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Stereoselective Synthesis of (*E*)-α,β-Unsaturated Esters via Carbene-Catalyzed Redox Esterification

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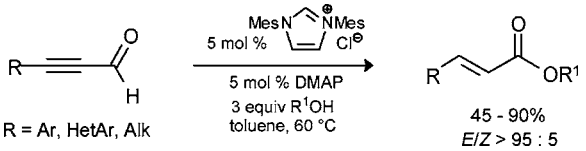
ABSTRACT



Stereoselective, carbene-mediated redox esterification of alkynyl aldehydes provides mild and atom economical access to (*E*)-configurated, α,β-unsaturated carboxylic esters. The organocatalytic method relies on the generation of activated carboxylates via extended/conjugated umpolung in the presence of catalytic amounts of carbene precursor and base.

α,β-Unsaturated alkyl- and aryl esters ("cinnamic esters") are versatile building blocks for organic synthesis and of significant importance for industrial applications.[1] Consequently, a great variety of powerful methods for their preparation has been developed;[2] most of these methods are *E*-stereoselective, and quite a number use aldehydes as precursors.[3] However, these reliable and often high-yielding reactions are mostly noncatalytic, lacking atom economy, and many require harsh reaction conditions. It is still a challenge to improve known methods and develop new procedures that will avoid the production of stoichiometric (or larger) amounts of byproducts, ensure operational simplicity, and provide mild conditions that will allow the use of sensitive substrates.

In this context, catalytic methods for direct condensation of carboxylic acids[4] or transesterifications[5] are pointing the way to sustainable, environmentally benign processes. Alternative approaches to circumvent major drawbacks (vide supra) include transformations that avoid the use of acids or acid derivatives.[6] The oxidative esterification of activated

(1) Selected recent examples of application include 1,4-additions: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (b) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377−10441. (c) López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2752−2756. Cycloadditions: (d) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388−6390. (e) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668−3669. Electrophilic addition: (f) Chen, D.; Guo, L.; Liu, J.; Kirtane, S.; Cannon, J. F.; Li, G. *Org. Lett.* **2005**, *7*, 921−924.

(2) For a general overview, see: (a) Katritzky, A. R. *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Ed.; Pergamon: Oxford, 1995; Vol. 5, pp 154−161. (b) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451−2465. Some recent approaches include Heck reaction: (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066 and cross metathesis: (d) Chatterjee, A. K.; Toste, F. D.; Choi, T.-L.; Grubbs, R. H. *Adv. Synth. Catal.* **2002**, *344*, 634−637.

(3) Wittig olefination: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927. Horner−Wadsworth−Emmons reaction: (b) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369−379. Knoevenagel condensation: (c) List, B.; Doehring, A.; Hechavarria Fonseca, M. T.; Wobser, K.; van Thienen, H.; Torres, R. R.; Galilea, P. L. *Adv. Synth. Catal.* **2005**, *347*, 1558−1560. (d) List, B.; Doehring, A.; Hechavarria Fonseca, M. T.; Job, A.; Torres, R. R. *Tetrahedron* **2006**, *62*, 476−482 and references therein. Julia olefination: (e) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585. (f) Peterson olefination: van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, 195−200. (g) SmI_2- and $CrCl_2$-promoted reaction: Concellón, J. M.; Concellón, C.; Méjica, C. *J. Org. Chem.* **2005**, *70*, 6111−6113.

(4) (a) Sato, A.; Nakamura, Y.; Maki, T.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2005**, *347*, 1337−1340. (b) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140−1142. (c) Chen, C.-T.; Munot, Y. S. *J. Org. Chem.* **2005**, *70*, 8625−8627.

(5) Review: (a) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971−985. (b) Grasa, G. A.; Gueveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812−2819. (c) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587−3590. (d) For a catalytic amidation, see: Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453−2456.

