Homogeneous Catalysis

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The Thiolate-Catalyzed Intermolecular Crossed Tishchenko Reaction: Highly Chemoselective Coupling of Two Different Aromatic Aldehydes**

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In memory of Rory A. More O'Ferrall

The Tishchenko reaction,[1,2] which has been known for a century, is a Cannizzaro-reaction-like[3] process with two aldehyde molecules **1** disproportionating in the presence of a catalyst (usually based on a metal ion[4–6]) to form an ester product **2** (Figure 1A). Mechanistically the reaction is thought to involve hydride transfer (**3**) to furnish a reduced alkoxide and an acyl electrophile, which couple to form the ester adduct in an atom-economic, waste-free fashion.[2]

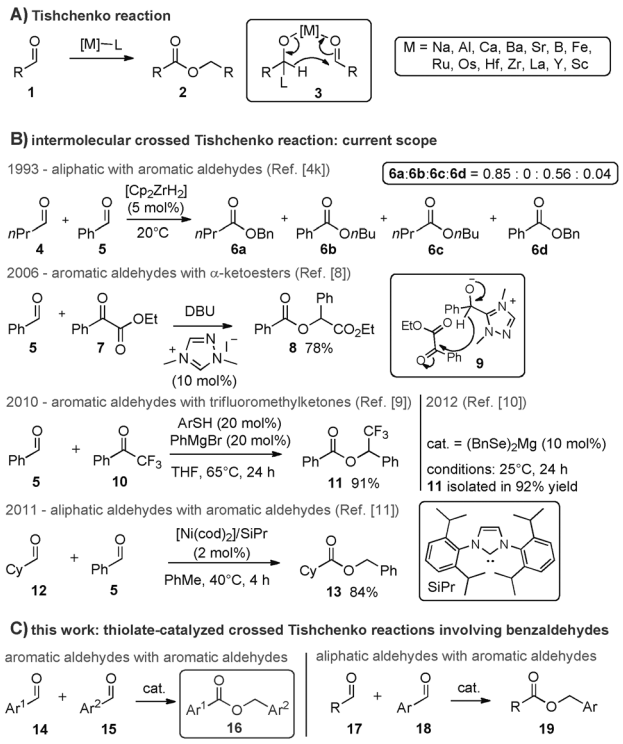

Figure 1. The crossed intermolecular Tishchenko reaction.

Despite detailed studies,[2,4] the reaction is generally not considered an important synthetic methodology, largely because of the difficulty in achieving selectivity: that is, when two different carbonyl compounds are involved, exercising control over which species acts as the hydride donor and which as the hydride acceptor has proven a near-intractable problem (Figure 1B). The difficulty resides in bringing about selective hydride transfer to give one ester product from four possible outcomes (two crossed products, two dimers).[7]

In 1993, Ishii and co-workers[4k] exploited the steric and electronic discrepancies between aliphatic and aromatic aldehydes in moderately selective Zr-complex-mediated crossed Tishchenko reactions. In these processes, only trace amounts of products derived from hydride transfer from **5** to either **5** or **4** were observed, the homodimerization of **4** could however not be avoided. Much later, Chan and Scheidt[8] disclosed the first carbene-catalyzed hydroacylation reactions between benzaldehydes and 1,2-dicarbonyl compounds such as **7** (Figure 1B) to afford **8** in high yield. In 2010, our group[9] utilized a similar strategy in the first thiolate-catalyzed (crossed) Tishchenko reactions (e.g., product **11**). Later, selenide ions were shown to promote this reaction with improved efficacy.[10]

Recently, a significant advance in this field was reported by Ogoshi and co-workers.[11] In a mechanistically distinct process, a nickel(0)/N-heterocyclic carbene complex was shown to promote selective crossed Tishchenko reactions between aliphatic and aromatic aldehydes. For example—the coupling of **12** and **5** to give the ester **13** occurred with excellent selectivity and in high isolated yield. While this is a leap forward in Tishchenko chemistry, thus far only unfunctionlized aldehydes have been utilized—the scope with respect to the electronic properties of the aldehyde and compatibility with either basic/chelating functionality or groups likely to participate in oxidative addition has not been established.[12]

This cursory survey serves to highlight a key missing component in the crossed Tishchenko reaction toolbox, that is, no methodologies for the selective catalytic crossed coupling of two different aromatic aldehydes are currently known.[13]

