC Reactions: Preliminary Experiments



Entry	Ar	Prod.	Yield **A** (%)[a]	Yield **B** (%)[a]	Yield **C** (%)[a]	Yield **D** (%)[a]
1[b]	Ph **6**	**22**	>2	8	>2	10
2	Ph **6**	**22**	26	20 (**7**)	11	48
3	4-Cl-C_6H_4 **15**	**23**	53	44	2	43
4	3-Cl-C_6H_4 **16**	**24**	44	34	6	50
5	2-Cl-C_6H_4 **9**	**13**	8	15	9	51
6	2-F-C_6H_4 **17**	**25**	52	45	14	34
7	2-MeO-C_6H_4 **18**	**26**	20	16	21	59
8	2-CF_3-C_6H_4 **19**	**27**	8	6	10	81
9	2-Br-C_6H_4 **20**	**28**	0	9	8	49
10[c]	2-Br-C_6H_4 **20**	**28**	4	10	5	73
11[d]	2-Br-C_6H_4 **20**	**28**	5	10	6	76
2[e]	2-Br-C_6H_4 **20**	**28**	>2	6	10	79
13[f]	2-Br-C_6H_4 **20**	**28**	>2	21	11	74
14[g]	2-Br-C_6H_4 **20**	**28**	31	4	7	84
15[h]	2-Br-C_6H_4 **20**	**28**	61	3	7	89
16[i]	2-Br-C_6H_4 **20**	**28**	84	0	10	90

[a] Yield determined by ^{1}H NMR spectroscopy using styrene as an internal standard. Note: yields of **12** and **22-28a** and **22-285b** account for the 2:1 stoichiometry. To obtain the mol% of these materials divide the yield by 2. [b] Phenyl-substitued triazolium precatalyst **21** was used instead. [c] 8 mol% catalyst. [d] 10 mol% catalyst loading. [e] 1.3 equiv of **20** and 8 mol% catalyst. [f] 1.5 equiv of **20** and 8 mol% catalyst. [g] 1.3 equiv of **11** and 8 mol% catalyst. [h] 1.5 equiv of **11** and 8 mol% catalyst. [i] 1.7 equiv of **11** and 8 mol% catalyst.

As expected the pentafluorophenyl-substituted catalyst **8** proved a superior system to **21** under these conditions (entries 1-2).[35] The coupling of benzaldehyde (**6**) and **11** proceeded with poor chemoselectivity – while a marked preference for the formation of products derived from the aliphatic Breslow intermediate (e.g. *via* initial attack of the catalyst on **11** (*i.e.* **22a+22d** *vs* **22b+22c**)) was observed, all four possible products (homodimers **22a**/**22b** and crossed products **22c**/**22d**) were formed

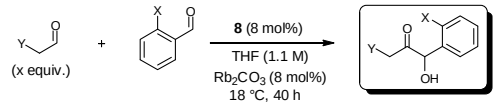
without any one being present at synthetically useful levels. The activation of the aromatic aldehyde component with a chlorine atom in either the *m*- or *p*-position failed to influence chemoselectivity to any appreciable extent (entries 3-4) the preference for the cross-coupled products **D** was slightly improved, at the expense of the formation of increased amounts of the aryl homobenzoins **B**. However, the use of the *o*-substituted analogue **9** generated **13d** as the dominant product in moderate yield (entry 5). Further investigation revealed that the improved chemoselectivity associated with the use of *o*-substituted aldehydes is primarily related to the steric requirement of the substituent, although its electronic characteristics do also seem to play a minor role. For instance, the small but highly electronegative fluorine atom does not confer high chemoselectivity (entry 6), however use of larger units such as the electron withdrawing methoxy- and the electron releasing trifluoromethyl-substituents (entries 7 and 8 respectively) allow relatively selective crossed AC reactions to occur – with the latter suppressing the pathways leading to **27a-c** to the extent that **27d** was formed in 81% yield.

