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

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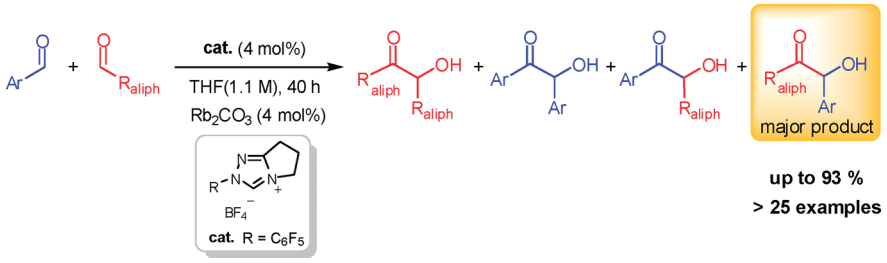

It has been shown for the first time that triazolium precatalysts promote (in the presence of base) highly chemoselective crossed acyloin condensation reactions between aliphatic and *ortho*-substituted aromatic aldehydes. An *o*-bromine atom can serve as a temporary directing group to ensure high chemoselectivity (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 preactivation of any of the coupling partners to ensure selectivtiy. Preliminary data indicate that highly enantioselective variants of the reaction are feasible using chiral precatalysts.

Introduction

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-catalyzed heteroatom transfer[4] and organocatalytic α-oxidation chemistry[5] has been extensively investigated recently.[6]

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.[7] For much of the intervening time, it has proven first an interesting mechanistic challenge[8,9] and later a process which inspired the development of a suite of N-heterocyclic

(1) (a) For use as photocleavable protecting groups see: Pirrung, M. C.; Shuey, S. W. *J. Org. Chem.* **1994**, *59*, 3890. (b) For use as an anchoring group for materials see: Fuhrmann, G.; Nelles, G.; Zilai, B.; Obermaier, M. WO 2010/049042 A2.

(2) Hoyos, P.; Sinisterra, J. -V.; Molinari, F.; Alcántara, A. R.; Domínguez de María, P. *Acc. Chem. Res.* **2010**, *43*, 288.

(3) For instance, (−)-ephedrine is available from a thiamine-dependent enzyme-catalyzed reaction which produces (*R*)-phenylacetylcarbinol: Rosche, B.; Sandford, V.; Breuer, M.; Hauer, B.; Rogers, P. L. *J. Mol. Catal. B* **2002**, *19*, 109.

(4) For selected reviews, see: (a) Plietker, B. *Tetrahedron: Asymmetry* **2005**, *16*, 3453. (b) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919.

(5) For selected examples on organocatalytic α-hydroxylations and α-oxyaminations, see: (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435. (d) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124. (e) Gotoh, H.; Hayashi, Y. *Chem. Commun.* **2009**, 3083. (f) Palomo, C.; Vera, S.; Velilla, I.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8054. (g) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166. (h) Poe, S. L.; Bogdan, A. R.; Mason, B: P.; Steinbacher, J. L.; Opalka, S. M.; McQuade, D. T. *J. Org. Chem.* **2009**, *74*, 1574.

(6) Recent reviews: (a) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995. (b) Marigo, M.; Jørgensen, K. A. α-Heteroatom Functionalization. *Enantioselective Organocatalysis*; Wiley: Weinheim, Germany, 2007.

(7) Wöhler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249.

(8) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

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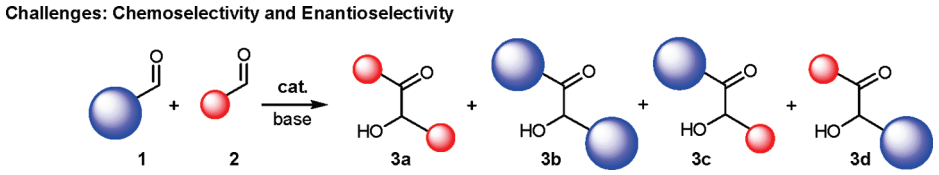
SCHEME 1. Challenges Associated with Direct Crossed Acyloin Condensations



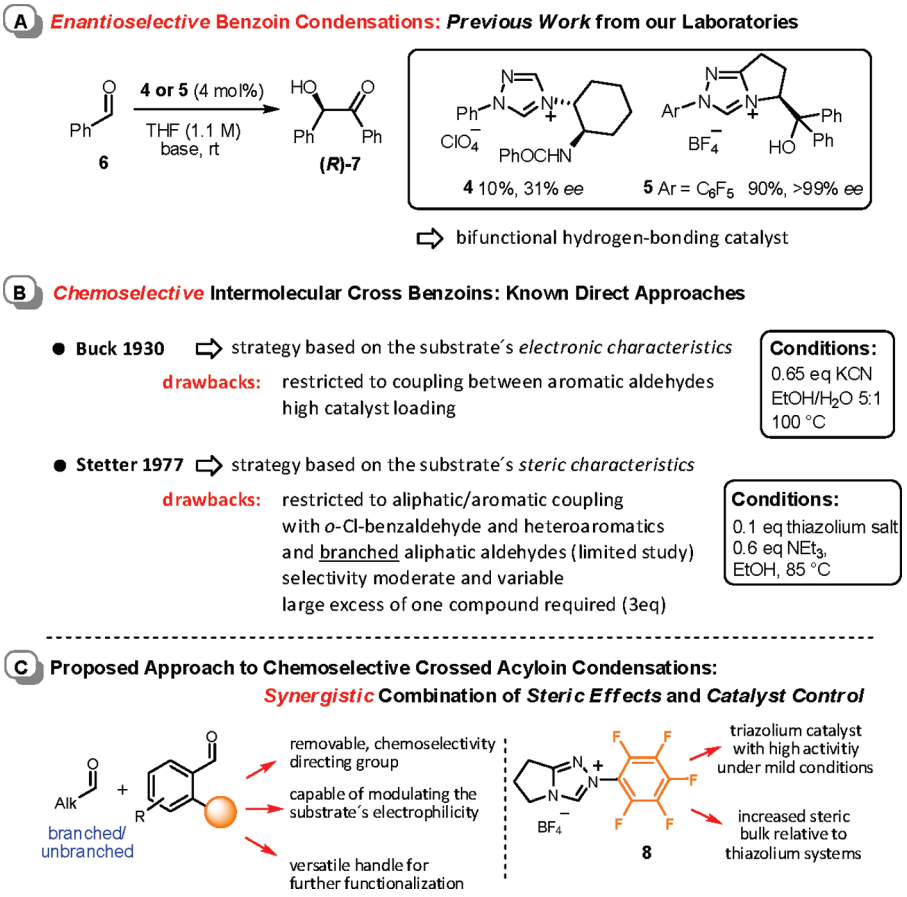
carbene-based catalysts.[10] While significant advances in the catalysis of the (asymmetric) carbene-catalyzed homo-AC reaction have been made recently,[11−15] the absence of a *selective* carbene-mediated methodology capable of promoting the intermolecular reaction[16] between two different aldehydes 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 1) in good yield.[17]