The strategies outlined in Figure 1B all rely on a discrepancy in characteristics (either steric or electronic or both) between very different coupling partners (e.g., between aliphatic and aromatic aldehydes or between aldehydes and

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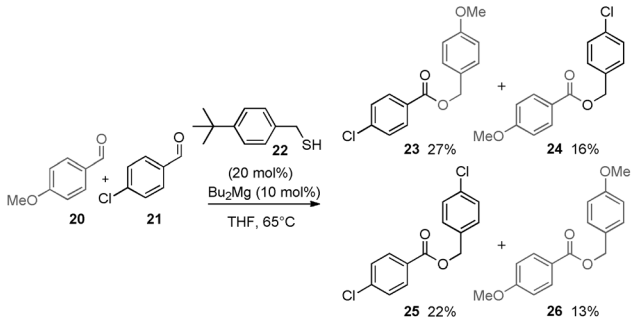
ketones etc.). Engendering and then exploiting such a scenario in a synthetically useful manner, in which both aldehyde partners are aromatic (flat, conjugated, similar in size) is a considerable challenge. Herein, we disclose the results of a study aimed at developing the first such crossed Tishchenko reactions between aromatic aldehydes (i.e., toward products **16**, Figure 1C).

Our investigation began with an attempt to bias the reaction outcome through manipulation of the electronic characteristics of the substrate (Scheme 1).[14] Accordingly, we



Scheme 1. Preliminary investigation into the effects of electronic characteristics on chemoselectivity.

reacted *p*-anisaldehyde (**20**) with the more activated *p*-chlorobenzaldehyde (**21**) in the presence of the magnesium thiolate derived from thiol **22** (20 mol%). This inexpensive thiol (considerably less smelly than benzyl mercaptan) was previously found to serve as a convenient precatalyst for the promotion of the Tishchenko homodimerization of benzaldehydes.[9] All four possible benzyl ester products were formed in a relatively unselective process.

The inherent difficulties associated with this process are apparent from an examination of the proposed catalytic cycle (Figure 2).[9a,15] From a chemoselectivity standpoint, the two

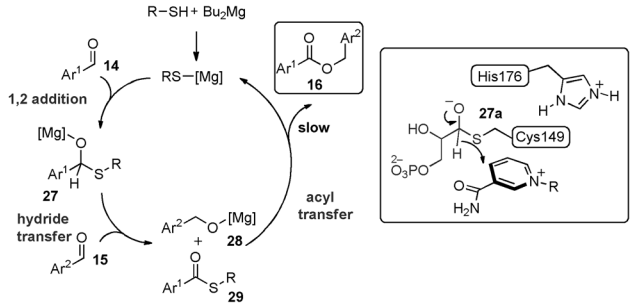
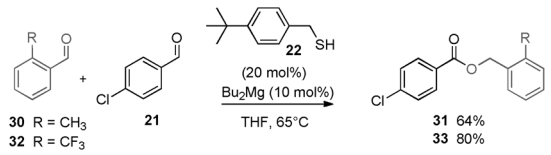


Figure 2. Proposed catalytic cycle for the thiolate-catalyzed crossed Tishchenko reaction.

key steps in the catalytic cycle are: a) 1,2 addition of the thiolate (e.g., **14**), and b) hydride transfer from the resultant adduct **27** to **15** (in a process reminiscent of the hydride transfer catalyzed by the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase,[16] that is, **27a**), to give alkoxide **28** and thioester **29**. An obvious impediment to achieving selectivity in such a reaction is that in both chemoselectivity-determining processes the aldehyde component is the electrophile. Therefore, if one attempts to render the process selective by further increasing the electrophilicity of one component relative to the other, homodimerization of the more electrophilic aldehyde is likely to result.

We therefore attempted to influence the reaction through the modification of the steric properties of one aldehyde. Our hypothesis was simple: while a solution to the problem outlined above was not obvious right away, the greatest difference between the two selectivity-determining steps is the bulk of the attacking nucleophilic components (i.e., the magnesium thiolate catalyst and the hemithioacetal conjugate base **27**). Therefore, the perhaps most promising tactic to influence the process is to modulate the bulk of the electrophilic aldehyde component.[17] Gratifyingly, exchange of **20** for *o*-tolylaldehyde (**30**) led to the formation of the crossed product **31** as the major component of the crude material (Scheme 2).



Scheme 2. Preliminary investigation into the effects of steric characteristics on chemoselectivity.