Particularly gratifying was the performance of the *o*-bromo derivative **20**. This coupling partner is of considerable potential interest for two reasons: firstly, the bromine atom in the product (*i.e.* **28d**) can serve as a functional handle for further elaboration (radical generation, participation in transition metal catalyzed coupling reactions *etc*.), while secondly, as mentioned earlier (*vide supra*), we envisaged that it should be possible to cleanly remove the halogen from the product - which allows one to aspire towards the use of an *o*-bromo substituent as a removable tool to control chemoselectivity in these processes, thereby providing access to products (after debromination) which would be otherwise difficult to prepare in good yield *via* carbene-catalyzed crossed AC chemistry. It was found that **20** coupled to **11** with very good chemoselectivity and moderate yield initially (entry 9). Subsequent optimization of the reaction conditions (entries 10-16) allowed the synthesis of **28d** in 90% yield by employing a small excess of **11** (1.7 equiv.) in the presence of 8 mol% of **8**.

The scope of the process with respect to the 'aliphatic' or '*umpolung*' aldehyde component was next investigated. *o*-Substituted electrophiles **19** and **20** were coupled to a range of unbranched aldehydes **11** and **29**-**32** under our optimized conditions in the presence of catalyst **8** at room temperature (Table 3). Acetaldehyde (**29**) proved a challenging substrate to utilize at ambient temperature due to its low boiling point (entry 1), however use of a tenfold excess (feasible due to the low cost of this reagent) resulted in good isolated yield of its cross product with **19** (*i.e.* **33**, entry 2). The less volatile

unbranched aldehydes *n*-propanal (**30**, entries 3-5), *n*-pentanal (**31**, entries 6-7), hydrocinnamaldehyde (**11**, entries 8-9) and phenylacetaldehyde (**32**, entries 10-11) could be efficiently coupled to either **19** or **20** with good product yields without difficulty using a smaller excess of 1.7-2.5 equiv. *It is perhaps interesting to note that coupling of* ***11*** *(1.7 equiv.) to* ***19*** *at 5 °C is less chemoselective than an otherwise identical reaction at 18 °C* (entries 8-9). In the case of the reaction at the lower temperature, **27d** was still obtained as the major product, however significantly elevated levels of products derived from initial attack of the catalyst on **19** (*i.e.* **27b** and **27c**) were detected, indicating that these coupling reactions may proceed under a significant degree of thermodynamic control.[38]

Table 3. Evaluation of Substrate Scope: Unbranched Aldehydes



29 Y = H
30 Y = CH_3
31 Y = n-C_3H_7
11 Y = CH_2Ph
32 Y = Ph

19 X = CF_3
20 X = Br

33 Y = H, X = CF_3
34 Y = CH_3, X = CF_3
35 Y = CH_3, X = Br
36 Y = n-C_3H_7, X = CF_3
37 Y = n-C_3H_7, X = Br
38 Y = Ph, X = CF_3
39 Y = Ph, X = Br

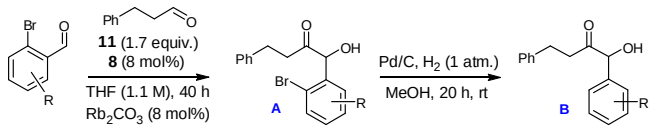
Entry	'Aliphatic' Aldehyde	X	'Aromatic' Aldehyde	Product	Yield D (%)[a]
1	**29**	1.7	**19**	**33**	50[b]
2	**29**	10.0	**19**	**33**	78
3	**30**	1.7	**19**	**34**	79
4	**30**	1.7	**20**	**35**	68[b]
5	**30**	2.5	**20**	**35**	73
6	**31**	1.7	**19**	**36**	84
7	**31**	1.7	**20**	**37**	77
8[c]	**11**	1.7	**19**	**27d**	60[b]
9[d]	**11**	1.7	**19**	**27d**	86
10	**32**	1.7	**19**	**38**	81
11	**32**	1.7	**20**	**39**	76