Known Approaches. 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 2B).[18,19] Over 30 years ago, Stetter et al.,[20] in an attempt to develop efficient routes to 1,2-diketones, reported in a short, limited study that an achiral thiazolium salt-derived carbene catalyzed the crossed AC between aromatic and aliphatic aldehydes: good crossed product yields could be obtained if the aliphatic aldehyde was utilized in quite high excess (3.0 equiv); however, chemoselectivity was both highly variable and substrate-dependent.[21−23]

Miller et al. carried out a single *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%).[24] Other approaches to the catalytic synthesis of products (formally) derived from intermolecular AC reactions have been developed, including the use of enzyme catalysts[25] and polymer-bound aldehydes,[26] in addition to indirect methods where chemoselectivity is derived from the preformation of an *umpolung* reagent, such as acyl silanes,[27] acyl phosphonates,[28] and aldehyde thiazolium carbene adducts.[29] 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;[30] however, to the best of our knowledge a general carbene-catalyzed process capable of promoting the direct, chemoselective[31] (and enantioselective)

(9) For a more recent kinetic study see: White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124.
(10) Recent reviews: (a) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *291*, 77. (b) Enders, D. *J. Org. Chem.* **2008**, *73*, 7857. (c) Rovis, T. *Chem. Lett.* **2008**, *37*, 1. (d) Zeitler, K. *E. Schering Found. Symp. Proc.* **2007**, *2*, 183. (e) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5506. (f) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (g) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (h) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632. (i) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (j) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326.
(11) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217.
(12) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891.
(13) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743.
(14) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367.
(15) Ma, Y.; Wei, S.; Wu, J.; Yang, F; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal.* **2008**, *350*, 2645.
(16) Highly enantioselective intermolecular AC reactions between aldehydes and ketones are known. For representative examples, see: (a) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463. (b) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (c) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431. (d) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008**, 2263. (e) For a recent example on a sterically controlled intramolecular aldehyde ketone AC reaction in the context of a multicatalytic cascade sequence, see: Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628.
(17) In addition, the use of enolizable aldehydes is potentially problematic due to competitive aldol pathways under the basic reaction conditions.
(18) Ide, W. S.; Buck, J. S. *Org. React.* **1948**, *4*, 269.
(19) It is noteworthy that establishing the levels of chemoselectivity in this study proved difficult due to the reactivity of the benzoins in the derivatization process to establish the structures of the products. For a ^{1}H NMR spectroscopy based structural assignment, also see ref 23.
(20) (a) Stetter, H.; Dämbkes, G. *Synthesis* **1977**, 403. (b) Stetter, H.; Dämbkes, G. *Synthesis* **1980**, 309.
(21) For a related report using aliphatic aldehydes see: Heck, R.; Henderson, A. P.; Köhler, B.; Rétey, J.; Golding, B. T. *Eur. J. Org. Chem.* **2001**, 2623.
(22) For a later demonstration of the potential utility of formaldehyde as a coupling partner in these reactions, see: Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* **1985**, *50*, 603.
(23) In addition, most likely due to the lack of high-field NMR instrumentation and the focus of the study on the oxidized benzil products (cf. their NMR characterization data), we have found that in some instances the chemoselectivity reported in this study was over estimated due to misassignment of products in the crude ^{1}H NMR spectra. In our hands, Stetter's conditions provided compound **12** as major product (see Table 1 and ref 37.). Further details will be reported in due course. For a more recent report using NMR spectroscopy for the structural assignment in mixed aromatic benzoin systems, see: Simion, C.; Simion, A. M. *UPB Sci. Bull., Ser. B* **2007**, *69*, 49.
(24) Mennen, S. M.; Miller, S. J. *J. Org. Chem.* **2007**, *72*, 5260.
(25) (a) Lehwald, P.; Richter, M.; C. Röhr, C.; Liu, H.-W.; Müller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2389. (b) Müller, M.; Gocke, D.; Pohl, M. *FEBS J.* **2009**, *276*, 2894. (c) Demir, A. S.; Şeşengolu, Ö.; Dünkelmann, P.; Müller, M. *Org. Lett.* **2003**, *5*, 2047. (d) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Linden, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084. (e) Demir, A. S.; Şeşengolu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelmann, P.; Müller, M. *Adv. Synth. Catal.* **2002**, *344*, 96. (f) Pohl, M.; Lingen, B.; Müller, M. *Chem.—Eur. J.* **2002**, *8*, 5288. (g) Demir, A. S.; Pohl, M.; Janzen, E.; Müller, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 633.
(26) (a) Kuriakose, S.; Rajasekharan Pillai, V. N. *Eur. Polym. J.* **1994**, *30*, 881. (b) Kuriakose, S; Rajasekharan Pillai, V. N. *Angew. Makromol. Chem.* **1994**, *221*, 53. (c) Kuriakose, S; Rajasekharan Pillai, V. N. *Polymer* **1994**, *35*, 1339.
(27) (a) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534. (b) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070. (c) Bausch, C. C.; Johnson, J. S. *J. Org. Chem.* **2004**, *69*, 4283. (d) Linghu, X.; Bausch, C. C; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833. (e) Tarr, J. C.; Johnson, J. S. *Org. Lett.* **2009**, *11*, 3870.
(28) (a) Demir, A. S.; Esiringü, I.; Göllü, M.; Reis, Ö. *J. Org. Chem.* **2009**, *74*, 2197. (b) Demir, A. S.; Reis, B.; Reis, Ö.; Eymür, S.; Göllü, M.; Tural, S.; Saglam, G. *J. Org. Chem.* **2007**, *72*, 7439. (c) Demir, A. S.; Reis, Ö.; Esiringü, I.; Reis, B.; Baris, S. *Tetrahedron* **2007**, *63*, 160. (d) Demir, A. S.; Reis, Ö.; Ciğdem, C.; Esiringü, I.; Eymur, S. *J. Org. Chem.* **2005**, *70*, 10584. (e) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1207.
(29) (a) Mathies, A. K.; Mattson, A. E.; Scheidt, K. A. *Synlett* **2009**, 377. (b) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932. (c) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508.
(30) (a) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749. (b) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun.* **2010**, *46*, 6282.