Since **31** derives from **30**, which acts as a hydride acceptor in the reaction, we next evaluated the corresponding trifluoro-derivative **32**, which is more electrophilic than **30** but possesses similar steric characteristics. A very selective reaction between this aldehyde and **21** occurred, which furnished the expected crossed product **33** in 80% yield.

While these examples represent a step toward high selectivity in crossed Tishchenko reactions involving aromatic aldehydes, the process would not be synthetically useful, while the scope is limited by a requirement for permanent bulky substituents at the *ortho* position of one of the reacting aldehydes. The precise origin of the observed chemoselectivity was also unclear. Hindering one aldehyde would certainly reduce the rate of its dimerization; however, it might also be expected to increase the relative rate of dimerization of the other, less-hindered aldehyde, which could then (relatively) easily participate in both the 1,2 addition and hydride transfer steps of the catalytic cycle (see Figure 2).

If both these steps are reversible, the chemoselectivity could (at least in part) be due to the difference in stability of the sp^3-hybridized adducts arising from these steps. For example, initial addition of the thiolate to the hindered aldehyde **34** would generate **35**, a species that would be unable to avoid the steric strain associated with interaction of the *ortho* substituent and the methine group (Figure 3A). Thus, one would expect the formation of the hemithioacetal conjugate base, derived from attack of the catalyst on the less-hindered aldehyde **21**, to be more energetically favorable. In the hydride-transfer step (Figure 3B), the alkoxide adduct **37** is less sterically congested than **35**, and thus steric effects may

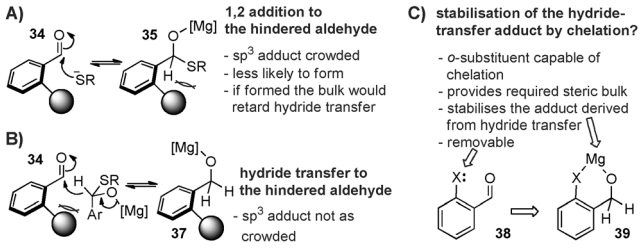


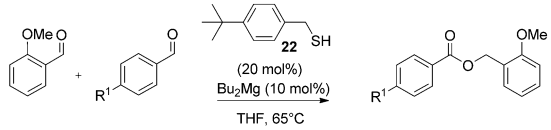
Figure 3. Rationalization of the observed chemoselectivity and the proposed influence of an *ortho* chelating group.

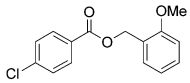
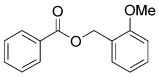
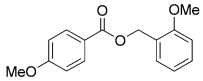
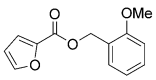
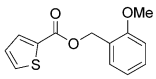
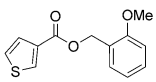
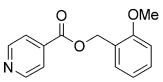
have less influence over this reaction than in the catalyst-addition step. This argument explains the formation of **31** and **33** (Scheme 2), however, it fails to account for the fact that the homodimers of **21** are not formed as the major product.[18]

We wished to develop a process that was both selective but also of the broadest possible scope and potential synthetic utility. To this end, we speculated that the use of a group capable of chelating magnesium ions in the *ortho* position could be advantageous (**38**, Figure 3C). Such a group could provide the requisite steric bulk, yet also serve to stabilize the hydride-transfer adduct (**39**, Figure 3C),[19] which we hoped would reinforce the previously observed bias toward the hindered aldehyde acting as the hydride acceptor.

To test this hypothesis, we evaluated the use of *o*-anisaldehyde as a coupling partner (Table 1). The expected crossed products of reactions with either activated (product **40**, entry 1), electron-neutral (**41**, entry 2), or deactivated aldehydes (**42**, entry 3) were obtained in good to excellent yields of isolated products. When both aldehyde partners contained chelating functionality in close proximity to the aldehyde, the resulting selectivity was poor (**43** and **44**, entries 4–5). However, heteroaromatic aldehydes that were not predisposed to chelation, such as thiophene-3-carbaldehyde (which contains a sulfur atom that is potentially incompatible with soft-transition-metal-based catalysts; **45**, entry 6) and the highly electrophilic (and hence dimerizable) pyridine-4-carbaldehyde (**46**, entry 7) were compatible with the reaction.