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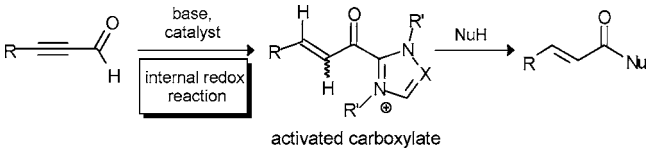
alcohols and aldehydes in the presence of equimolar or excess amounts of cyanide and MnO_2 or AgO as oxidant is a well-known synthetic tool and proceeds via an acyl cyanide intermediate.[7] Additionally, intramolecular redox reactions, especially redox esterifications, while a powerful methodological concept, have only been rarely used in organic synthesis.[8] Recent reports on carbene-mediated extended umpolung reactions[9] of α-heterosubstituted,[10] α,α-diheterosubstituted,[11] and α,β-unsaturated aldehydes[12] present the first applications of this promising concept. In this context, we rationalized the potential use of propargylic aldehydes as synthetic precursors of α,β-unsaturated carboxylic derivatives. Herein, we disclose an atom economical, catalytic method for the stereoselective preparation of α,β-unsaturated esters from such substrates in good yields.[13]

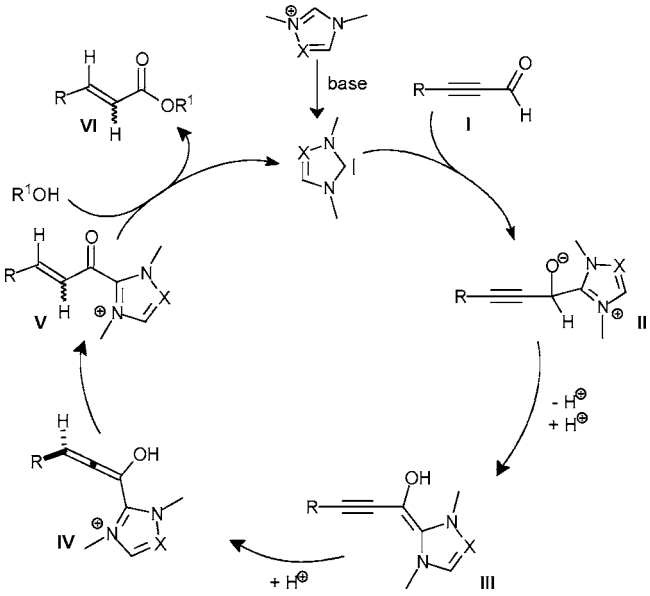
Alkynyl aldehydes react via catalytic generation of an activated carboxylate with nucleophiles to form alkenoate derivatives.



In our proposed mechanism (Scheme 1), nucleophilic carbene,[14] generated from the deprotonation of the heterazolium salt, adds to the alkynyl aldehyde **I** to form intermediate **II**, which subsequently undergoes H-migration to produce an alkynyl enaminol **III**. Protonation of **III** provides allenol **IV**, a tautomer of activated carboxylate **V**, which regenerates the catalyst upon acylation of appropriate nucleophiles.

An alternative mechanism, involving an oxycumulene intermediate **VIII**, was claimed by Walia and Vishwakarma[15]

Scheme 1. Postulated Mechanism for the Synthesis of Unsaturated Esters



to explain the observed 1:1-*E*/*Z* ratio for the final products in an overstoichiometric CN^--mediated transformation of phenylpropynal with MeOH. In contrast, we realized the need of sterically demanding carbene precursors to provide access to stereochemical defined acyl azolium species **V**.

Following the hypothesis of the formation of the more stable *E*-isomer under thermodynamic conditions, we started our investigation with a survey of different catalyst/base combinations (Table 1). In addition to the challenge of stereocontrol, the product-determining role of the base needed to be faced.[16]

Preparation of the required propargylic aldehydes is straightforward. They can be conveniently prepared either by oxidation of propargylic alcohols, easily accessed through Sonogashira coupling with unprotected propargylic alcohol,[17] or alternatively via formylation of deprotonated acetylene derivatives with DMF.[18]

The conversion of phenylpropynal **6** to ethyl cinnamate **7** was chosen as our test reaction (Table 1).