SCHEME 2. Previous Approaches and the Proposed Strategy Detailed in This Work

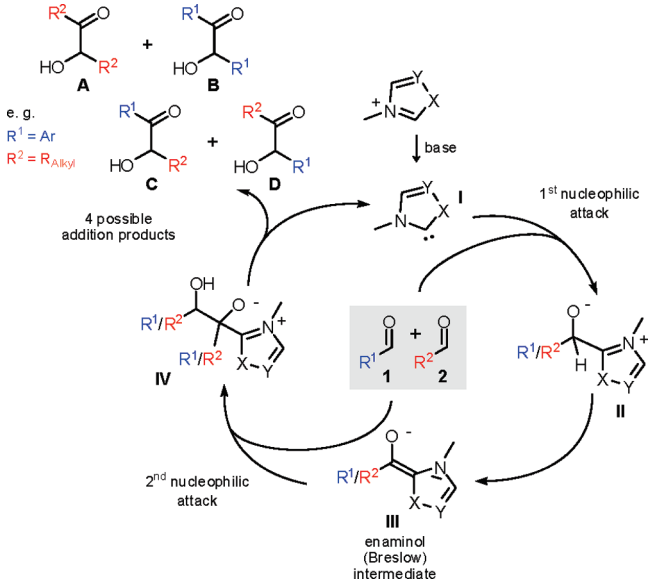


crossed AC reaction between two different aldehydes remains elusive.[32]

Results and Discussion

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 product (and stereocenter)-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 stereocenter-forming step (Scheme 3: **III**→**IV**), leading to the homodimer **3a** instead of cross-product **3d** (Scheme 1B and Scheme 3: **A** respectively **D**)?

SCHEME 3. General Mechanism for NHC-Catalyzed Benzoin/Acyloin Condensations



Recently, we reported that hydrogen bonding could be utilized as a control element in enantioselective homobenzoin condensation reactions.[33,34] The pentafluorophenyl-substituted triazolium precatalyst **5** (which followed our first generation system **4**) could promote the formation of

(31) For contributions to the ongoing discussion on the importance of chemoselectivity for efficient syntheses, see: (a) Trost, B. M. *Science* **1983**, *219*, 245. (b) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530. (c) Maurigo, M.; Melchiorre, P. *ChemCatChem* **2010**, *2*, 621.

(32) For an example of a preceding intermolecular aldehyde ketone cross-acyloin reaction in the context of a cyclopentene-forming annulation via NHC-catalyzed acyloin-oxy-Cope reaction, see: Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520.

(33) O'Toole, S. E.; Connon, S. J. *Org. Biomol. Chem.* **2009**, *7*, 3584.

(34) (a) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214. (b) The pK_a of catalyst **8** (H_2O) has been determined to be 17.7. To the best of our knowledge, the corresponding pK_a of **21** has yet to be determined: Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. *Chem. Commun.* **2008**, 3528.

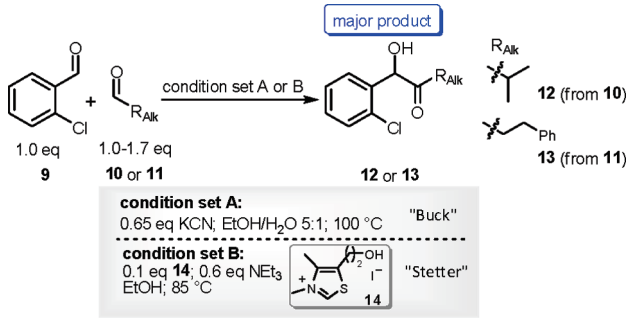
benzoin (**7**) from benzaldehyde (**6**) with excellent efficiency and stereocontrol (Scheme 2A). We postulated that the rigid, hindered nature of **5**, coupled with the presence of a catalyst hydrogen bond donating group,[35] would allow the catalyst to potentially distinguish between the *two* aldehyde electrophiles based on the recognition of *two different substrate properties*: steric bulk and Brønsted basicity. However, as an important further control element in addition to catalyst control,[36] 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.[20] 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 utilized 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 *direct* crossed acyloin chemistry was not possible using existing technology. For instance, while Buck et al.[18] did not employ aliphatic aldehydes in their study and Stetter[20] utilized 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 focused on conditions which would not employ a large excess of either coupling partners (i.e., aliphatic aldehyde $\leq$1.7 equiv).[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.)[18] or thiazolium-derived carbene (conditions defined by Stetter et al.)[20] 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 and 2). Utilization 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 equiv of the aliphatic aldehyde component was employed (entries 3−6).