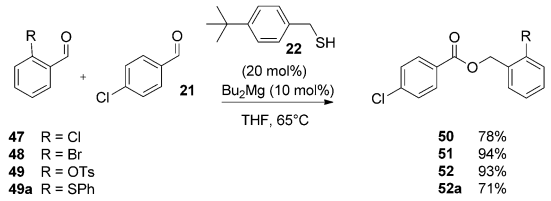
Table 1: Selective crossed Tishchenko reactions with *o*-anisaldehyde.



Entry	Product		*t* [h]	Yield [%][a]
1		**40**	24	88
2		**41**	24	73
3		**42**	24	69
4		**43**	24	16[b]
5		**44**	24	38[b]
6		**45**	24	71
7		**46**	36	63

[a] Yields of isolated products after chromatography. [b] Determined by ^{1}H NMR spectroscopy using an internal standard.

These data strongly indicate that a combination of steric bulk and chelating ability in just one of the aldehyde components is sufficient to render the crossed Tishchenko process highly selective. In order to improve the utility of the process, we next probed the use of removable chelating functionality. This would allow the aspiration toward the use of an *ortho* substituent as a chemoselectivity-directing group, which could be either removed later or utilized as a handle for further elaboration.[20] Upon reaction with **21**, *o*-chloro-, *o*-bromo-, and *o*-tosyl-benzaldehyde (**47**, **48**, and **49** respectively) participated in selective crossed couplings to form **50**, **51**, and **52**; with the latter two substrates providing the product in more than 90% yield (Scheme 3).[21] The use of a hydrogenolysis-labile sulfide chelating group (i.e., **49a**) is also feasible, but produces the product in lower yield.[21]

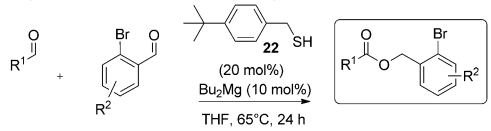


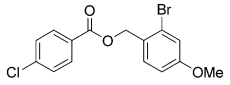
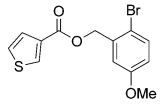
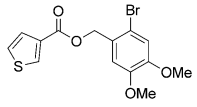
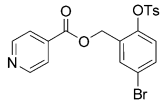
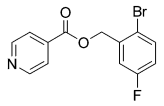
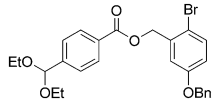
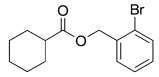
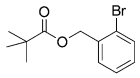
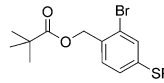
Scheme 3. Use of removable chelating substituents.

To demonstrate that this is a general phenomenon, we carried out crossed Tishchenko reactions in which one of the benzaldehyde partners contained two substituents, one of which was an *ortho* chelating group (Table 2). Chemoselectivity again was determined by the presence of the *ortho* substituent, irrespective of the overall electronic characteristics of the aldehyde, with possible yields of isolated products of more than 90%, even using challenging heteroaromatic and relatively electron-rich coupling partners (**53**–**55**, entries 1–3). The electrophilic pyridine-4-carbaldehyde was again compatible with the reaction, allowing the formation of the highly manipulatable esters **56** and **57** (entries 4 and 5). The tolerance toward chelating functionality is underlined by the efficient formation of **58**, which contains an acetal-protected aldehyde and a benzylated phenol group (entry 6).

It was also found that the *ortho* substituent could facilitate crossed coupling with aliphatic aldehydes (**59** and **60**, entries 7 and 8) in moderate to good yields. The sulfide group, which has the potential to poison soft-metal-ion catalysts, could also be tolerated without loss of catalytic efficiency (i.e., **61**, entry 9). Thus, while this thiolate-mediated reaction (the

Table 2: Expansion of the reaction scope.

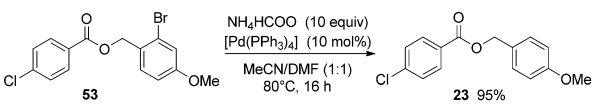


Entry	Product		Yield [%][a]
1		**53**	93
2		**54**	95
3		**55**	99
4		**56**	72
5		**57**	69
6		**58**	92
7		**59**	58 (72)[b]
8		**60**	63
9		**61**	62

[a] Yields of isolated products after chromatography. [b] Using 2.0 equivalents of the *o*-bromobenzaldehyde.

primary application of which is in aromatic–aromatic aldehyde couplings) is not as efficient as the Ni^0[11] system in aliphatic–aromatic coupling reactions, it could serve as a complementary strategy for use with functionalized aldehydes.[22]

Finally, we demonstrated that the directing bromine atom can be easily removed after reaction to provide highly efficient access to products that were hitherto formed only through unselective Tishchenko chemistry. Benzyl ester **53** was prepared through a selective crossed Tishchenko reaction (Table 2, entry 1) and subsequently debrominated by using ammonium formate in the presence of catalytic Pd^0 to give **23** in 95% yield (88% over two steps from the parent aldehydes, Scheme 4). This compares very favorably with the unselective



Scheme 4. Removal of the chelating substituent.