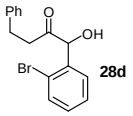
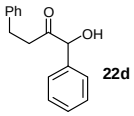
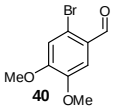
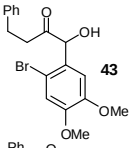
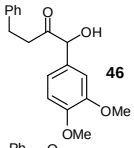
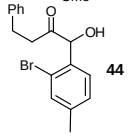
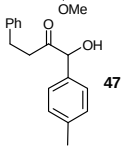
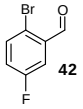
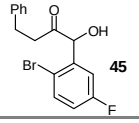
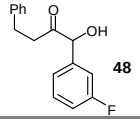
[a] Isolated yield. [b] Yield determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [c] At 5 °C: 17% and 16% yields of homo- and heterocoupling products respectively derived from initial attack of the catalyst on **19** were obtained. [d] At 18 °C: 10% yields of both homo- and heterocoupling products derived from initial attack of the catalyst on **19** were obtained.

To demonstrate the potential of the use of an *ortho*-bromo substituent as a solution to circumvent the inherent lack of chemoselectivity in crossed AC reactions involving aromatic aldehydes and unbranched aliphatic aldehydes, we carried out the coupling of a variety of *o*-bromobenzaldehydes (**20** and **40**-**42**)

equipped with both electron neutral (entry 1), electron donating (entries 2-3) and electron withdrawing (entry 4) substituents with **11** (Table 4). Good to excellent yields of coupled products were obtained in each case under standard conditions. Adducts **28d** and **43-45** were then smoothly and conveniently debrominated under an atmosphere of hydrogen in the presence of Pd/C to give hydroxyketones **18d** and **46-48** respectively in uniformly excellent yields. Thus we would submit, that the *o*-bromo substituent can be employed as a temporary directing group which can first divert the course of an otherwise relatively unselective (see Table 1, entry 2 *vs.* entries 9 and 16) coupling reaction towards the formation of a single major product (irrespective of the overall electronic nature of the aromatic aldehyde coupling partner), and then either serve as a functional handle if required or be cleanly removed to give debrominated products *not otherwise accessible in high yield directly from a operationally simple carbene-catalysed AC process*.

Table 4. Exploitation of a Removable 2-Bromo Substituent



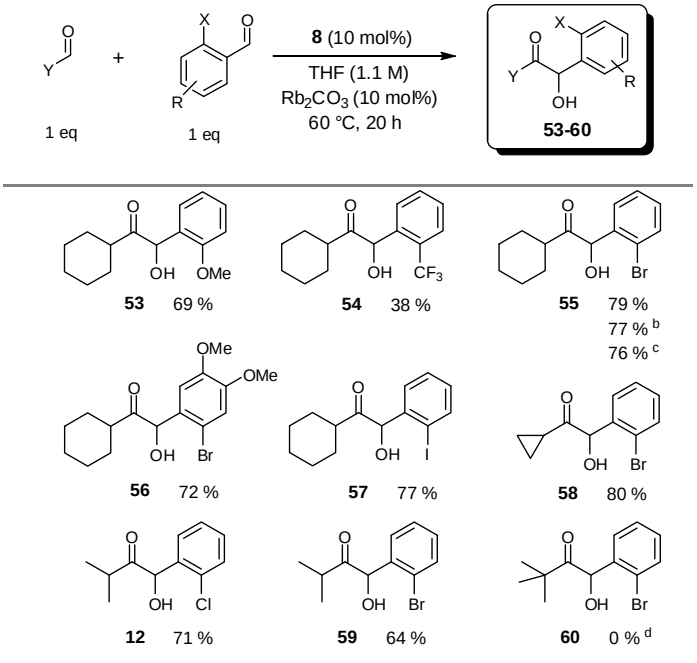
Entry	Aldehyde	Acyloin Product (**A**)	Yield (%)[a]	Reduction Product (**B**)	Yield (%)[a]
1	 **20**	 **28d**	90	 **22d**	90
2	 **40**	 **43**	93	 **46**	96
3	 **41**	 **44**	88	 **47**	93
4	 **42**	 **45**	80	 **48**	92

[a] Isolated yield after chromatography.

