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Selenide Ions as Catalysts for Homo- and Crossed-Tishchenko Reactions of Expanded Scope

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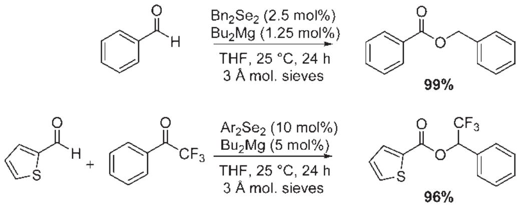
ABSTRACT



Selenide ions have been shown to catalyze the Tishchenko reaction for the first time. These catalysts are superior to previously reported thiolate analogues and promote the disproportionation of aldehydes with increased reaction rates and broader scope at lower catalyst loadings and temperatures. Significantly improved catalyst performance was also observed in the aryl selenide mediated crossed intermolecular Tishchenko reaction.

The Tishchenko reaction (in its simplest form) involves the disproportionation of two aldehyde molecules to generate a single coupled ester product.[1] Several promoters have been developed for this metal-ion-catalyzed[2−6] Cannizzaro-type[7] process. However, it has been regarded more as a mechanistic curiosity than as a powerful synthetic tool by contemporary chemists, despite over a century of research, largely due to a narrow substrate scope, which until recently[8] was limited (in an intermolecular context) to the homocoupling of aldehydes, in often variable yields.[9] Inspired by the mode of action of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase, involving hydride transfer from a hemithioacetal-based intermediate (**A**, Scheme 1),[10] we recently developed the first thiolate-catalyzed Tishchenko processes (**A**, Scheme 1).[11,12] The smooth conversion of benzaldehyde (**1**) to the corresponding

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

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(4) Transition-metal-based catalysts (selected examples): (a) Yamashita, M.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3597. (b) Ito, T.; Horino, H.; Koshiro, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 504. (c) Bergens, S. H.; Fairlie, D. P.; Bosnich, B. *Organometallics* **1990**, *9*, 566. (d) Morita, K.; Nishiyama, Y.; Ishii, Y. *Organometallics* **1993**, *12*, 3748. (e) Yamashita, M.; Ohishi, T. *Appl. Organomet. Chem* **1993**, *7*, 357. (f) Barrio, P.; Esteruelas, M. A.; Onate, E. *Organometallics* **2004**, *23*, 1340. (g) Suzuki, T.; Yamada, T.; Matsuo, T.; Watanabe, K.; Katoh, T. *Synlett* **2005**, 1450. (h) Ogoshi, S.; Hoshimoto, Y.; Ohashi, M. *Chem. Commun.* **2010**, *46*, 3354.

(5) Alkali metal salts: (a) Mojtahedi, M. M.; Akbarzadeh, E.; Sharifi, R.; Abaee, M. S. *Org. Lett.* **2007**, *9*, 2791. (b) Waddell, D. C.; Mack, J. *Green Chem.* **2009**, *11*, 79. (c) Werner, T; Koch, J. *Eur. J. Org. Chem.* **2010**, 6904.

(6) Alkali-earth-metal-based catalysts: (a) Crimmin, M. R.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A. *Org. Lett.* **2007**, *9*, 331. (b) Day, B. M.; Mansfield, N. E.; Coles, M. P.; Hitchcock, P. B. *Chem. Commun.* **2011**, *47*, 4995.

(7) Cannizzaro, S. *Justus Liebigs. Ann.* **1853**, *88*, 129.

(8) Very recently the first examples of the selective intermolecular cross-coupling of aliphatic with aromatic aldehydes has been reported: Ogoshi, S.; Hoshimoto, Y.; Ohashi, M. *J. Am. Chem. Soc.* **2011**, *133*, 4668.

(9) Recent reviews: (a) Seki, T.; Nakajo, T.; Onaka, M. *Chem. Lett.* **2006**, *35*, 824. (b) Törmäkangas, O. P.; Koskinen, A. M. P. *Rec. Res. Dev. Org. Chem.* **2001**, *5*, 225.

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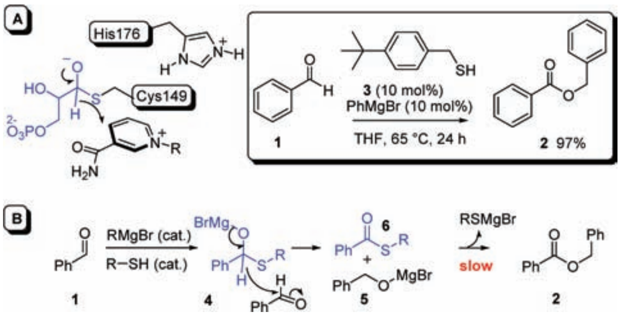
10.1021/ol203439g

benzoate ester **2** upon exposure to an *in situ* formed simple bromomagnesium thiolate derived from 4-*tert*-butylbenzylmercaptan (**3**) was possible in excellent yield. The proposed mechanism (**B**, Scheme 1) involves initial attack of the thiolate on the aldehyde to furnish **4**, which then transfers a hydride to another molecule of **1** to form both the alkoxide **5** and thioester **6**, which then couple to give **2** and the regenerated catalyst, which re-enters the cycle. Somewhat suprisingly, it is the acyl transfer (and not the hydride transfer) process which is rate-determining.[11]

