Synthetic Methods

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Tunable Bromomagnesium Thiolate Tishchenko Reaction Catalysts: Intermolecular Aldehyde–Trifluoromethylketone Coupling**

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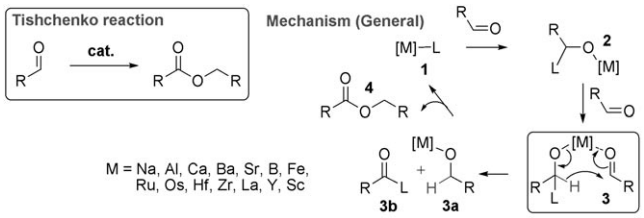
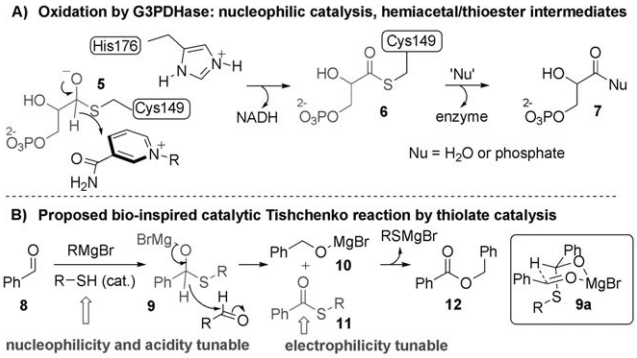
The Tishchenko reaction[1] (discovered by Claisen[2] in 1887) is the disproportionation of two aldehyde molecules to furnish an ester product (Scheme 1).[3] Aluminum alkoxides[1,4] and boric acid,[5] were the first classes of synthetically relevant homogeneous catalysts[6] for this reaction, these were then followed by a range of transition-metal complexes of low to high catalytic activity but often limited practical utility.[7,8] More recently, lanthanide,[9] actinide,[10] and calcium[11] complexes capable of promoting aldehyde dimerization with excellent activity have been reported. A generalized mechanistic outline of the process is given in Scheme 1: reaction of the transition-metal complex **1** with the aldehyde generates the metal alkoxide **2**, which acts as the hydride-transfer agent in a metal-mediated redox process (i.e. **3**) leading to ester **4**.[12]



Scheme 1. The Tishchenko reaction.

The Tishchenko reaction is an unusual process from a mechanistic standpoint with the potential to allow chemists to plan the synthesis of ester products through an unconventional disconnection. While recent advances in catalyst development have resulted in increased promise as a general synthetic methodology, the utility of the Tishchenko reaction is somewhat limited by two factors: a) Often the reported catalyst systems result in lower yields of isolated products from *substituted* benzaldehydes, and b) intermolecular crossed-Tishchenko reactions between equimolar amounts of two different carbonyl moieties are generally not possible. In particular no examples of intermolecular cross-coupling[13,14] between an aldehyde and a ketone are known, meaning that the intermolecular reaction cannot currently be utilized to generate new stereogenic centers.

We were therefore encouraged to attempt the development of an alternative catalyst system for the intermolecular Tishchenko process. Our objective was to devise a simple, inexpensive, and easy to use small-molecule promoter, the steric and electronic characteristics of which could be readily tuned, with the eventual goal of broadening the scope of the Tishchenko reaction to include ketone substrates. We were inspired by the mode of action of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (G3PDHase), which promotes aldehyde oxidation through base-catalyzed addition of a cysteine residue to the aldehyde substrate to give the corresponding hemithioacetal conjugate base **5** (Scheme 2, **A**), which participates in an intermolecular hydride-transfer reaction with enzyme-bound NAD^+. The resulting electrophilic thioester **6** then undergoes either hydrolysis or substitution by inorganic phosphate (depending on the enzyme variant).[15–17]



Scheme 2. Proposed thiolate-catalyzed Tishchenko reaction.

We postulated the viability of an artificial process in which an analogous hemithioacetal anion **9** generated from benzaldehyde (**8**) and a bromomagnesium thiolate[18] could transfer hydride[19,20] to another carbonyl moiety to give magnesium alkoxide **10** and thioester **11**,[21] which would subsequently couple to form the ester product **12** with regeneration of the thiolate catalyst (Scheme 2, **B**).