For this methodology to be genuinely synthetically useful, its scope with respect to the 'nucleophilic' component must not be limited to unbranched aldehydes. Initial experiments involving the coupling of α-substituted aldehydes at room temperature resulted in poor conversion (<50%) even after prolonged

reaction times. At 60 °C however, these substrates will participate in efficient crossed AC reactions (Table 5). The reaction between cyclohexane carbaldehyde (**49**) and *o*-anisaldehyde (**18**) furnished **53** in good yield. We found that *o*-trifluoromethyl benzaldehyde **19** performed unsatisfactorily under these conditions (the stability of product **54** under the reaction conditions appears to be problematic, *vide infra*[38]; product **54**). *o*-Bromobenzaldehydes **20** and **40** both coupled with cyclohexanecarbaldehyde (**49)** to afford **55** and **56** respectively in good isolated yield. *o*-Iodobenzaldehyde (**52**) is also compatible with the methodology (the first time this aldehyde has been evaluated as a AC substrate, product **57**). The first use of the interesting substrate **50** led to the formation of the densely functionalised cyclopropyl-substituted ketone **58** in 80% yield. 2-Methylpropanal (**10**) proved a challenging substrate due to its low boiling point but could still be converted to **12** and **59** in good yields in the presence of **9** resp. **20**, while at this stage it appears that pivaldehyde is too bulky a substrate to form a nucleophilic Breslow intermediate under these conditions. Importantly, this cross coupling procedure employing branched aldehydes does not require an excess of one of the coupling partners, thus providing a catalytic and relatively waste-free, selective access to such valuable cross acyloin products.

Table 5. Evaluation of substrate scope: branched aldehydes



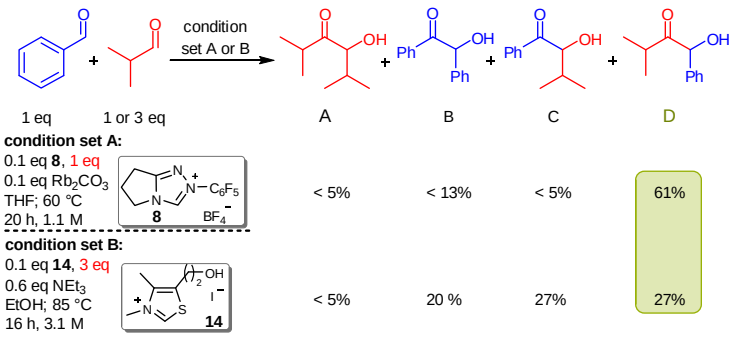
[a] Isolated yield. [b] 1.5 equiv. of aldehyde **49**. [c] K_2CO_3 used instead of Rb_2CO_3. [d] No cross AC product detected; only 16% of aromatic homocoupled product was obtained (yield determined by ^{1}H NMR spectroscopy using stilbene as an internal standard)

The question regarding the origin of the chemoselectivity observed is both intriguing and difficult to definitively answer at this juncture. It is reasonable to assume that the presence of the *o*-substituent retards the rate of attack of the carbene on the aromatic aldehyde, resulting in increased concentrations of the Breslow intermediate derived from initial attack on the aliphatic aldehyde. What is unclear, is why this intermediate (rather counter intuitively) then prefers to react with the presumably more hindered *o*-substituted benzaldehyde over another molecule of aliphatic aldehyde?

