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Tishchenko Reaction

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Selective Crossed-Tishchenko Reaction—A Waste-Free Synthesis of Benzyl Esters[**]

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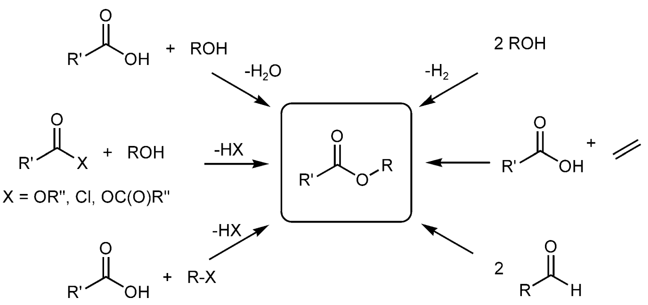
Dedicated to Dr. Christian Bruneau on the occasion of his 60th birthday

aldehydes · esters · homogeneous catalysis · N-heterocyclic carbenes · nickel

The synthesis of esters is one of the most fundamental transformations in organic chemistry. Whole books have been filled with efficient synthetic methods.[1] Still, not all types of esters can be accessed by effective and atom-economical procedures.

The most straightforward synthetic route to esters is the condensation of carboxylic acids with alcohols. However, the inherent difficulty connected to this approach results from the reversibility of the reaction, which makes it necessary to either use an excess of one of the reagents or to add a coupling reagent or drying agent. Only recently, catalytic processes have been discovered that allow full conversion of equimolar amounts of carboxylic acids and alcohols.[2] Alternatively, esters can be synthesized by the alcoholysis of activated carboxylic acids derivatives such as acyl chlorides, anhydrides, imidazolides, and esters. Further high-yielding but waste-intensive methods include alkylations of carboxylates with carbon electrophiles and decarboxylative esterifications.[3] A contemporary, atom-economical ester synthesis is Milstein's dehydrogenative coupling of alcohols in the presence of ruthenium catalysts (Scheme 1).[4]



Scheme 1. Synthetic routes to esters.

In the industrial synthesis of bulk products, it is vital to make optimal use of available feedstocks and minimize waste streams. For ester syntheses, these requirements are best fulfilled for the addition of carboxylic acids to alkenes (AVADA process, 220 kilotons of ethyl acetate per year)[5] or the Tishchenko reaction of acetaldehyde (500 kilotons per year).[6]

The Tishchenko reaction is not necessarily the first reaction that comes to mind when one considers sustainable esterifications. This is surprising in view of its long and successful history.[6] In 1887 Claisen discovered that benzyl benzoate is formed when benzaldehyde is treated with sodium methoxide.[7] By using aluminum alkoxide catalysts, which are more Lewis acidic and less basic, Tishchenko turned this reaction into a synthetically useful process.[8] It allows the homocoupling of a broad scope of aldehydes to give the corresponding esters, incorporating all atoms of the starting materials into the product.

The metal alkoxide was initially believed to act simply as a Lewis acid that coordinates to one aldehyde molecule, thus facilitating the addition of another aldehyde molecule. Based on mechanistic studies, a more complex mechanism has been established that starts with the addition of the metal alkoxide to the carbonyl group and formation of a metal hemiacetalate.[9] In a concerted process, a second molecule of the aldehyde coordinates, and a hydride is transferred from the acetal to the carbonyl carbon. Release of the ester regenerates the initial metal alkoxide. Not only main-group alkoxides but also transition-metal,[10] lanthanide,[11] and actinide[12] catalysts were shown to operate by this mechanism (Scheme 2).[6]

The key limitation of the Tishchenko reaction which precluded its general use as an ester synthesis was that it could be applied only for the coupling of two molecules of the same aldehyde. In early attempts to steer the reaction toward the selective formation of a mixed ester, particularly reactive aldehydes were added to mixtures of a metal catalyst with an excess of substantially less reactive aldehydes. In this context, aldehydes with electron-donating groups (e.g. aliphatic aldehydes) were found to be better hydride donors than aldehydes with electron-withdrawing groups (e.g. aryl aldehydes), which are the better hydride acceptors.[9] However, the differences in reactivity are too small to translate to useful selectivity levels. A record of 71 % selectivity (54 % yield) was achieved