Scheme 1. Thiolate-Catalyzed Tishchenko Reactions: Conditions and Mechanistic Rationale

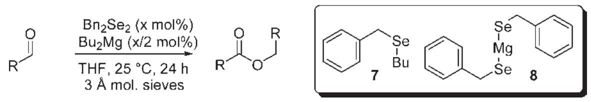


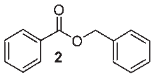
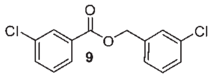
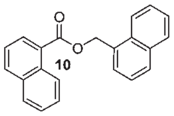
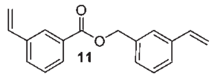
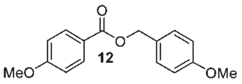
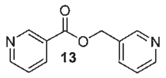
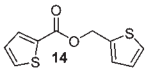
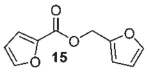
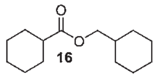
The process is of relatively broad scope and provided consistently high yields of homodimers from a range of substituted benzaldehydes for the first time. A key strength of the methodology is the control achievable through the modification of the thiol component, which is present in two key reaction steps: the addition of the thiolate to the aldehyde to form **4**, and the acyl transfer process (as the leaving group associated with thioester **6**). This allowed the development of the first crossed intermolecular Tishchenko reactions between aldehydes and (trifluoromethyl)ketones catalyzed by less nucleophilic substituted aryl thiolates. We later found that the use of microwave irradiation allowed a significant reduction in the reaction time,[12] with little impact on either scope or efficacy.

Nonetheless, significant scope for improvement remained. In particular, it was desirable to remove the requirement for reflux temperatures, relatively high catalyst loadings, and extended reaction times up to 96 h. The extension of the substrate scope to include aldehydes that incorporated metal-chelating functionality and an increase in the efficiency of reactions involving aliphatic aldehydes would also be important, if the process was to be considered of general utility.

Since the key to efficient promotion of this reaction appeared to be the use of a catalyst which was nucleophilic

Table 1. Homo-Tishchenko Reaction of Aldehydes at 25 °C



entry	x (mol%)	product	yield (%)[a]
1	2.5	 2	99
2	2.5	 9	99
3	5	 10	84[b]
4	5	 11	93
5	10	 12	91
6	5	 13	95
7	5	 14	96
8	20	 15	63
9	10	 16	98

[a] Isolated yield. [b] Determined by ^1H NMR spectroscopy using an internal standard.

enough to generate the reductant (i.e., **4**) efficiently, while also serving as a powerful leaving group in the subsequent acyl transfer process, we postulated that the corresponding alkyl selenide anions might serve as superior catalyst systems. Examples of selenium-based catalysts are rare,[13] and to the best of our knowledge, only one report has emerged involving the use of a nucleophilic (*in situ* generated) selenide ion as a catalyst (to promote the formation of alkenes from 1,2-dimesylalkanes) in the literature.[14]

Our preliminary investigations were hampered by the difficulty in generating the requisite magnesium selenide counterpart of the previously used thiolates conveniently in the absence of other metal ions, oxygen (which leads to rapid oxidation of the alkylselenide to

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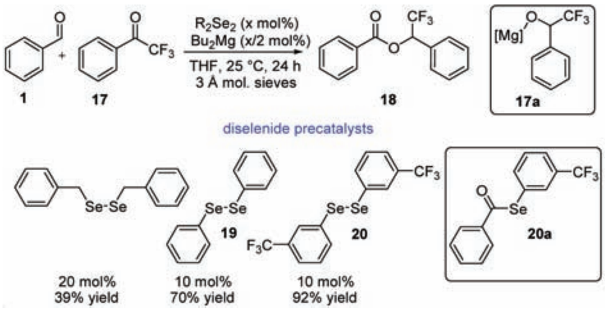
(11) Cronin, L.; Manoni, F.; O'Connor, C. J.; Connon, S. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3045.

(12) O'Connor, C. J.; Manoni, F.; Curran, S. P.; Connon, S. J. *New J. Chem.* **2011**, *35*, 551.