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

TABLE 1. Short study on the general applicability of known direct cross-acyloin procedures using branched and unbranched aliphatic aldehydes with *o*-chloro benzaldehyde as aromatic aldehyde partner



Entry	Condition[a]	Equivalents of $R_{Alk}CHO$	'Aliphatic' Aldehyde $R_{Alk}CHO$	Yield (%)
1	A	1.0	10	**12** 21
2	A	1.0	Ph 11	0
3	B	1.0	10	**12** 38
4	B	1.7	10	**12** 36
5	B	1.0	Ph 11	**13** 38
6	B	1.7	Ph 11	**13** 39

[a]For details, see Supporting Information.

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,[36] we first wished to orient ourselves with respect to the natural bias (if any) a triazolium-derived carbene devoid of protic substituents would display toward 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 (i.e., conditions which had proven conducive to the promotion of homobenzoin condensation reactions in our previous studies[33,34a]). The results of these experiments are outlined in Table 2.

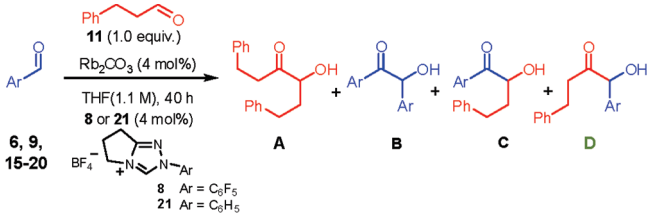
As expected, the pentafluorophenyl-substituted catalyst **8** proved to be a superior system to **21** under these conditions (entries 1 an 2).[34] The coupling of benzaldehyde (**6**) and **11** proceeded with poor chemoselectivity; while a marked preference for the formation of products derived from 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 and 4), and the preference for the cross-coupled products **D** was slightly improved, at the expense of the formation of increased

(35) For a recent report on the synthesis of a bifunctional thiourea carbene catalyst, see: Brand, J. P.; Siles, J. I.; Osuna; Waser, J. *Synlett* **2010**, 881.

(36) Our investigations on catalyst control are ongoing and will be reported in due course.

(37) Conducting the experiment with an excess of 3 equiv of the aliphatic aldehyde (here, isobutyraldehyde) provides a main cross-product[23] in 64% yield in accordance with the results of Stetter et al.;[20,23] however, application of similar conditions to unbranched aldehydes such as **11** clearly revealed the limitations of the process as this—even in combination with the potentially "privileged" *o*-substituted aryl aldehydes—only yields a major product in 40% yield (together with significant amounts of the homodimer of hydrocinnamaldehyde), providing some evidence for the requirement of both large excess of aliphatic aldehydes and sterical demand of the aryl aldehyde for successful transformations.

TABLE 2. Crossed AC Reactions with Unbranched Aldehydes: 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	1:1 ratio of ArCHO and HCA (**11**)
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	
12[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	variable ratios of ArCHO and HCA (**11**)
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**	68	0	10	90	

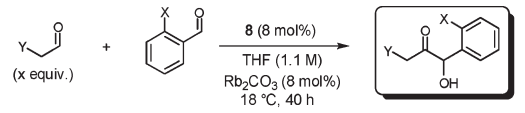
[a]Yield determined by ^{1}H NMR spectroscopy using styrene as an internal standard. Note: yields of **13** and **22**−**28a** and **22**−**28b** account for the 2:1 stoichiometry. To obtain the mol % of these materials, divide the yield by 2. [b]Phenyl-substituted triazolium precatalyst **21** was used instead. [c]With 8 mol % catalyst. [d]With 10 mol % catalyst loading. [e]With 1.3 equiv of **20** and 8 mol % catalyst. [f]With 1.5 equiv of **20** and 8 mol % catalyst. [g]With 1.3 equiv of **11** and 8 mol % catalyst. [h]With 1.5 equiv of **11** and 8 mol % catalyst. [i]With 1.7 equiv of **11** and 8 mol % catalyst.

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-releasing methoxy and the electron-withdrawing trifluoromethyl substituents (entries 7 and 8, respectively) allows 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: first, 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 second, 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 toward 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), which could already be drastically improved by employing 8 mol % of catalyst **8** (entry 10). 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**.[38]

(38) The concurrently formed homodimer **28a** can be easily separated by column chromatography. In our subsequent studies employing unbranched aliphatic aldehydes in 1.7 equiv (Table 3 and Table 4), we only report the yields of the cross-product **D** for clarity reasons.

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

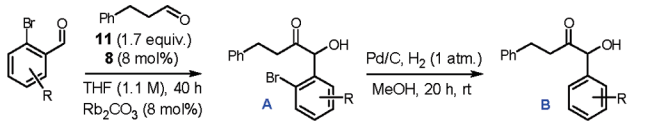
Entry	'Aliphatic' Aldehyde	X	'Aromatic' Aldehyde	Product	Yield **D**[38] (%)
1	**29**	1.7	**19**	**33**	50[a]
2	**29**	10.0	**19**	**33**	78
3	**30**	1.7	**19**	**34**	79
4	**30**	1.7	**20**	**35**	68[a]
5	**30**	2.5	**20**	**35**	73
6	**31**	1.7	**19**	**36**	84
7	**31**	1.7	**20**	**37**	77
8[b]	**11**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

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

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 10-fold excess (feasible due to the low cost of this reagent) resulted in good 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 and 7), hydrocinnamaldehyde (**11**, entries 8 and 9), and phenylacetaldehyde (**32**, entries 10 and 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 and 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.[39]

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 and 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 **22d** 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 toward 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