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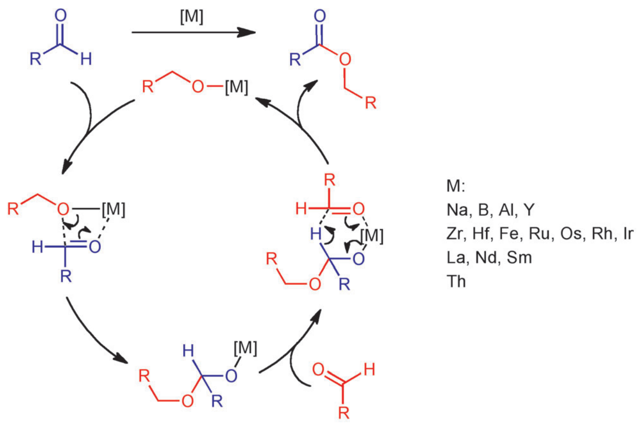


Scheme 2. The mechanism of the Tishchenko reaction mediated by metal alkoxides.

for the reaction of butyraldehyde with 2 equivalents of benzaldehyde in the presence of a zirconocene catalyst.[13]

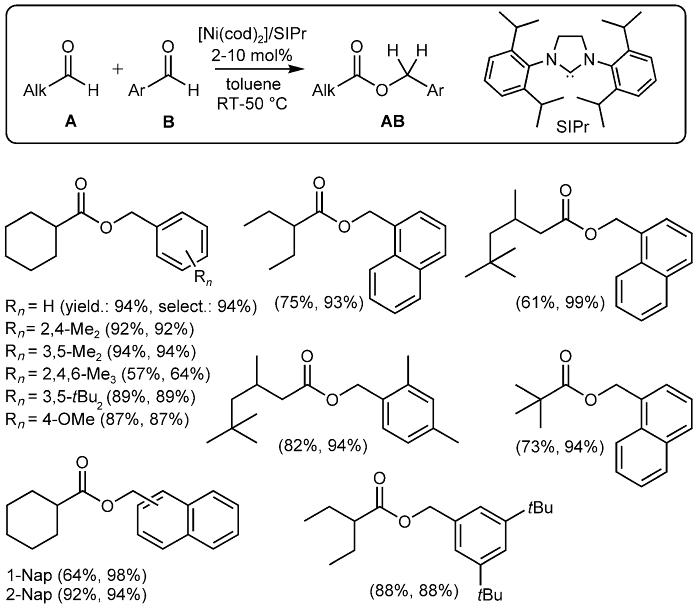
Up until now, highly selective crossed-Tishchenko reactions have been successfully performed only for very special substrate combinations. Examples are the coupling of aryl aldehydes with α-keto esters in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and an N-heterocyclic carbene (NHC) organocatalyst,[14] or with trifluoromethyl ketones using a combination of a thiol and phenylmagnesium bromide as the catalyst,[15] and the yttrium-catalyzed asymmetric Aldol/Tishchenko reaction by White, Morken et al.[16]

The group of Ogoshi recently reported what might turn out to be the long-awaited breakthrough in this field. They discovered that nickel complexes bearing the sterically demanding SiPr-NHC ligand promote the crossed-Tishchenko reaction of equimolar mixtures of aromatic and aliphatic aldehydes with selective formation of alkylcarboxylic acid benzyl esters.[17] In preceding studies, they had found that Ni-NHC complexes are active catalysts for symmetrical Tishchenko reactions.[18] They had also observed that when these catalysts are used, aliphatic aldehydes react much faster than their aromatic counterparts. This difference in reactivity opened up an opportunity to achieve selectivity in crossed esterifications. The reaction of a 1:1 mixture of benzaldehyde and cyclohexyl carbaldehyde initialy provided the desired benzyl cyclohexanecarboxylate in only moderate yield and selectivity. However, after optimization of the catalyst and reaction conditions, near-quantitative conversion was achieved along with an unprecedented selectivity of 94 % in favor of the isomer in which the aliphatic aldehyde is oxidized to the carboxylate and the aromatic aldehyde is reduced to the alcohol part.

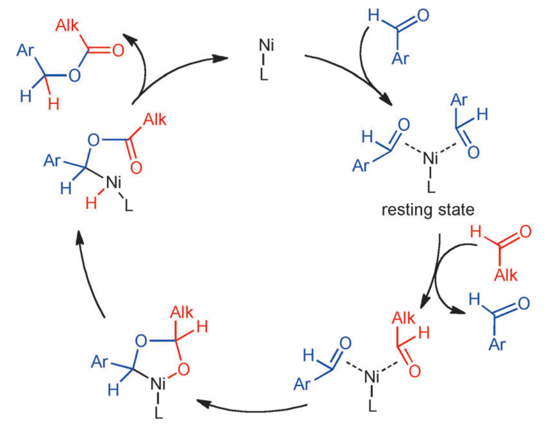
The new protocol has been been applied successfully to the coupling of several branched aliphatic aldehydes (**A**) with electron-rich aromatic aldehydes (**B**, Scheme 3). In all cases, the crossed products (**AB**) were obtained in high yields. These are spectacular results! However, the choice of the examples may be interpreted as an indication that this prototype catalyst still has some limitations with regard to the electronic properties of the substrates as well as the functional-group tolerance.