The results of our preliminary experiments to test this hypothesis are outlined in Table 1. We were pleased to observe the disproportionation of aldehyde **8** to ester **12** (together with trace amounts of benzyl alcohol **13**) in the presence of the bromomagnesium salts (readily prepared in situ from the addition of phenylmagnesium bromide to the thiol in THF)[22] of either thiophenol (**15a**), cyclohexane thiol (**15b**), or benzyl mercaptan (**15c**) at 5 mol% levels (Table 1,

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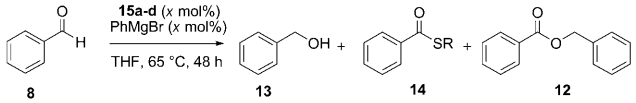
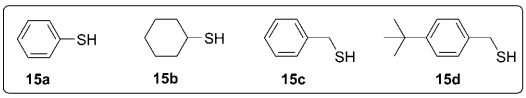
Table 1: Thiolate-catalyzed Tishchenko reactions.





Entry	Cat.	*x* (mol%)	Conc. [M]	Yield **13** [%][a]	Yield **14** [%][a]	Yield **12** [%][a]
1	**15a**	5	0.90	6	0	48
2	**15b**	5	0.90	5	0	48
3	**15c**	5	0.90	4	0	87
4[b]	**15c**	5	0.68	5	0	71
5[c]	**15c**	20	0.34	1	0	98
6[b]	**15c**	10	0.68	0	0	100
7	**15d**	5	0.90	6	0	66
8[b]	**15d**	5	0.68	7	4	23
9[b]	**15d**	10	0.68	6	2	89
10[c]	**15d**	10	1.00	2	1	97

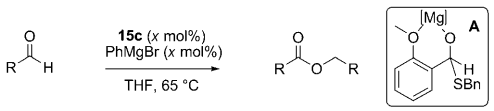
[a] Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b] 72 h reaction time. [c] 24 h reaction time.

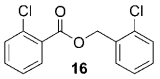
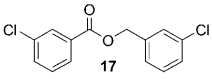
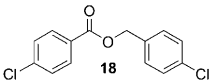
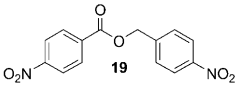
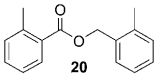
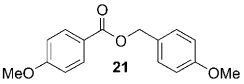
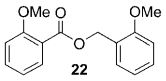
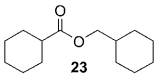
entries 1–3). Of the three anionic catalysts, benzyl mercaptan proved the most active, affording benzyl benzoate in good yield. While lowering either the catalyst loading or the reaction concentration led to a decrease in efficiency, at catalyst loadings of 5–20 mol% excellent to quantitative product yields could be obtained (Table 1, entries 4–6). We found that the significantly less malodorous 4-*tert*-butyl analogue **15d** could serve as an acceptable substitute for **15c** in these reactions (Table 1, entries 7–10). Interestingly, in a number of reactions where conversion into **12** was incomplete, both alcohol **12** and thioester **14** could be detected by ^{1}H NMR spectroscopic analysis,[23] which supports the mechanistic proposal outlined in Scheme 2.

The question of substrate scope (Table 2) was next examined. Both activated and relatively electron rich aldehydes underwent the dimerization reaction to afford the corresponding esters **16**–**19** (Table 2, entries 1–4) and **20**–**21** (entries 5 and 6), respectively, in excellent yields in the presence of 10–20 mol% of catalyst. *o*-Anisaldehyde proved a somewhat recalcitrant substrate, furnishing only moderate yields of **22** even under forcing conditions and extended reaction times (Table 2, entry 7). We would suggest that this is related to the chelating ability of the *o*-methoxy group, which could stabilize the hemithioester conjugate base **A** to such a degree that the hydride-transfer process is significantly slowed. Little information is available in the literature regarding the Tishchenko chemistry of aromatic aldehydes with electron-donating *o*-substituents; however, it has previously been suggested that chelation could explain the relatively poor performance of furfural in lanthanum-complex-catalyzed Tishchenko chemistry.[9b,c] We were pleased to find that the enolizable substrate cyclohexane carbaldehyde could be dimerized efficiently to form **23** in good yield (Table 2, entry 8).