There are several possible explanations, such as a π-iminium interaction in the developing TS as the enolamine attacks the aromatic aldehyde,[27, 39] a stabilising (and selectively formed) hydrogen bond between the more basic aromatic aldehyde carbonyl oxygen and the enolamine hydroxyl group, or perhaps most importantly given the supporting evidence uncovered as this study progressed - a degree of thermodynamic product control. Based on the well-established mechanistic picture of acyloin/benzoin condensations,[11e, 40] it is also reasonable to assume that the properties of the Breslow intermediate should also be dependant to a significant extent on the nature of the catalyst it is derived from. What is certain is that these issues are now ripe for investigation.

We were first interested in examining the influence of the choice of catalyst on the outcome of these reactions from a chemoselectivity perspective. We challenged our optimized catalytic system (condition set A, Scheme 4) with the reaction between benzaldehyde – lacking the selectivity-controlling *ortho*-substituent – and *iso*butyraldehyde and then repeated the experiment under Stetter´s conditions (condition set B, Scheme 4) employing a thiazolium derived carbene instead of the triazolium pre-catalyst. In contrast to the results reported by Stetter,[21] in our hands condition set B provides both cross-products and the homo arylbenzoin in a *ca*. 1:1:1 ratio (combined yield of cross-acyloin products: 54%).[41] Use of condition set A on the other hand, involving the triazolium catalyst **8**, results in remarkably high selectivity for the cross-coupled acyloin **D**, which could be isolated in 61% yield. Neither the cross-coupled **C** nor homobenzoin **B** was formed in significant amounts. It is therefore clear that the catalyst exerts a significant degree of control over the process from a chemoselectivity standpoint.

Scheme 4. Influence of the Catalytic System on Chemoselectivity



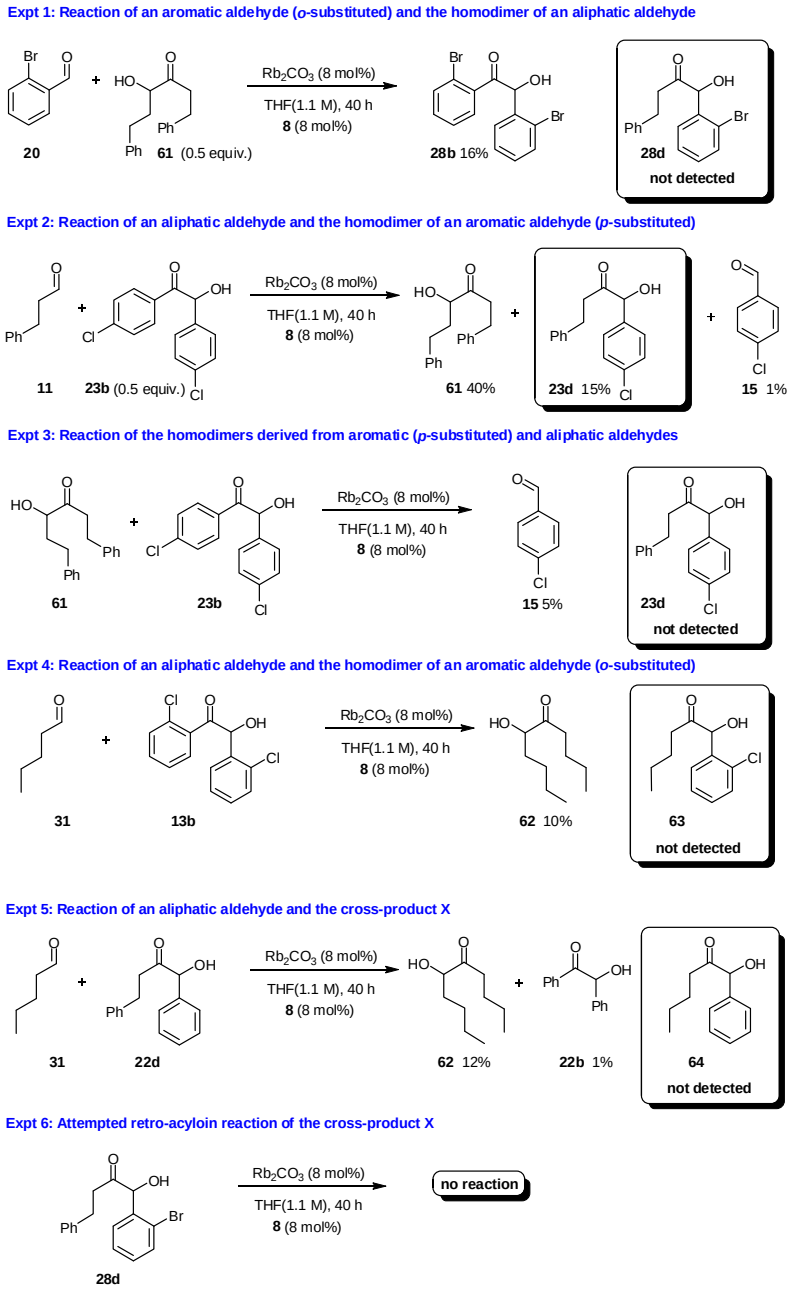
[a] Yields determined by ^{1}H NMR spectroscopy using stilbene as internal standard. See supporting information for details.