Mechanistic investigations including in situ NMR studies, kinetic measurements, and the determination of kinetic isotope effects indicate that the reaction does not follow the standard Tishchenko mechanism. The authors propose a catalytic cycle that starts from a resting state in which two aromatic aldehyde molecules coordinate to the Ni^0 center in η^2 fashion.[19] After the exchange of one of the coordinated aldehydes for an aliphatic aldehyde, a nickelacycle reversibly forms.[20] Subsequently, a nickel hydride species forms through β-hydride elimination, which reductively eliminates the ester product (Scheme 4).[21]

In conclusion, Ogoshi's protocol is an important milestone on the way toward establishing crossed-Tishchenko reactions



Scheme 3. Crossed-Tishchenko reaction catalyzed by a nickel–NHC catalyst system.



Scheme 4. The proposed mechanism of the nickel-catalyzed crossed-Tishchenko reaction.

as a waste-free route to unsymmetrical esters. The next step would be extending the reaction to a broader range of functionalized substrates by optimizing the catalyst system. It will also be interesting to see whether other catalysts can be found that discriminate between aldehydes based on other distinguishing features rather than whether the aldehydes are aromatic or aliphatic.

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[1] For an overview, see: J. Otera, *Esterification*, Wiely-VCH, Weinheim, **2003**.

[2] K. Ishihara, S. Ohara, H. Yamamoto, *Science* **2000**, *290*, 1140–1142.

[3] L. Gooßen, A. Döhring, *Adv. Synth. Catal.* **2003**, *345*, 943–947.

[4] J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005**, *127*, 10840–10841.

[5] M. Johnson, *Frontiers* **2002**, *4*, 12–15.

[6] T. Seki, T. Nakajo, M. Onaka, *Chem. Lett.* **2006**, *35*, 824–829.

[7] L. Claisen, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 646–650.

[8] W. Tischtschenko, *Zh. Russ. Fiz.-Khim. O-va.* **1906**, *38*, 355–418.

[9] Y. Ogata, A. Kawasaki, *Tetrahedron* **1969**, *25*, 929–935.

[10] For recent examples, see: a) C. Tejel, M. A. Ciriano, V. Passarelli, *Chem. Eur. J.* **2011**, *17*, 91–95; b) M. O. Simon, S. Darses, *Adv. Synth. Catal.* **2010**, *352*, 305–308; c) S. Omura, T. Fukuyama, Y. Murakami, H. Okamoto, I. Ryu, *Chem. Commun.* **2009**, 6741–6743.

[11] a) S. Onozawa, T. Sakakura, M. Tanaka, M. Shiro, *Tetrahedron* **1996**, *52*, 4291–4302; b) M. R. Bürgstein, H. Berberich, P. W. Roesky, *Chem. Eur. J.* **2001**, *7*, 3078–3085.

[12] M. Sharma, T. Andrea, N. J. Brookes, B. F. Yates, M. S. Eisen, *J. Am. Chem. Soc.* **2011**, *133*, 1341–1356.

[13] K. Morita, Y. Nishiyama, Y. Ishii, *Organometallics* **1993**, *12*, 3748–3752.

[14] A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2006**, *128*, 4558–4559.

[15] L. Cronin, F. Manoni, C. J. O'Connor, S. J. Connon, *Angew. Chem.* **2010**, *122*, 3109–3112; *Angew. Chem. Int. Ed.* **2010**, *49*, 3045–3048.

[16] a) C. M. Mascarenhas, S. P. Miller, P. S. White, J. P. Morken, *Angew. Chem.* **2001**, *113*, 621–623; *Angew. Chem. Int. Ed.* **2001**, *40*, 601–603; b) J. Mlynarski, *Eur. J. Org. Chem.* **2006**, 4779–4786.

[17] Y. Hoshimoto, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2011**, *133*, 4668–4671.

[18] S. Ogoshi, Y. Hoshimoto, M. Ohashi, *Chem. Commun.* **2010**, *46*, 3354–3356.

[19] See also: M. Massoui, D. Beaupère, L. Nadjo, R. Uzan, *J. Organomet. Chem.* **1983**, *259*, 345–353.

[20] For a related stoichiometric reaction, see: A. Greco, M. Green, S. K. Shakshooki, F. G. A. Stone, *J. Chem. Soc. D* **1970**, 1374–1375.

[21] A mechanism proceeding by oxidative addition of the formyl C–H bond to the nickel cannot be ruled out. See: Z. Shen, P. K. Dornan, H. A. Khan, T. K. Woo, V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 1077–1091, and references therein.