TABLE 4. Exploitation of a Removable 2-Bromo Substituent



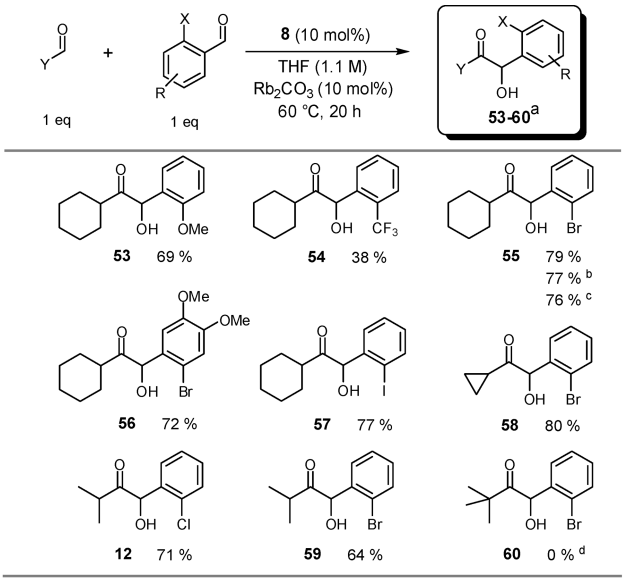
Entry	Aldehyde	Acyloin Product (**A**)	Yield (%)	Reduction Product (**B**)	Yield (%)
1	**20**	**28d**	90	**22d**	90
2	**40**	**43**	93	**46**	96
3	**41**	**44**	88	**47**	93
4	**42**	**45**	80	**48**	92

(39) Carrying out the coupling reaction at temperatures higher than 18 °C invariably led to lower overall yields due to decomposition of the *o*-trifluoromethylbenzaldehyde. See also the results outlined in Scheme 4.

removed to give debrominated products *not otherwise accessible in high yield directly from a operationally simple carbene-catalyzed AC process.*

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 (Scheme 4). 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;[39] product **54**). *o*-Bromobenzaldehydes **20** and **40** both coupled with cyclohexane carbaldehyde (**49**) to afford **55** and **56**, respectively, in good 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 use of the interesting substrate **50** led to the formation of the densely functionalized 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** and **20**, respectively, while at this stage, it appears that pivaldehyde is too bulky as 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.

SCHEME 4. Evaluation of Substrate Scope: Branched Aldehydes



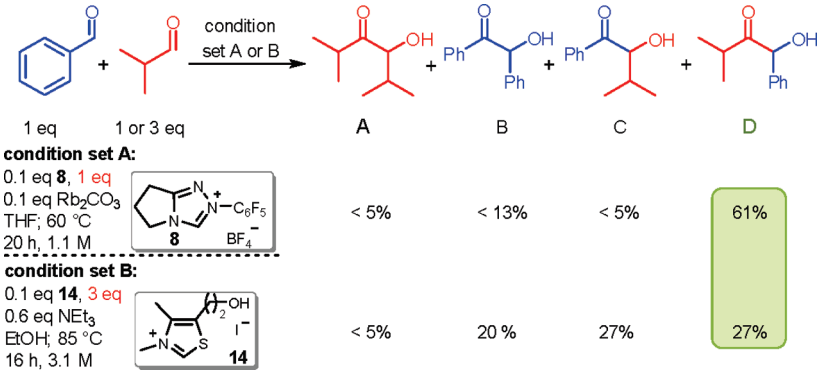
[a] Neither the homobenzoins nor cross-product **C** are formed in significant amounts; sometimes formation of corresponding acids can be observed. [b] 1.5 equiv. of aldehyde **49**. [c] K_2CO_3 used instead of Rb_2CO_3. [d] No cross AC product detected; only 16% of aromatic homocoupled product was obtained (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 counterintuitively) 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,[27,40] a stabilizing (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. On the basis of the well-established mechanistic picture of acyloin/benzoin condensations,[10e,41] it is also reasonable to assume that the properties of the Breslow intermediate should also be dependent 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.

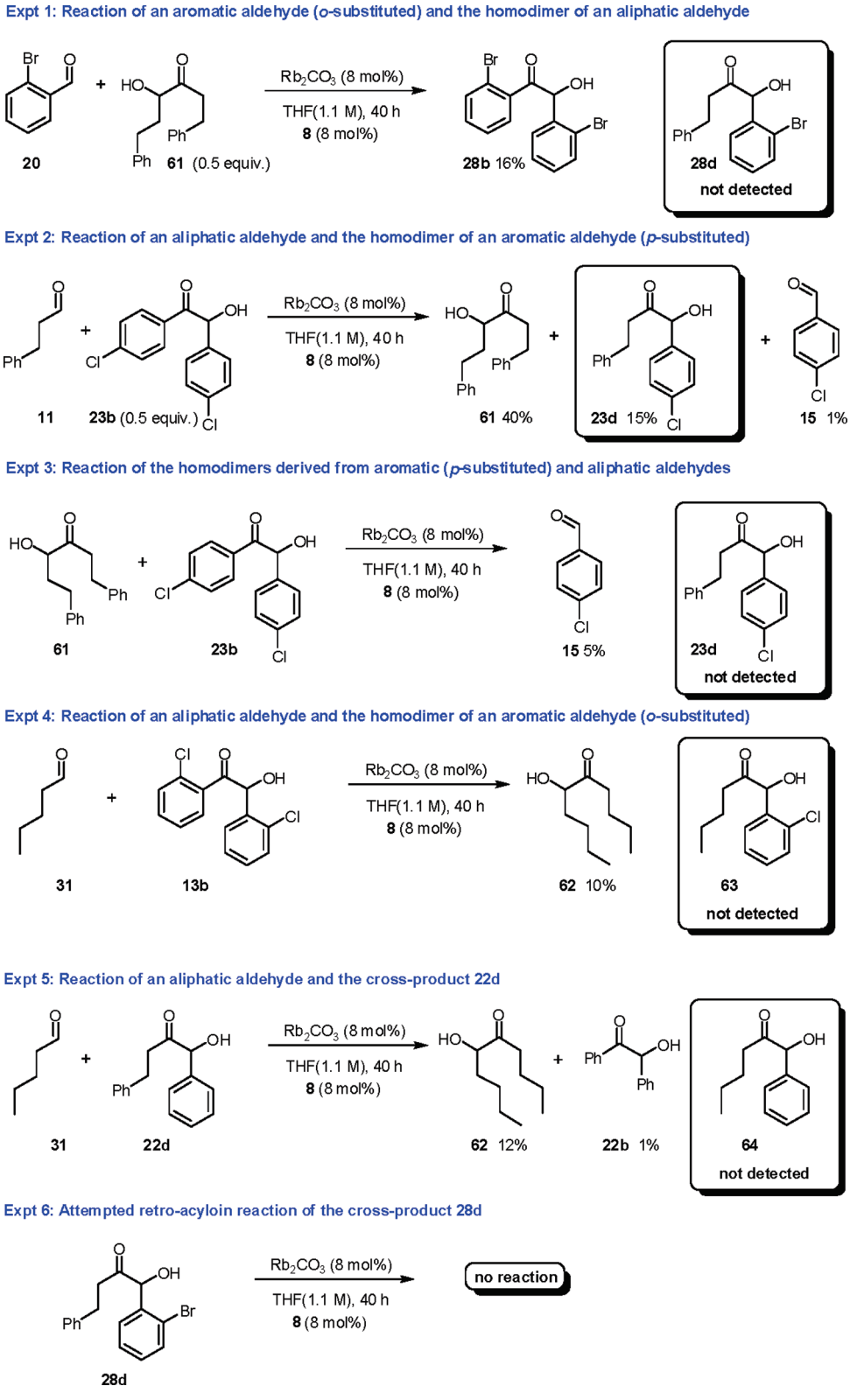
We were first interested in examining the influence of the choice of catalyst on the outcome of these reactions from a chemoselectivity perspective. We challenged our optimized catalytic system (condition set A, Scheme 5) with the reaction between benzaldehyde, lacking the selectivity-controlling