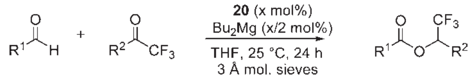
Scheme 2. Crossed-Tishchenko Reactions: Catalyst Screening

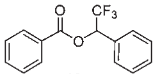
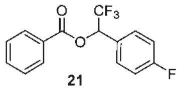
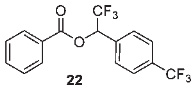
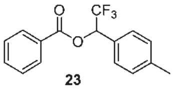
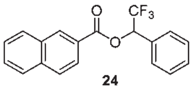
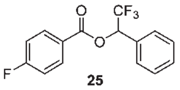
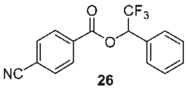
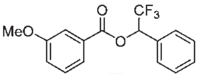
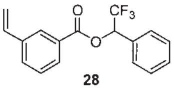
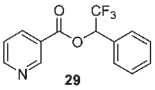
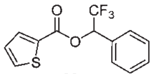
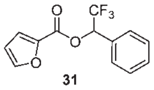
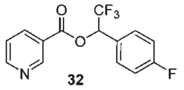
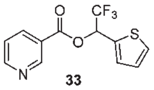


the diselenide), and moisture (resulting in competitive acyl selenide hydrolysis). After considerable experimentation, it was found that the addition of commercially available dibutyl magnesium to dibenzyl diselenide in THF at room temperature led to rapid formation of the desired alkyl selenide in solution. We then evaluated this reagent as a catalyst in the homo-Tishchenko reaction of aldehydes (Table 1).

We were delighted to find that the benzyl selenide anion, at only 2.5 mol % loading, was capable of promoting the dimerization of benzaldehyde in essentially quantitative isolated yield at 25 °C (entry 1). We found that the use of molecular sieves led to improved catalytic efficacy, most likely due to the suppression of deleterious acyl seleonate hydrolysis by adventitious water. The isolation of the butylbenzyl selenide **7** from the reaction mixture and the superiority of a catalyst derived from a 1:2 (as opposed to a 1:1) mole ratio of alkyl magnesium to diselenide strongly indicated that the catalytically active species was the selenide **8**. Electron-deficient, -neutral, and -rich aldehydes could be converted to the esters **9**, **10**, **11** (a product of potential interest as a polymer synthesis substrate), and **12** respectively (entries 2−5) in excellent yield at low loadings relative to those required in the analogous thiolate-catalyzed reactions.

Table 2. Crossed Intermolecular Tishchenko Reaction



entry	x (mol%)	product	yield (%)[a]
1	10	 **18**	92
2	20	 **21**	90
3	20	 **22**	93
4	10	 **23**	95
5	20	 **24**	87
6	20	 **25**	87
7	20	 **26**	73
8	20	 **27**	94
9	20	 **28**	84
10	20	 **29**	80
11	10	 **30**	95
12	20	 **31**	96
13	20	 **32**	63[b]
14	20	 **33**	56

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy using an internal standard.

A problem traditionally associated with Tishchenko chemistry is the transformation of substrates bearing metal-chelating functionality.[2−6,11] This has led to aldehydes possessing heterocyclic substituents residing largely outside the orbit of the methodology. Here, the conversion of pyridine-3-carbaldehyde and thiophene-2-carbaldehyde to **13** and **14** respectively occurs in excellent yield at 5 mol %

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(13) Electrophilic or radical selenium-based catalysts: (a) ten Brink, G.-J.; Vis, J.-M.; Arends, I. W. C. E.; Sheldon, R. A. *J. Org. Chem.* **2001**, *66*, 2429. (b) Wojtowicz, H.; Brzaszcz, M.; Kloc, K.; Młochowski, J. *Tetrahedron* **2001**, *57*, 9743. (c) Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319. (d) Miyake, Y.; Nishibayashi, Y.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2233. (e) Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513. (f) Ichikawa, H.; Usami, Y.; Arimoto, M. *Tetrahedron Lett.* **2005**, *46*, 8665. (g) Crich, D.; Patel, M. *Org. Lett.* **2005**, *7*, 3625. (h) Lenardão, E. J.; Mendes, S. R.; Ferreira, P. C.; Perin, G.; Silveira, C. C.; Jacob, R. G. *Tetrahedron Lett.* **2006**, *47*, 7439. (i) Browne, D. M.; Niyomura, O.; Wirth, T. *Org. Lett.* **2007**, *9*, 3169. (j) Clive, D. L. J.; Pham, M. P.; Subedi, R. *J. Am. Chem. Soc.* **2007**, *129*, 2713. (k) Browne, D. M.; Niyomura, O.; Wirth, T. *Phosphorus, Sulfur, and Silicon* **2008**, *183*, 1026. (l) Lenardão, E. J.; Feijó, J. O.; Thurow, S.; Perin, G.; Jacob, R. G.; Silveira, C. C.; Jacob, R. G. *Tetrahedron Lett.* **2009**, *50*, 5215. (m) Shahzad, S. A.; Venin, C.; Wirth, T. *Eur. J. Org. Chem.* **2010**, 3465. (o) Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504.