Whereas thiazolium salt **1** proved to be inactive, both benzimidazolium **2** (entry 2) and triazolium salt **4** (entry 3) gave moderate yields and selectivities of the desired product.

(6) For selected examples, see: (a) Bruneau, C.; Neveux, M.; Kabouche, Z.; Ruppin, C.; Dixneuf, P. H. *Synlett* **1991**, 755−763. (b) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840−10841.

(7) (a) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616−5617. (b) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055−1064. (c) Kawabata, H.; Hayashi, M. *Tetrahedron Lett.* **2002**, *43*, 5645−5647.

(8) Selected examples for intramolecular redox reactions: (a) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180−12181. (b) Högenauer, K.; Mulzer, J. *Org. Lett.* **2001**, *3*, 1495−1497. For organometallic redox esterifications, see: (c) Tanaka, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1607−1609. (d) de Vries, J. G.; Roelfes, G.; Green, R. *Tetrahedron Lett.* **1998**, *39*, 8329−8332.

(9) For a short review, see: Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506−7510.

(10) (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126−8127. (b) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518−9519.

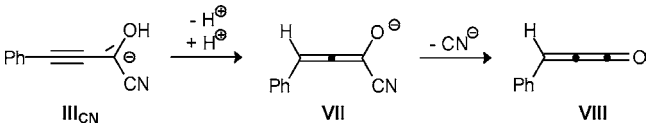
(11) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406−16407.

(12) (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205−6208. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905−908. (d) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131−3134.

(13) An atom-efficient decarboxylative modification of the Doebner−Knoevenagel reaction for the generation of α,β-unsaturated esters using malonic acid half esters in the presence of catalytic amounts of base has been published recently by List and co-workers: refs 3c,d.

(14) Reviews: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541. (b) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328.

(15) Walia, J. S.; Vishwakarma, L. C. *Chem. Commun.* **1969**, 396:



(16) It is noteworthy that homoenolate **III** seems not to undergo any C−C bond formation as a competing electrophilic trapping event as it is observed for alkenyl substrates that can yield homolactones depending on the reaction conditions. Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873−3876.

(17) Banerjee, M.; Roy, S. *Org. Lett.* **2004**, *6*, 2137−2140.

(18) Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427−6428.

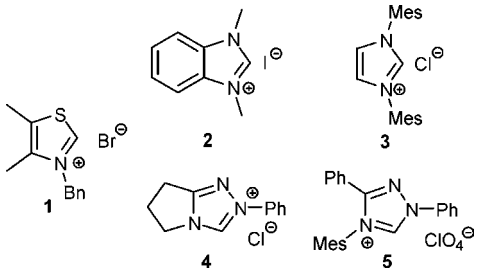
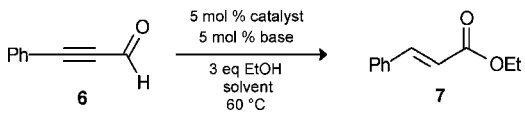


Figure 1. Heterazolium precatalysts for the catalytic generation of activated ester from phenylpropynal.

