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Iron-Catalyzed Cyclopropanation with Glycine Ethyl Ester Hydrochloride in Water

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ABSTRACT

An iron-catalyzed cyclopropanation reaction of styrenes in aqueous media is disclosed that employs glycine ethyl ester hydrochloride in a tandem diazotization/cyclopropanation reaction. The products are accessed in good yields and good diastereoselectivity using readily available and inexpensive starting materials. Moreover, a wide range of transition metals may be used under these conditions, thus opening new opportunities for efficient carbene-transfer reactions under user-friendly conditions.

Cyclopropanation has long been recognized as an important carbon–carbon bond forming reaction.[1] The products are useful building blocks for organic synthesis, and the cyclopropane motif is present in a wide range of structures.[2] Among the many cyclopropanes accessible by metal-catalyzed carbene generation from diazoalkanes, cyclopropyl esters have been studied extensively due to their versatility as intermediates in synthesis. On the basis of our recent work on the chemistry of trifluoromethyl diazomethane[3] generated in situ via diazotization in aqueous media, we sought an alternative for the preparation of cyclopropyl esters using glycine ethyl ester hydrochloride. This strategy would obviate the need to handle ethyl diazoacetate and offer the possibility of performing the reaction with an inexpensive, conveniently handled reagent in water. Prior to this work, case examples of similar attempts had been published in the literature. Barrett described the synthesis of cyclopropyl esters using a rhodium–porphyrin catalyst, glycine ethyl ester hydrochloride, and alkenes (10 equiv) in a CH_2Cl_2/water mixture.[4] The products were isolated in moderate yields after 4 days with no diastereoselectivity (1:1). Charette later showcased a single example with $Rh_2(CH_3(CH_2)_6COO^-)_4$ as a competent catalyst in the cylopropanation of styrene with glycine ethyl ester hydrochloride in aqueous media.[5] In the reaction, the product was isolated as a 1.5:1 mixture of diastereomers.

Aiming at developing a synthetically useful protocol for the *trans*-selective cyclopropanation of styrenes with glycine ethyl ester hydrochloride in water, we screened a number of transition-metal catalysts under the following reaction conditions: *p*-methoxystyrene (1 equiv, limiting reagent), glycine ethyl ester hydrochloride (2 equiv), $NaNO_2$ (2.4 equiv), and acetic acid (15 mol %) in water at 40 °C in an open vial (Table 1).

Three common catalysts used in cyclopropanation reactions ($Cu(OTf)_2$, $Pd(OAc)_2$, and $Rh_2(OAc)_4$) afforded poor results, giving low to moderate conversions with poor diastereoselectivity (entries 1–3). The use of ($Rh_2(CH_3(CH_2)_6COO^-)_4$ and $Rh_2(esp)_2$ gave good conversion, albeit with no diastereoselectivity (entries 4 and 5). The fact that the performance of the complexes correlates with

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[1] Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

[2] Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589 and references therein.

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[4] Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem.* **2001**, *66*, 8260.

[5] Wurz, R. P.; Charette, A. B. *Org. Lett.* **2002**, *4*, 4531.

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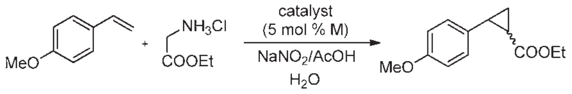
Table 1. Screening of Metal Catalysts[a]



entry	catalyst	conversion (%)[b]	dr[b]
1	$Cu(OTf)_2$	44	2:1
2	$Pd(OAc)_2$	25	1:1
3	$Rh_2(OAc)_4$	10	1:1.5
4	$Rh_2(CH_3(CH_2)_6COO^-)_4$	87	1:1
5	$Rh_2(esp)_2$	93	1:1
6	CoTPP	27	7:1
7	RuTPPCO	100	8:1
8	FeTPPCl	100	8:1

[a] General procedure: catalyst (5 mol % M), $EtO_2CCH_2NH_3Cl$ (2 equiv), $NaNO_2$ (2.4 equiv), substrate, AcOH (15 mol %), H_2O, 40 °C. [b] The trans/cis ratio was determined by ^1H NMR analysis of the unpurified reaction mixture.