(14) Crich, D.; Neelamkavil, S.; Sartillo-Piscil, F. *Org. Lett.* **2000**, *2*, 4029.

catalyst loading (entries 6−7). 2-Furfural was a more recalcitrant substrate, yet **15** could be prepared from this aldehyde in good yield (entry 8).

Another obstacle which the previous thiolate-based catalysts found difficult to negotiate was the disproportionation of the aliphatic aldehyde **16**, due to competing aldol pathways at high temperature. Gratifyingly, in the presence of catalyst **8**, ester **16** was isolated in near-quantitative yield (entry 9).

With a convenient methodology of improved activity and scope in hand, we next investigated its use in intermolecular crossed-Tishchenko chemistry using trifluoromethylketone electrophiles. This process was previously developed using thiolate catalysts, and it was found that the use of a catalyst which (when acylated) conferred high electrophilicity on the thioester was the key to securing high catalytic activity. This arises due to the poor nucleophilicity of the relatively hindered and less basic magnesium alkoxide **17a**, formed after the hydride transfer step, which retards an already inherently sluggish acyl transfer process.

Accordingly, we attempted the 1:1 coupling of benzaldehyde (**1**) with α,α,α-trifluoromethylacetophenone (**17**) in the presence of dibutylmagnesium and dibenzyldiselenide, diphenyldiselenide (**19**), or its *m*-CF_3 substituted analogue **20** at 25 °C (Scheme 2). As expected, the simple alkyl selenide **8** (i.e., derived from dibenzyldiselenide) was not efficacious in this more challenging reaction. The corresponding aryl selenide ions prepared from **19** and **20** proved superior, with the *m*-CF_3 substituted catalyst capable of synthetically useful activity. We would propose that this is mainly due to the formation of the highly electrophilic acylating agent **20a**.

We were now in a position to evaluate the scope of the intermolecular[15] crossed-Tishchenko process (Table 2).[16] Here the superiority of the selenide-based system is perhaps most readily apparent. Beginning by using benzaldehyde as the aldehyde component and varying the ketone substrate, it was found that both unsubstituted, activated, and deactivated α,α,α-trifluoromethylacetophenones were compatible with the methodology, furnishing the coupled products **18** and **21**−**23** in excellent yields (entries 1−4).

By keeping the ketone substrate constant and varying the aldehyde component, it was demonstrated that electron-neutral, -rich, and (strongly) -withdrawing substituents on the aromatic ring were also well tolerated by the catalyst (i.e., **24**−**28**, entries 5−9). Previously challenging heterocyclic aldehydes incorporating chelating functionality (even the particularly recalcitrant 2-furfural) proved amenable to coupling, allowing the synthesis of **29**−**31** in good to excellent yields for the first time (entries 10−12).[17]

Finally, the activity of this catalyst system allowed the coupling of a heterocyclic aldehyde with either a substituted trifluoroacetophenone (entry 10) or a heterocyclic analogue (entry 11) to generate ester products (**32** and **33**) also outside the scope of the previous literature benchmark methodology.

In summary, the exchange of selenide ions for thiolates as catalysts in the Tishchenko reaction leads to faster rates at lower catalyst loadings and reaction temperatures. A significant expansion of reaction scope is also possible; high yields of products derived from the disproportionation of a hitherto problematic hindered aliphatic aldehyde and heterocyclic substrates, previously capable of disrupting the catalytic cycle by metal chelation, can now be subjected to efficient homo- and crossed Tishchenko chemistry. A simple dibenzyldiselenide-derived catalyst can be utilized in the homo-Tishchenko reaction, while the crossed intermolecular variant involving activated ketones requires an arylselenide catalyst that is better able to accelerate the slow acyl-transfer step.

Studies to further explore the potential of alkyl/aryl selenides as nucleophilic catalysts are underway.

Acknowledgment. This material was based on work funded by The European Research Council.

Supporting Information Available. General experimental procedures, catalyst synthesis, ^1H and ^{13}C NMR spectra, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] For related intramolecular Tishchenko and Tishchenko-like processes, see: (a) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 84. (b) Hsu, J. L.; Fang, J. M. *J. Org. Chem.* **2001**, *66*, 8573. (c) Shen, Z.; Khan, H. A.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2916. (d) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608. (e) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741.

[16] We use the term 'crossed' in a Tishchenko reaction context. This does not refer to Tishchenko variants such as the Tishchenko-aldol (see ref 16a) or Tishchenko−Michael (for an example see ref 16b) reactions: (a) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779. (b) Michrowska, A.; List, B. *Nat. Chem.* **2009**, *1*, 225.

[17] Aliphatic aldehydes are currently incompatible with this crossed-Tishchenko methodology.