Tishchenko reaction detailed in Scheme 1, which produces **23** in only 27% yield as part of a mixture of four products.

In summary, we have developed the first highly selective Tishchenko coupling reactions between two different aromatic aldehydes. The protocol uses a readily prepared, inexpensive catalyst and produces crossed products in excellent yields. The reaction relies on the use of an *ortho* substituent (usually bromo), however, this can either be efficiently removed after reaction, or provide opportunities for further synthetic manipulation.[20] In the reactions detailed above, a very wide range of aromatic aldehydes are tolerated, and the methodology can be also utilized to bring about selective couplings between aliphatic and functionalized aromatic aldehydes.

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Keywords: disproportionation · esters · hydride transfer · thiols · Tishchenko reaction

[1] a) W. Tischtschenko, *J. Russ. Phys. Chem.* **1906**, *38*, 355; b) W. Tischtschenko, *Chem. Zentralbl.* **1906**, *771*, 1309; c) L. Claisen, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 646.

[2] For recent reviews, see: a) T. Seki, T. Nakajo, M. Onaka, *Chem. Lett.* **2006**, *35*, 824; b) O. P. Törmäkangas, A. M. P. Koskinen, *Recent Res. Dev. Org. Chem.* **2001**, *5*, 225.

[3] S. Cannizzaro, *Justus Liebigs. Ann.* **1853**, *88*, 129.

[4] Aluminium alkoxides: a) W. C. Child, H. Adkins, *J. Am. Chem. Soc.* **1925**, *47*, 798; b) F. J. Villani, F. Nord, *J. Am. Chem. Soc.* **1947**, *69*, 2605; c) L. Lin, A. R. Day, *J. Am. Chem. Soc.* **1952**, *74*, 5133; d) T. Saegusa, T. Ueshima, *J. Org. Chem.* **1968**, *33*, 3310; e) T. Ooi, T. Miura, K. Takaya, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 7695; f) T. Ooi, K. Ohmatsu, K. Sasaki, T. Miura, K. Maruoka, *Tetrahedron Lett.* **2003**, *44*, 3191; g) Y. Hon, C. Chang, Y. Wong, *Tetrahedron Lett.* **2004**, *45*, 3313; transition-metal-based catalysts (selected examples): h) M. Yamashita, Y. Watanabe, T. Mitsudo, Y. Takegami, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3597; i) T. Ito, H. Horino, Y. Koshiro, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 504; j) S. H. Bergens, D. P. Fairlie, B. Bosnich, *Organometallics* **1990**, *9*, 566; k) K. Morita, Y. Nishiyama, Y. Ishii, *Organometallics* **1993**, *12*, 3748; l) M. Yamashita, T. Ohishi, *Appl. Organomet. Chem.* **1993**, *7*, 357; m) P. Barrio, M. A. Esteruelas, E. Onate, *Organometallics* **2004**, *23*, 1340; n) T. Suzuki, T. Yamada, T. Matsuo, K. Watanabe, T. Katoh, *Synlett* **2005**, 1450; o) S. Ogoshi, Y. Hoshimoto, M. Ohashi, *Chem. Commun.* **2010**, *46*, 3354; alkali metal salts: p) M. M. Mojtahedi, E. Akbarzadeh, R. Sharifi, M. S. Abaee, *Org. Lett.* **2007**, *9*, 2791; q) D. C. Waddell, J. Mack, *Green Chem.* **2009**, *11*, 79; r) T. Werner, J. Koch, *Eur. J. Org. Chem.* **2010**, 6904; alkali-/earth-metal-based catalysts: s) M. R. Crimmin, A. G. M. Barrett, M. S. Hill, P. A. Procopiou, *Org. Lett.* **2007**, *9*, 331; t) B. M. Day, N. E. Mansfield, M. P. Coles, P. B. Hitchcock, *Chem. Commun.* **2011**, *47*, 4995.