We were next interested in employing this strategy towards the development of an intermolecular aldehyde–

Table 2: Aldehyde disproportionation: substrate scope.

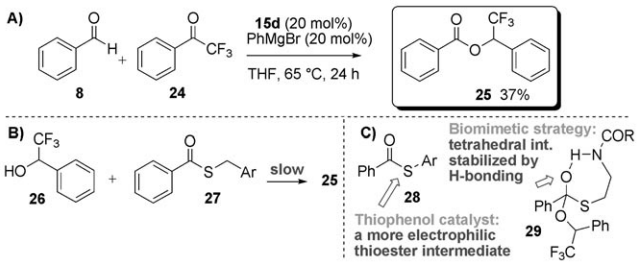


Entry	Product	*x* (mol%)	Conc. [M]	*t* [h]	Yield [%][a]
1	 **16**	20	0.68	18	93
2	 **17**	10	0.68	18	94
3	 **18**	10	0.68	12	92
4	 **19**	10	0.68	18	90
5	 **20**	20	0.68	96	87
6	 **21**	20	0.90	48	92
7	 **22**	20	0.90	96	56
8	 **23**	20	0.68	48	63

[a] Yield of isolated product after chromatography.

ketone Tishchenko coupling process. Such a reaction would be clearly afflicted by two key issues: a) the inherent lack of reactivity of ketones relative to aldehydes, meaning that aldehyde dimerization is likely to be the favored pathway; and b) with the hydride-transfer step likely to be slower using ketone electrophiles, a competing aldol process must be avoided. We therefore decided to utilize non-enolizable trifluoromethylketone substrates, with the expectation that they would be of sufficient activity to react with the hemithioacetal intermediate preferentially over another aldehyde molecule.

Treatment of equimolar amounts of benzaldehyde (**8**) and trifluoroacetophenone (**24**) with 20 mol% of **15d** and PhMgBr resulted in formation of the coupled product **25** in 37% yield (Scheme 3, **A**). Despite considerable experimentation this process could not be significantly improved by optimizing the reaction conditions. Examination of the crude spectra from these reactions revealed considerable amounts of reduced ketone **26** and thioester **27** (ca. 20%, Scheme 3, **B**), indicating that the coupling process is the rate-limiting step in this reaction (unsurprising perhaps given the increased hindrance and presence of the CF_3 group in the attacking alkoxide relative to that derived from **8**). This is clearly a cycle-terminating problem, as it is attack on the thioester which releases the catalyst and allows turnover. We devised two strategies to circumvent this: Firstly, the use of a more

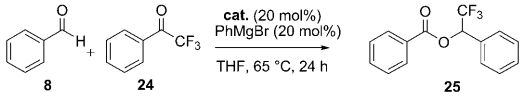


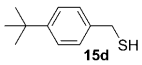
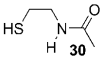
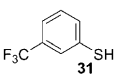
Scheme 3. Intermolecular aldehyde–ketone coupling.

acidic thiol precatalyst, would generate a more electrophilic thioester (i.e. **28**, Scheme 3, **C**). If a balance between thiolate nucleophilicity and thioester electrophilicity could be found then turnover could be promoted without slowing the redox step prohibitively (Scheme 3, **B**). Secondly, inspired by G3PDHase and serine/cysteine proteases, which utilize hydrogen bonding (together with general base catalysis) in the hydrolysis of their acyl–enzyme (thio)ester complexes,[15] we posited that a catalyst capable of hydrogen-bond donation could possibly achieve superior turnover rates by stabilizing the tetrahedral intermediate derived from attack of the alkoxide on the thioester (i.e. **29**, Scheme 3, **C**).