In an attempt to further shed light on the origins of the observed chemoselectivity a number of crossover experiments were carried out. The results of these experiments are outlined below (Scheme 5). In the first instance, we wished to establish the degree of reversibility of these processes. We therefore treated the *o*-substituted aldehyde **20** with the catalyst **8** under our standard conditions in the presence of homodimer **61** (Expt 1). The slow dimerization of **20** was observed but no products (such as **28d**) derived from the retro-acyloin of **61** could be detected. Next we investigated the opposite pairing of starting materials, *i.e.* an 'aliphatic' aldehyde **11** and a homodimer derived from a (*para*-substituted) aromatic aldehyde (*i.e.* **23b**, Expt 2**)**. Interestingly, this experiment afforded significant amounts of the cross-product **23d**, along with free aldehyde **15** (which also stems from a retro-acyloin reaction) and the homodimer **61**. When the experiment was repeated where the aliphatic aldehyde **11** was replaced with its homodimers **61** (Expt 3), again retroacyloin of **23b** was observed but in this case no coupling to form cross-product **23d** occurred. These results seemed to indicate that the benzoin **23b** is able to revert to its parent aldehyde under the reaction conditions, whereas the homodimer **61** derived from hydrocinnamaldehyde is not. To probe this further, the *ortho*-isomer of benzoin **23b** (*i. e.* **13b**, Expt 4) was treated with an aliphatic aldehyde **31** in the presence of the catalyst. Gratifyingly, no cross product **63** was detected in this experiment (Expt 4).

Thus it would appear that the *o*-substituted **13b** is more stable towards the catalyst than its *p*-isomer **23b**, which, together with the rather slow rate of dimerization of *o*-bromobenzaldehyde (**20**) and hydrocinnamaldehyde (**11**) and the reluctance of the 'aliphatic' homodimer **61** to undergo a retro-acyloin reaction, goes some way towards explaining the chemoselectivity observed in these processes.

In a similar cross-over experiment involving the cross product **22d** and the aliphatic aldehyde **31** we observed trace amounts of benzoin (**22b** - which could only arise from the retroacyloin of **22d)** and homodimer **62** (Expt 5). No cross product **64** was detected. Finally, exposure of the cross product **28d** derived from reaction of *o*-bromobenzaldehyde (**20**) and hydrocinnamaldehyde (**11**) to the catalyst under standard conditions failed to produce any products.