However, sterically hindered IMes·HCl (**3**) (entries 4−10) and mesityl-substituted triazolium catalyst **5** (entry 11) provided the unsaturated ester in higher than 95:5 *E*/*Z* stereoselectivity as determined by NMR.[19] An NMR experiment[20] (d^8-toluene) in the presence of IMes·HCl (**3**) did not show any formation of the *Z*-configurated isomer during the reaction; this supports the decisive role of the catalyst for the stereochemical outcome of the reaction. Figure 1 shows

Table 1. Optimization of Conditions for Redox Esterification[a]



entry	catalyst	solvent	base	yield[b] (%)	ratio *E*/*Z*[c]
1[d]	**1**	toluene	DBU	–	–
2	**2**	toluene	DMAP	22	80:20
3	**4**	THF	DMAP	38	80:20
4	**3**	THF	DBU	<10	>95:5
5	**3**	toluene	pyridine	10	>95:5
6	**3**	toluene	DABCO	47	>95:5
7	**3**	CH_3CN	DMAP	30	>95:5
8	**3**	toluene	DMAP	98[e]/65	>95:5
9[f]	**3**	toluene	imidazole	70	>95:5
10	**3**	toluene	DMAP[g]	20	>95:5
11	**5**	THF	DIPEA[g]	50/63[h]	>95:5
12	**5**	THF	DMAP	60[i]	–

[a] All reaction were performed on a 0.4 mmol scale, 2 h; entries 3, 4, 5, 11, and 12 needed >12 h for full conversion. DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA = di*iso*propylethylamine; DMAP = (dimethylamino)pyridine. [b] Isolated yields following chromatography; full conversion by GC. [c] Determined by NMR. [d] 10 mol % catalyst was used. [e] Determined by GC using method of internal standard (see Supporting Information). [f] Performed at 110 °C, 24 h. [g] Performed with 10 mol % base. [h] Reaction in the presence of Na_2SO_4. [i] Only diethoxyacetale of phenylpropynal was isolated.

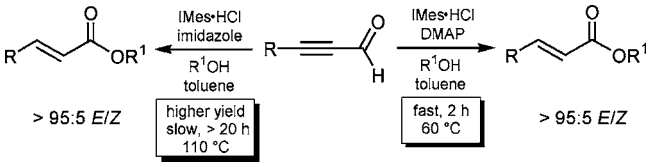
the heterazolium precatalysts for the catalytic generation of activated ester from phenylpropynal. Both efficient, sterically demanding catalysts **3** and **5** are easily accessible in multigram scale in two and three steps, respectively, from inexpensive starting material.[21]

Following the reaction progress by NMR showed a very clean transformation without generation of any byproducts (i.e., <5%).[20] The reactions show full conversion by GC,[22] suggesting a possible loss of material through azeotropic distillation. The use of strong base or excess of DMAP as base (>5 mol %, entries 4 and 10) proved to be counterproductive in terms of the yield of the reaction.

Further studies on catalyst, base, and solvent identified two reaction conditions as superior showing different advantages for the performance of the reaction.

Whereas application of imidazole as a milder base requires higher temperature and elongated reaction times, the use of (dimethylamino)pyridine (DMAP) allows fast access to *E*-configurated unsaturated esters in only slightly lower yields. Depending on the solvent, conspicuous amounts of acetal byproducts of the alkynyl aldehyde were observed in the presence of the more acidic triazolium precatalyst (entry 12).[16,23] Na_2SO_4 as additive proved to be beneficial for the yield in the case of triazolium catalyst **5** (entry 11). Scheme 2 compares the "best conditions".

Scheme 2. Comparison of "Best Conditions"



Primary alcohols are competent nucleophiles (Table 2; entries 1−3); secondary alcohols are lower yielding and require extended reaction times (entry 4).

The stereoselective catalytic generation of activated carboxylates succeeds from both electron-rich and heteroaryl propargylic aldehyde precursors (Table 2; entries 5−8) as well as from sterically hindered, alkyl-substituted alkynal (entry 9).