SCHEME 5. Influence of the Catalytic System on Chemoselectivity[a]



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

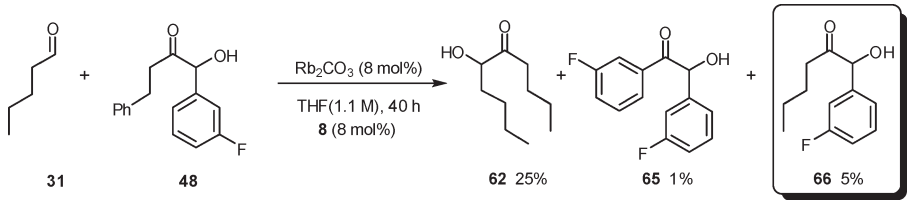
SCHEME 6. Crossover Experiments under Optimized Conditions Using Triazolium Precatalyst 8



ortho-substituent, and isobutyraldehyde and then repeated the experiment under Stetter's conditions (condition set B, Scheme 5), employing a thiazolium-derived carbene instead of the triazolium precatalyst. In contrast to the results reported by Stetter,[20] in our hands, condition set B provides both cross-products and the homoarylbenzoin in a ca. 1:1:1 ratio (combined yield of cross-acyloin products: 54%).[42] Use

(40) Duddling, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770.
(41) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124.

SCHEME 7. Investigation of the Use of Cross-Products Derived from Activated Yet Unhindered Aldehydes



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.

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 in Scheme 6. 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 retroacyloin of **61** could be detected. Next, we investigated the opposite pairing of starting materials, that is, 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 retroacyloin reaction) and the homodimer **61**. When the experiment was repeated, where the aliphatic aldehyde **11** was replaced with its homodimer **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 toward 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 retroacyloin reaction, goes some way toward explaining the chemoselectivity observed in these processes.

In a similar crossover 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.

(42) Stetter et al.[20] report a combined yield of 56% for the cross-acyloins **C** and **D** in a ratio of 1.9:1; no information is provided on the amount of homobenzoin **B**.

A number of conclusions can be drawn from these reactions:

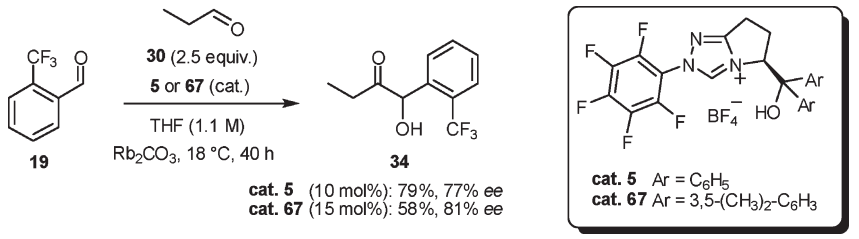
Aliphatic and *o*-substituted benzaldehydes dimerize, but do so only slowly (Expts 1, 2, 4, and 5). This is central to attaining high chemoselectivity in these processes. The homodimers derived from aliphatic aldehydes do not participate in retroacyloin chemistry under these conditions and are essentially formed irreversibly (Expts 1 and 3). Unhindered benzoins (i.e., homodimers of aromatic aldehydes) *will* participate in retroacyloin 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 retroacyloin 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.[43]

To support the theory that cross-products derived from reactions involving activated, unhindered benzaldehydes are more amenable to retroacyloin 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 retroacyloin reaction of **48** relative to those observed using benzaldehyde as the reacting partner (see Scheme 7 and Expt 6, Scheme 6). 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.

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 retroacyloin 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; that is, the more

(43) Calculation of the free energy of the two regioisomers of the cross-acyloin products of *o*-chlorobenzaldehyde (**9**) and isobutyraldehyde (**10**) revealed a preference for the α-aryl ketone **13d** as compared to the aromatic ketone **13c** by 3.60 kcal/mol. Similar results were obtained for the calculation using unbranched *n*-propanal as aliphatic aldehyde for the cross-acyloins (lower energy for the α-aryl ketone vs aromatic ketone: 3.43 kcal/mol). Calculations of the free energy were performed with SPARTAN-06 by geometry optimization using Hartree−Fock methods (6-31G) starting from the corresponding minimun conformer as obtained in a PM3-based Monte Carlo conformer search.