Scheme 5. Crossover Experiments under Optimized Conditions Using Triazolium Precatalyst **8**

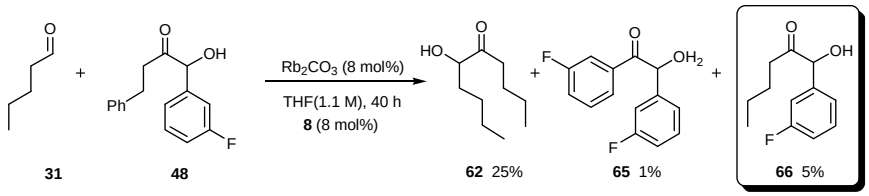


A number of conclusions can be drawn from these reactions:

- 'Aliphatic' and *o*-substituted benzaldehydes dimerize, but do so only slowly (Expts 1, 2 and 4-5). This is central to attaining high chemoselectivity in these processes.
- The homodimers derived from 'aliphatic' aldehydes do not participate in retro-acyloin chemistry under these conditions and are essentially formed irreversibly (Expts 1 and 3)
- Unhindered benzoins (*i.e.* homodimers of aromatic aldehydes) will participate in retro-acyloin chemistry under these conditions, whereas *o*-substituted isomers will not (Expts 2-4).
- The α-arylketone cross-product (the major product under our conditions) from the reaction of an 'aliphatic' and an aromatic aldehyde undergoes retro-acyloin either slowly (Expt 5) or not at all (Expt 6).
- The crossed acyloin reactions involving unhindered benzaldehydes are subject to a far greater degree of thermodynamic control than those involving hindered analogues (Expts 1-6). Given that the energy differences between the acyloin products is likely to be small – this results in relatively unselective reactions where benzaldehydes devoid of *o*-substitution are employed.[42]

To support the theory that cross-products derived from reactions involving activated, unhindered benzaldehydes are more amenable to retro-acyloin reactions (and hence are formed in lower yields) we synthesized **48** and subjected it to the reaction conditions in the presence of pentanal (**31**). We were pleased to observe increased levels of products derived from the retro-acyloin reaction of **48** relative to those observed using benzaldehyde as the reacting partner (see Scheme 6 and Exp 6, Scheme 5). Thus it is clear that the reversibility of the process is also influenced by the electronic nature of the benzaldehyde partner, with more activated aldehydes participating in less chemoselective reactions.

Scheme 6. Investigation of the Use of Cross Products Derived from Activated yet Unhindered Aldehydes



Overall, it is clear that crossed-coupling is facilitated by the slow dimerizability of the aliphatic aldehyde and *o*-substituted benzaldehydes. Given that none of the products derived from the cross-coupling of these aldehydes could demonstrably participate in retro-acyloin reactions, why cross-coupling is faster than dimerization and why the α-arylketone cross-product is favored over the other still require explanation. We would propose that it is reasonable to assume that initial attack of the carbene on the aliphatic aldehyde is preferred on electronic grounds – *i. e.* the more electron rich benzaldehyde carbonyl moieties make for poorer electrophiles in the first step of the catalytic cycle. This is supported by the observation that the use of more activated, halogen-substituted benzaldehydes generates greater levels of homobenzoin products derived from initial attack on the benzaldehyde moiety (see entries 3-6 and 9, Table 2). In the case of *o*-substituted benzaldehydes this preference for the aliphatic partner as the initial site of attack would obviously be exaggerated for steric reasons; this argument can be underlined by the decreasing amount of these homobenzoins detected with increasing size of the *ortho*-halogen substituent (*o*-F, *o*-Cl, *o*-Br with 45%, 15% and 9% of homo-coupled product, see entries 5, 6 and 9, Table 2).

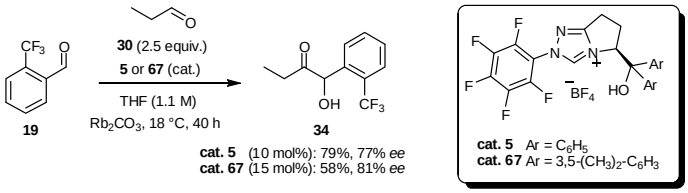
It is difficult to establish why the BI then prefers to attack the hindered aromatic aldehyde over another molecule of aliphatic aldehyde. In a natural product synthesis study involving an intramolecular AC step Miller[25] has suggested that a stabilizing interaction between orthogonally aligned carbonyl and aromatic moieties known to exist in α-phenyl ketones (in cases where it is stereoelectronically permitted) may influence the chemoselective outcome of AC reactions between aliphatic and aromatic aldehyde components. It is tempting to draw parallels in this study, *i.e.* that the observed preference for the α-arylketone cross product over the α-substituted aromatic ketone analogue is related to the contribution of this interaction, which presumably results in greater reversibility of the latter cross-