Electron-poor aldehydes showed only minor reactivity for the desired conversion even under prolonged reaction times using DMAP/IMes·HCl as catalytic system. To circumvent this problem, we considered applying the above-mentioned more "acidic" conditions with triazolium precursor **5**. Gratifyingly, we could isolate the desired products in moderate to good yield (Table 2; entries 10−12). An additional benzaldehyde function in bisaldehyde substrate (entry 12) seems to be problematic for the transformation. In addition to decomposed material, ethyl cinnamate was the

(19) Only low selectivities (*E*/*Z* < 1:4) are observed in the final protonation event of 1,2,4-triazole-substituted ethoxy allenolate: Katritzky, A. R.; Feng, D.; Lang, H. *J. Org. Chem.* **1997**, *62*, 715−720.

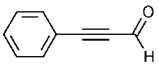
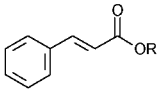
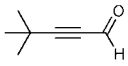
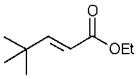
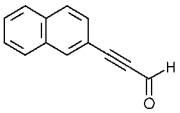
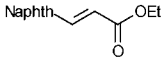
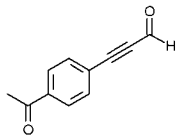
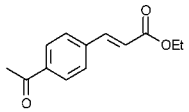
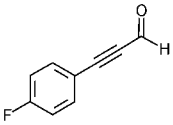
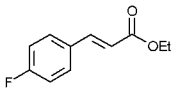
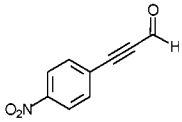
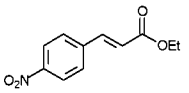
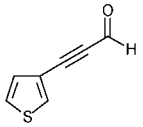
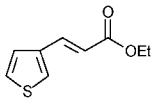
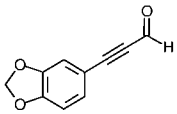
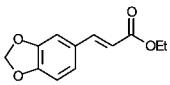
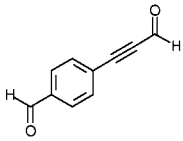
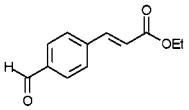
(20) For details, see Supporting Information.

(21) IMes·HCl is commercially available (1 g ≈ $40). For its preparation, see: Arduengo, A. J., III. U.S. Patent 5,077,414, 1991. Triazolium precatalyst **5** was prepared according to a known procedure: Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer, T. *Synthesis* **2003**, 1292−1295.

(22) For an exemplary GC/MS of a crude reaction mixture (Table 1, entry 8), see Supporting Information.

(23) Olofson, R. A.; Landesberg, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 4263−4265.

Table 2. Catalytic Esterifications of Alkynals: Substrate Scope[a]

entry	alkynal	Nu	product	yield (%)[b]	entry	alkynal	Nu	product	yield (%)[b]
1		EtOH		65	9[d]		EtOH		90
2		MeOH		63					
3		BnOH		55					
4		*i*PrOH	R = Bn, Et, Me, *i*Pr	30/38[c]					
5		EtOH		48	10[c]		EtOH		66
6		EtOH		46	11[c]		EtOH		41
7		EtOH		50					
8		EtOH		60	12[c]		EtOH		18

[a] Reaction conditions: 5 mol % of **3**, 5 mol % of DMAP, 0.4 mmol alkynal, 3 equiv of ROH, toluene, 60 °C, 2 h. [b] Isolated yield following chromatography. [c] Performed with 5 mol % of **5**, 10 mol % DIPEA in THF, Na_2SO_4, 24 h. [d] Performed with 5 mol % imidazole at 110 °C for 48 h.

solely isolable product (no benzoin, Stetter, or lactone product, etc.), pointing to the strong dependence of the NHC-catalyzed reactions upon reaction conditions and applied catalyst.

In conclusion, an organocatalytic approach for the synthesis of *trans*-α,*β*-unsaturated esters with excellent *E*/*Z*-stereoselectivity has been described. The catalytic generation of the pivotal activated carboxylate intermediates from alkynals and *N*-heterocyclic carbenes proceeds under mild conditions, is atom economic, and requires only substoichiometric amounts of base. Efforts to extend the scope of this promising reaction and further optimization are currently underway.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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