SCHEME 8. Chemo- and Enantioselective Crossed Acyloin Condensation



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 homocoupled 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[24] 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, that is, 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 retroacyloin 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 8).

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 chemoselective intermolecular crossed AC reactions between two aldehyde partners 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 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 generally complementary to existing methodologies based on enzymatic catalysis. The feasibility of highly enantioselective crossed AC reactions has also been established—investigations aimed at further refining the asymmetric catalysis and elucidating the origins of the chemoselectivity are now underway.

Experimental Section

General Methods. Unless otherwise noted, all commercially available compounds were used as provided without further purification.

NMR spectra were recorded on 300 MHz (300.13 MHz), 400 MHz (400.13 MHz), or 600 MHz (600.13 MHz) spectrometers using the solvent peak as internal reference ($CDCl_3$ δ H 7.26, δ C 77.0; and DMSO-d_6 δ H 2.51, δ C 39.5). Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet); coupling constants (*J*) are in Hertz (Hz). Mass spectra (MS ESI) were recorded using a mass spectrometer equipped with a TOF analyzer. All reactions were monitored by thin-layer chromatography using gel plates 60 F_{254}; visualization was accomplished with UV light and/or staining with appropriate stains ($KMnO_4$, anisaldehyde, vaniline, ninhydrin, or phosphomolybdic acid). Standard flash chromatography procedures were followed (particle size 40−63 μm). Infrared spectra were obtained using neat samples on spectrometers equipped with a universal ATR (attenuated total reflectance) sampling accessory. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Analytical CSP-HPLC was performed using an OJ-H (4.6 mm × 25 cm) column.

Tetrahydrofuran was distilled from sodium/benzophenone. All reactions were carried out under a protective atmosphere of dry nitrogen or argon using oven-dried glassware unless otherwise stated.

Catalyst **5** was prepared as per the procedure described by Connon and Zeitler et al.[34] and catalyst **8** as per the method described by Rovis.[44]

General Procedure for the Crossed Acyloin Condensation with Unbranched Aldehydes. To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar, was added Rb_2CO_3 (99.8%) that had been finely ground using a mortar and pestle. The reaction vessel was put under vacuum and heated with a heat gun for four 1 min intervals. When cooled to ambient temperature, the appropriate catalyst (0.09 mmol) was added and the flask was fitted with a septum seal. The flask was evacuated for 1 min and put under an atmosphere of Ar. The required aldehydes were distilled under vacuum and used directly. THF was charged to the reaction, followed by consecutive addition of each aldehyde. The reaction was stirred at room temperature for 40 h. CH_2Cl_2 (3.0 cm^3) and deionized H_2O (3.0 cm^3) were added. The organic layer was removed, and the aqueous layer was washed with CH_2Cl_2 (4 × 3.0 cm^3). The organic layers were combined, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The product was purified using column chromatography.

1-Hydroxy-4-phenyl-1-(2-trifluoromethyl-phenyl)-butan-2-one (27d). Yield 275 mg; 81%, colorless to pale yellow oil; R_f (CH_2Cl_2/hexanes 3/2) 0.25. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), α,α,α-trifluoromethyl benzaldehyde (**19**) (145.1 μL, 1.10 mmol), hydrocinnamaldehyde (**11**) (246.2 μL, 1.87 mmol), and THF (610 μL): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, 1H, J = 7.5 Hz), 7.51−7.45 (m, 2H), 7.26−7.23 (app. t, 2H), 7.18 (t, 1H, J = 7.4 Hz), 7.12 (d, 1H, J = 7.5 Hz), 7.06 (d, 2H, J = 7.5 Hz), 5.48 (s, 1H), 4.39 (s (broad), 1H), 2.95−2.86 (m, 2H), 2.75−2.70 (m, 1H), 2.58−2.53 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.6, 139.8, 136.3, 132.5, 128.8, 128.8 (q, J = 30.2 Hz), 128.6, 128.4, 128.0, 126.2, 126.1 (q, J = 5.5 Hz), 124.0 (q, J = 274.1 Hz), 74.5, 39.4, 29.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.59; HRMS ($C_{17}H_{15}F_3O_2$+Na) calcd 331.0922, found 331.0923; IR (cm^{-1}) $\tilde{\nu}$ = 3456, 3031, 2930, 1717, 1605, 1497, 1454, 1311, 1159, 1108, 1034, 768, 747, 696.

1-(2-Bromo-phenyl)-1-hydroxy-4-phenyl-butan-2-one (28d). Yield 316 mg; 90%, colorless to pale yellow oil; R_f (CH_2Cl_2/hexanes 2/3) 0.17. Procedure used Rb_2CO_3 (20.3 mg, 0.09 mmol), **8** (31.9 mg, 0.09 mmol), *ortho*-bromobenzaldehyde (**20**) (128.4 μL, 1.10 mmol), hydrocinnamaldehyde (**11**) (246.2 μL, 1.87 mmol), and THF (630 μL): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, 1H, J = 8.1 Hz), 7.28 (t, 1H, J = 7.3 Hz), 7.27−7.24 (app. t, 2H), 7.23−7.17 (m, 3H), 7.09 (d, 2H, J = 7.3 Hz), 5.59 (s, 1H), 4.39 (s (broad), 1H), 2.98−2.93 (m, 1H), 2.88−2.82 (m, 2H), 2.70−2.64 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8, 139.9, 137.1, 133.3, 130.0, 129.0, 128.4, 128.1, 128.0, 126.2, 123.7, 78.3, 39.4, 29.5; HRMS ($C_{16}H_{15}BrO_2$ + Na) calcd 341.0153, found 341.0152; IR (cm^{-1}) $\tilde{\nu}$ = 3456, 3063, 3028, 2925, 1713, 1536, 1496, 1454, 1024, 749, 698, 672.