Table 3 details the results of our investigations along these lines. As expected, aliphatic thiols **15b** and **15d** performed poorly in this reaction (Table 3, entries 1–4). Subsequently, it was gratifying to find that use of the simple bifunctional (i.e. hydrogen-bond-donating) thiol **30** allowed the generation of **25** in a greatly improved yield of 65% (Table 3, entries 5 and 6). However, activation of the thioester through the use of an aromatic precatalyst proved the superiority of the two strategies: thiophenol (**15a**) promoted smooth coupling after 24 h reaction time (Table 3, entries 7 and 8), while augmenting the thioester intermediate's electrophilicity further through the use of the 3-trifluoromethyl ($\sigma_m = 0.46$) substituted thiophenol **31** resulted in clean Tishchenko coupling and excellent product yield (Table 3, entries 9 and 10).

Table 3: Crossed Tishchenko coupling: catalyst optimization.



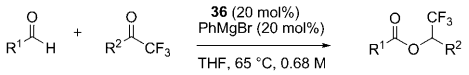
Entry	Catalyst	*t* [h]	Yield [%][b]
1	 **15b**	4	6
2		24	25
3	 **15d**	4	11
4[b]		24	37
5	 **30**	4	32
6		24	65
7	 **15a**	4	48
8		24	90
9	 **31**	4	75
10		24	96
11[c]		90	91

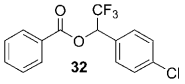
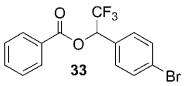
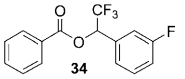
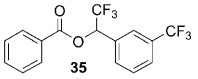
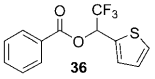
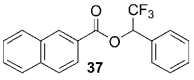
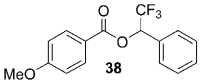
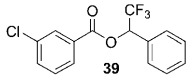
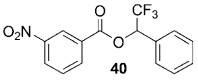
[a] Yield determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b] From Scheme 3. [c] 10 mol% **31**, 0.9 M reaction concentration.

Next we evaluated the scope of the coupling process (Table 4). Using the optimum thiol precatalyst **31**, trifluoromethylketones[24] with various aromatic ring substitutents could be coupled with benzaldehyde to afford products **32–35** without difficulty (Table 4, entries 1–4). The heterocylic benzoate **36** and the 2-naphthaldehyde-derived product **37** could also be prepared in good yield by using this methodology (Table 4, entries 5 and 6). Smooth coupling to form benzoates derived from *p*-anisaldehyde and *m*-chlorobenzaldehyde (i.e. **38** and **39**, respectively) in excellent yields was also possible (Table 4, entries 6 and 7), whereas crossed Tishchenko reactions involving the highly electron deficient *m*-nitrobenzaldehyde (entry 9) proceeded in lower yield due to competition from the homodimerization pathway (a reaction not observed in any of the reactions outlined in entries 1–8).

To summarize, inspired by the mode of action of enzymes which exploit nucleophilic sulfur to promote oxidation processes, we have developed an efficient and reliable thiolate-catalyzed intermolecular Tishchenko reaction. The

Table 4: Crossed Tishchenko coupling: substrate scope.



Entry	Product	*t* [h]	Yield [%][a]
1	 **32**	30	91
2	 **33**	30	93
3	 **34**	40	94
4	 **35**	40	80
5	 **36**	40	78
6	 **37**	24	86
7	 **38**	67	92[b]
8	 **39**	24	87
9	 **40**	24	46[c]

[a] Yield of isolated product after chromatography. [b] 0.9 M reaction concentration. [c] Average of three experiments, the average yield of aldehyde dimerization product was 22%.

reaction is of broad scope and can be utilized to dimerize a range of aromatic and aliphatic aldehydes with uniformly good to excellent product yields. To the best of our knowledge this represents the first example of such an intermolecular thiolate-catalyzed process in the literature. In addition, a key advantage associated with the use of this thiolate-mediated system relative to more complex transition-metal-catalyzed predecessors is tunability: the isolation of intermediates consistent with the proposed biomimetic catalytic cycle (which also allows the relatively slow steps of the catalytic cycle to be identified) together with the involvement of the thiol component in two of the key reaction steps (as a nucleophile in the hemithioacetal-generating step and as a leaving group in the acyl-transfer step) allows one to rationally select catalysts to address the specific challenges presented by either a particular reaction or substrate, as exemplified by the demonstration of two catalytic solutions to the problem of intermolecular aldehyde–ketone coupling.