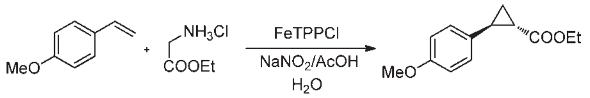
ligand lipophilicity illustrates the importance of the phase separation in the process and emphasizes the need to have the catalyst dissolved in the substrate phase. Although giving good diastereoselectivity (7:1), a cobalt–porphyrin complex gave low conversion (entry 6). To our delight, a Ru- and Fe-porphyrin complexes performed well under these conditions and afforded full conversion to the product with good selectivity (entries 7 and 8). The inexpensive iron catalyst was selected for further studies due to the good result obtained and the recent interest for this metal as an alternative to noble metal catalysts.[6] Interestingly, the catalyst loading could be reduced to 1 mol % after further optimization.[7]

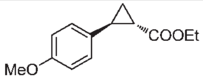
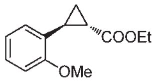
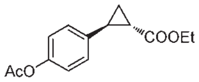
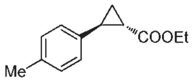
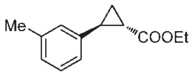
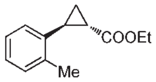
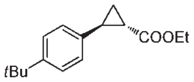
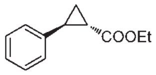
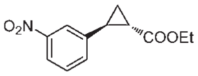
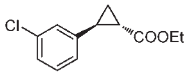
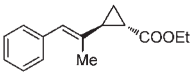
Having identified user-friendly and efficient reaction conditions, we studied the scope of styrene derivatives that can be transformed to the corresponding *trans*-cyclopropyl esters (Table 2).

Both electron-donating (entries 1–7) and electron-withdrawing (entries 9 and 10) substrates gave the corresponding aromatic cyclopropyl esters in good isolated yields of pure *trans*-products. A diene substrate also afforded the corresponding product, albeit in a lower yield (entry 11).

In conclusion, we have developed a new cyclopropanation reaction using glycine ethyl ester hydrochloride as an inexpensive and safe carbene precursor. The transformation produces the *trans*-cyclopropyl esters selectively using a simple iron catalyst with low catalyst loading. This synthetically useful protocol (absent inert atmosphere, water as sole solvent) should find broad use in the preparation of cyclopropanes and stimulate the design of asymmetric catalysts that are active under these reaction conditions. Development of active asymmetric catalysts under these conditions is currently ongoing and will be reported in due time.

Table 2. Scope of the Cyclopropanation[a]



entry	product	yield[b]	dr[c]
1		79%	8:1
2		70%	10:1
3		68%	8:1
4		74%	9:1
5		64%	8:1
6		62%	10:1
7[d]		72%	7:1
8		71%	10:1
9[d]		55%[e]	6:1
10[f]		67%	7:1
11[d]		39%	Nd

[a] FeTPPCl (1 mol %), $EtO_2CCH_2NH_3Cl$ (2 equiv), $NaNO_2$ (2.4 equiv), substrate, AcOH (15 mol %), H_2O, 40 °C. [b] Isolated yield of pure *trans*-product. [c] Determined by ^1H NMR analysis of the unpurified reaction mixture. [d] FeTPPCl (1.5 mol %), $EtO_2CCH_2NH_3Cl$ (3 equiv), $NaNO_2$ (3.6 equiv). [e] Isolated yield of 66% (83% purity). [f] FeTPPCl (1 mol %), $EtO_2CCH_2NH_3Cl$ (4 equiv), $NaNO_2$ (4.8 equiv).

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

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