General Procedure for the Hydro-debromination of Crossed Acyloin Condensation Products. To a 25 cm^3 round-bottomed flask, equipped with a stirring bar, were added brominated crossed acyloin (0.3 mmol), 10% Pd/C (6 wt %), Et_3N (1.2 equiv), and MeOH (0.36 M). The flask was evacuated and then purged with N_2. This cycle was performed twice. The reaction was stirred vigorously at ambient temperature (ca. 20 °C) under an atmosphere of hydrogen (hydrogen generator) overnight. The reaction mixture was filtered and concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (10 cm^3) and H_2O (10 cm^3), and the organic layer was washed with brine (10 cm^3), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The product was purified using column chromatography.

1-(3,4-Dimethoxyphenyl)-1-hydroxy-4-phenylbutan-2-one (46). Yield 87 mg; 96%, yellow oil; R_f (hexanes/CH_2Cl_2 1/4) 0.9. Procedure used **43** (113.7 mg, 0.30 mmol), NEt_3 (50.1 μL, 0.36 mmol), 10% Pd/C (6.8 mg), and MeOH (6.0 cm^3): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.18−7.06 (m, 3H), 6.97 (d, J = 7.0 Hz, 2H), 6.77 (d, J = 2.1 Hz, 2H), 6.59 (s, 1H), 4.91 (d, J = 4.1 Hz, 1H), 4.18 (d, J = 4.1 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.87−2.69 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 209.0, 149.5, 149.3, 139.7, 130.1, 128.3, 128.0, 126.2, 120.5, 111.5, 109.8, 79.8, 55.8, 55.7, 39.4, 29.6; HRMS ($C_{15}H_{20}O_3$ + Na) calcd 323.1259, found 323.1244; IR (cm^{-1}) $\tilde{\nu}$ = 3448, 3064, 3028, 2927, 1715, 1603, 1580, 1496, 1467, 1454, 1404, 1361, 1264, 1229, 1147, 1100, 1079, 1055, 1025, 964, 875, 812, 745.

General Procedure for the Crossed Acyloin Condensation with α-Branched Aldehydes. A flame-dried Schlenk flask equipped with a magnetic stirring bar was charged with Rb_2CO_3 (12 mg, 0.05 mmol). The reaction vessel was evacuated, heated to 650 °C for 1 min, and cooled to rt under N_2. After this procedure had been repeated once, triazolium precatalyst **8** (18 mg, 0.05 mmol) was added. The precatalyst/base mixture was put under vacuum and dried at rt for 45 min. Subsequently, absolute THF (0.45 mL) was added, and the resulting mixture was allowed to stir at rt for 15 min. After sequential addition of the appropriate benzaldehyde (0.5 mmol) and α-branched aldehyde (0.5 mmol), the reaction vessel was equipped with a reflux condenser and stirred at 60 °C under an atmosphere of N_2. After 20 h, the reaction mixture was allowed to cool to rt, diluted with 5 mL of $CHCl_3$, and extracted with H_2O. The aqueous layer was back-extracted twice with 5 mL of $CHCl_3$, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent under reduced pressure affords the crude product, which was purified by column chromatography.

2-(2-Bromophenyl)-1-cyclohexyl-2-hydroxyethanone (55). Yield 117 mg; 79%, colorless to pale yellow oil; R_f(10% Et_2O/*n*-pentane) 0.18; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.57 (m, 1H), 7.31 (td, J = 7.5 and 1.3 Hz, 1H), 7.24−7.14 (m, 2H), 5.71 (d, J = 4.7 Hz, 1H), 4.45 (d, J = 4.7 Hz, 1H), 2.46 (tt, J = 11.3 and 3.4 Hz, 1H), 2.04−1.92 (m, 1H), 1.84−1.55 (m, 3H), 1.51−0.96 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 211.9, 137.4, 133.4, 130.1, 129.2, 128.1, 124.1, 76.6 (overlapping with $CDCl_3$ resonance), 46.2, 29.9, 27.7, 25.7, 25.5, 25.0; MS (EI) m/z (%) 217 (13) $[M - Br]^+$, 185 (19), 111 (52) $[C_6H_{11}CO]^+$, 83 (100) $[C_6H_{11}]^+$; HRMS ($C_{14}H_{17}BrO_2$ + H) calcd 297.0490, found 297.0497; IR (cm^{-1}) $\tilde{\nu}$ = 3452, 2930, 2854, 1707, 1470, 1448, 1369, 1313, 1192, 1127, 1058, 1023, 993, 754, 632, 537, 495.

2-(2-Bromophenyl)-1-cyclopropyl-2-hydroxyethanone (58). Yield 102 mg; 80%, colorless oil; R_f(10% Et_2O/*n*-pentane) 0.13; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.59 (m, 1H), 7.38−7.29 (m, 1H), 7.25−7.17 (m, 2H), 5.78 (d, J = 4.1 Hz, 1H), 4.45 (d, J = 4.1 Hz, 1H), 1.94 (tt, J = 7.5 and 4.9 Hz, 1H), 1.27−1.15 (m, 1H), 1.11−0.96 (m, 2H), 0.90−0.79 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.1, 137.6, 133.3, 130.1, 129.4, 128.2, 124.2, 78.7, 17.6, 12.8, 12.6; MS (EI) m/z (%) 185 (56) $[M - C_4H_5O^+]$, 175 (31) $[M - Br]^+$, 77 (43) $[C_6H_5]^+$, 69 (100) $[C_4H_5O]^+$; HRMS ($C_{11}H_{11}BrO_2$ + H) calcd 255.0021, found 255.0012; IR (cm^{-1}) $\tilde{\nu}$ = 3450, 3009, 1695, 1568, 1471, 1438, 1373, 1271, 1193, 1134, 1051, 1017, 907, 757, 732, 672, 632, 531, 499.

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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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