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[8] Two other recent strategies involving group I metal salts as catalysts are noteworthy: Abaee et al. demonstrated that LiBr could act as an effective Tishchenko catalyst for the dimerization of aromatic aldehydes if used at 50 mol% levels under solvent free conditions (liquid substrates essential), while Mack and Waddell found that NaH catalyzed the same reaction class at 10 mol% loading if used in the absence of solvent in a ball mill, see: a) M. M. Mojtahedi, E. Akbarzadeh, R. Sharifi, M. S. Abaee, *Org. Lett.* **2007**, *9*, 2791; b) D. C. Waddell, J. Mack, *Green Chem.* **2009**, *11*, 79.
[9] a) S. Y. Onozawa, T. Sakakura, N. Tanaka, M. Shino, *Tetrahedron* **1996**, *52*, 4291; b) H. Berberich, P. W. Roesky, *Angew. Chem.* **1998**, *110*, 1618; *Angew. Chem. Int. Ed.* **1998**, *37*, 1569; c) M. R. Bürgstein, H. Berberich, P. W. Roesky, *Chem. Eur. J.* **2001**, *7*, 3078; d) A. Zuyls, P. W. Roesky, G. B. Deacon, K. Konstas, P. C. Junk, *Eur. J. Org. Chem.* **2008**, 693.
[10] T. Andrea, E. Barnea, M. S. Eisen, *J. Am. Chem. Soc.* **2008**, *130*, 2454.
[11] M. R. Crimmin, A. G. M. Barrett, M. S. Hill, P. A. Procopiou, *Org. Lett.* **2007**, *9*, 331.
[12] Several variants of this general mechanism have been proposed, for a discussion see Ref. [3].
[13] Intramolecular cross-coupling is known: Fang et al. demonstrated that six-membered lactones can be synthesized by intramolecular Tishchenko coupling of an aldehyde and a ketone, however no examples of a corresponding intermolecular process were reported, 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.
[14] It should be noted that the term "cross-coupling" is used in a Tishchenko reaction context and does not refer to Tishchenko variants such as the Tishchenko–aldol (for a review see Ref. [14a]) or Tishchenko–Michael (for an example see Ref. [14b]) reactions: a) J. Mlynarski, *Eur. J. Org. Chem.* **2006**, 4779; b) A. Michrowska, B. List, *Nat. Chem.* **2009**, *1*, 225.
[15] J. M. Berg, J. L. Tymoczko, L. Stryer, *Biochemistry*, 5th ed., Freeman, New York, **2002**.
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[18] For representative examples of thiolate catalysis of Michael addition reactions see: a) J. K. Ergüden, H. W. Moore, *Org. Lett.* **1999**, *1*, 375; b) C. E. Aroyan, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 256.
[19] A related intramolecular version of this process had been suggested to explain thiol catalysis of apparent transfer of hydride in glyoxal derivarives; however, this was later shown to occur through a proton-transfer mechanism, see: a) V. Franzen, *Chem. Ber.* **1955**, *88*, 1361; b) S. Shinkai, T. Yamashita, Y. Kusano, O. Manabe, *Chem. Lett.* **1979**, 1323; c) S. Shinkai, T. Yamashita, Y. Kusano, O. Manabe, *J. Am. Chem. Soc.* **1981**, *103*, 2070.
[20] For a recent enantioselective variant of the chemistry described in Ref. [22], see: E. Schmitt, I. Schiffers, C. Bolm, *Tetrahedron Lett.* **2009**, *50*, 3185.
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[22] The disproportionation did not proceed in other solvents such as CH_2Cl_2, MeCN, PhMe, or EtOAc.
[23] The formation and consumption of these types of intermediate could be followed by ^1H NMR spectroscopy, and their catalytic competency was confirmed by crossover experiments. See the Supporting Information for details.
[24] We found that the reaction did not proceed with less electrophilic ketones such as acetophenone under any condition set evaluated.