product over the former. However, it should be pointed out that the seemingly logical extension of this argument to account for the preference for cross-product formation over aliphatic aldehyde dimerization is less sound at this juncture, since we could not observe any retro-acyloin chemistry involving the aliphatic dimers.

What can be safely inferred is that chemoselectivity in these processes is not governed by a single factor alone but rather a confluence of factors depending on the catalyst employed and the steric and electronic nature of the reactants. That being said, it is clear that one can achieve high selectivity in the diverse array of AC reactions examined in this study by using catalyst **8** in the presence of an aromatic aldehyde incorporating an (removable) *o*-bromo substituent, irrespective of other substrate characteristics.

While the methodologies outlined above allow one to carry out highly chemoselective crossed AC reactions using a combination of catalyst properties and the steric effects of the substrates, the ability to control the stereochemical outcome of these reactions is of course the ultimate goal. To this end **19** was coupled with **30** in the presence of the bifunctional chiral triazolium salt **5** (10 mol%) to afford the expected product **34** in good yield and enantiomeric excess (Scheme 7).

Scheme 7. Chemo- and Enantioselective Crossed Acyloin Condensation



The novel precatalyst **67**, which possesses a larger diarylcarbinol unit, is less active than **5** but promoted the same reaction with improved enantioselectivity (81% *ee*). While this aspect of the study is currently at an early stage of development, it is clear from analysis of these preliminary data that the process is amenable to the efficient transfer of stereochemical information from catalyst to product.

Conclusions

In summary, we have developed the first efficient, chemoselective intermolecular crossed AC reactions involving triazolium precatalysts. A key discovery is the use of an *o*-bromo substituent as a temporary chemoselectivity-controlling group which can subsequently be removed conveniently in high yield. The methodology is of very broad scope: hindered, activated and electron-rich aromatic aldehydes are compatible, as are both unbranched and more hindered branched aliphatic aldehydes. Importantly, unlike the previous benchmark study in the literature involving a thiazolium catalyst, in these reactions the expected product from the cross-coupling of two aldehydes can be confidently predicted beforehand, and the methodology is complementary to existing methodologies based on enzymatic catalysis, as it consistently furnishes the opposite (in an *umpolung* context) crossed-product in high yield (with the exception of some pyruvate decarboxylases capable of accepting aliphatic aldehydes as donors in place of their natural α-ketoacid substrates). It was found that the use of the triazolium catalyst **8** is also critical for the promotion of chemoselective reactions. A series of crossover experiments revealed that the aliphatic dimer products did not demonstrably participate in retro-acyloin processes and that the presence of an *o*-substituent in the aromatic aldehyde component prevents both the benzoin and α-arylketone products from reverting to starting materials under the reaction conditions. The feasibility of highly enantioselective crossed AC reactions has also been established for the first time – investigations aimed at further refining the asymmetric catalysis and elucidating the origins of the chemoselectivity are now underway.

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Supporting Information Available: Experimental details, general procedures and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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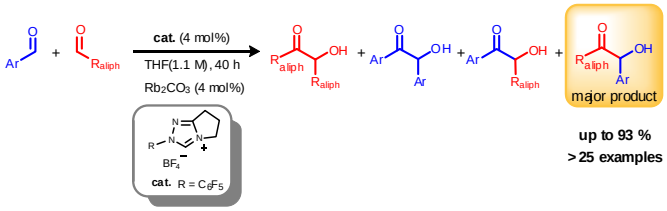
SYNOPSIS TOC (Word Style "SN_Synopsis_TOC").



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