[5] For the use of boric acid as a catalyst, see: P. R. Stapp, *J. Org. Chem.* **1973**, *38*, 1433.

[6] a) D. Ulrich, H. Jankowski, *Chem. Tech.* **1988**, *40*, 393; b) K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, 4th ed., Wiley-VCH, Weinheim, **2003**; c) A. S. Hester, K. Himmler, *Ind. Eng. Chem.* **1959**, *51*, 1424.

[7] For intramolecular crossed Tishchenko reactions, see: a) J. L. Hsu, J. M. Fang, *J. Org. Chem.* **2001**, *66*, 8573; b) L. Lu, H. Y. Chang, J. M. Fang, *J. Org. Chem.* **1999**, *64*, 84.

[8] A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2006**, *128*, 4558.
[9] a) L. Cronin, F. Manoni, C. J. O'Connor, S. J. Connon, *Angew. Chem.* **2010**, *122*, 3109; *Angew. Chem. Int. Ed.* **2010**, *49*, 3045; b) C. J. O'Connor, F. Manoni, S. P. Curran, S. J. Connon, *New J. Chem.* **2011**, *35*, 551.
[10] S. P. Curran, S. J. Connon, *Org. Lett.* **2012**, *14*, 1074.
[11] Y. Hoshimoto, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2011**, *133*, 4668.
[12] For a Highlight article, see: W. I. Dzik, L. J. Gooßen, *Angew. Chem.* **2011**, *123*, 11241; *Angew. Chem. Int. Ed.* **2011**, *50*, 11047.
[13] For example, Ogoshi and co-workers (Ref. [11]) attempted both these types of reactions under conditions previously found to be beneficial to selective aliphatic–aromatic Tishchenko chemistry. However, reactions involving either two different aliphatic or two different aromatic aldehydes were found to be unselective.
[14] Eisen had already shown that actinide-complex-catalyzed crossed Tishchenko reactions involving aromatic aldehydes of similar electronic characteristics were unselective: T. Andrea, E. Barnea, M. S. Eisen, *J. Am. Chem. Soc.* **2008**, *130*, 2454.
[15] The thioester- and alkoxide-derived alcohol can be observed during the reaction by ^{1}H NMR spectroscopy and both have been shown to serve as competent intermediates in the cycle. See Ref. [9a].
[16] a) J. M. Berg, J. L. Tymoczko, L. Stryer, *Biochemistry*, 5th ed., Freeman, New York, **2002**; b) A. Soukri, A. Mougin, C. Corbier, A. Wonacott, C. Branlant, G. Branlant, *Biochemistry* **1989**, *28*, 2586; c) K. D'Ambrosio, A. Pailot, F. Talfournier, C. Didierjean, E. Benedetti, A. Aubry, G. Branlant, C. Corbier, *Biochemistry* **2006**, *45*, 2978.
[17] Our group in collaboration with Zeitler and co-workers employed a similar strategy to develop highly selective (mechanistically distinct) crossed acyloin reactions. S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2011**, *76*, 347.
[18] It is tempting to ascribe this observation to reduced conjugation between the carbonyl group and the electron-rich aromatic ring, however, attempts to rationalize this observation are perhaps best left until after the emergence of a clearer mechanistic picture.
[19] Naturally, the chelating substituent would also stabilize the hemithioacetal conjugate base. However, as we have pointed out, steric effects are likely to make more of a contribution to the stability (or lack thereof) of that species than to the hydride-transfer adduct.
[20] For example, Nicolaou et al. have employed benzyl benzoates containing *o*-bromo substituents (similar to **51**) as key components in the total synthesis of balanol (and analogues thereof): K. C. Nicolaou, K. Koide, M. E. Bunnage, *Chem. Eur. J.* **1995**, *1*, 454.
[21] The coupled product **47** could not be cleanly isolated from the crude material. Therefore the yield of this compound was determined unambiguously by ^{1}H NMR spectroscopy using styrene as an internal standard. The yields given for **48**, **49**, and **49a** are those of isolated products. For a review of the hydrogenolysis of sulfur-containing compounds using Raney nickel, see: H. Hauptmann, W. F. Walter, *Chem. Rev.* **1962**, *62*, 347.
[22] Aliphatic aldehydes containing α-unbranched aldehydes undergo preferential aldol condensation under these conditions.

