Synthetic Methods

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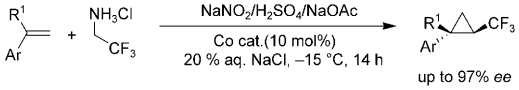
Enantioselective Cobalt-Catalyzed Preparation of Trifluoromethyl-Substituted Cyclopropanes**

*Bill Morandi, Brian Mariampillai, and Erick M. Carreira**

There is scarcity of approaches for the enantioselective generation of trifluoromethyl-substituted cyclopropanes.[1–4] We have been interested in the discovery and identification of catalysts that are compatible with conditions necessary to generate reactive intermediates in situ in order to access new building blocks for drug discovery.[5] Towards that aim, we have documented reaction processes involving diazotization of 2,2,2-trifluoroethylamine in the presence of Fe-porphyrin or [{Rh(esp)}$_2$] (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate) catalysts as ways of accessing trifluoromethyl-substituted cyclopropanes and cyclopropenes, respectively. The generation of the reactive intermediate and concomitant cyclopropanation in water comprise a tandem sequence that avoids preparation, purification, and handling of the diazoalkane.[5] Herein, we report an enantioselective cobalt-catalyzed[6] process that furnishes trifluoromethyl-substituted cyclopropanes in high *ee*, d.r. and yield [Eq. (1)]. The reaction proceeds smoothly in aqueous media with the alkene as limiting reagent and in situ generation of the reactive F_3CCHN_2 from 2,2,2-trifluoroethylamine hydrochloride.[7,8]



(1)

The only asymmetric synthesis of disubstituted cyclopropanes incorporating a trifluoromethyl group was carried out with distilled F_3CCHN_2 and proceeded in moderate yield and modest enantioselectivity (17–69 % *ee*) with a chiral iron–porphyrin complex.[9] Davies et al. have also reported the preparation of trisubstituted cyclopropanes incorporating a trifluoromethyl moiety using stabilized donor/acceptor rhodium carbenoids (prepared from precursor hydrazones and excess MnO_2) and 5 equivalents of the alkene.[2c]

[*] B. Morandi, Dr. B. Mariampillai, Prof. Dr. E. M. Carreira
Laboratorium für Organische Chemie, ETH Zürich
8093 Zürich (Switzerland)
Fax: (+41) 1-632-1328
E-mail: carreira@org.chem.ethz.ch
Homepage: http://www.carreira.ethz.ch

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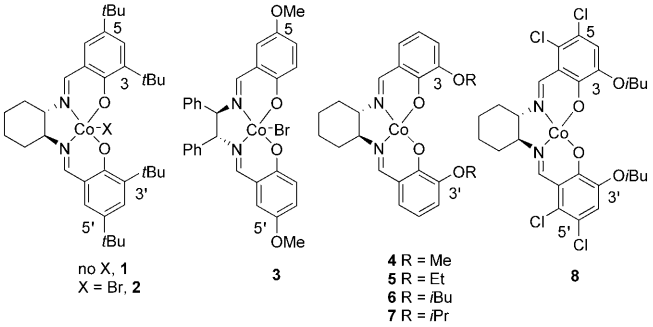
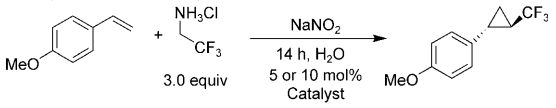
Our entry point into catalyst identification and development was the observation that Co^{II} complex **1** (Scheme 1) is



Scheme 1. Catalysts screened for the asymmetric cyclopropanation.

competent in catalyzing the cyclopropanation of *p*-methoxystyrene in 45 % *ee* and 55 % conversion (conditions: $F_3CCH_2NH_3Cl$, NMI (*N*-methyl imidazole), H_2O, slow addition of aqueous solution of $NaNO_2$) as shown in Table 1, entry 1. Cobalt(III)–salen complexes have been described in the literature for enantioselective cyclopropanation with diazoacetates in organic media. Consequently, catalyst **2** as

Table 1: Optimization study.[a]



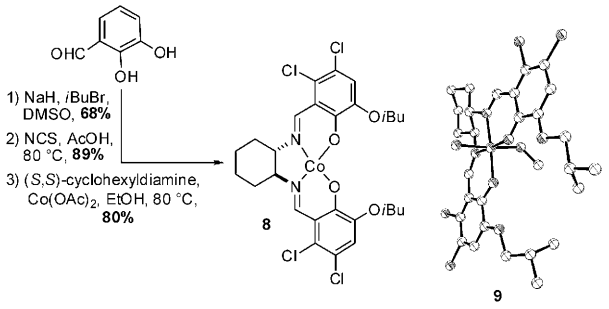
Entry	Cat.	*T* [°C]	Conv [%][b]/ *ee* [%][c]	Remarks[d]	Additive
1	**1**[e]	23	55/45	A	NMI (10 mol%)
2	**2/3**[e]	23	–	A	NMI (10 mol%)
3	**4**[e]	23	12/40	A	NMI (10 mol%)
4	**5**[e]	23	50/68	A	NMI (10 mol%)
5	**6**[e]	23	100/65	A	NMI (10 mol%)
6	**7**[e]	23	42/47	A	NMI (10 mol%)
7	**8**[e]	23	74/80	A	NMI (10 mol%)
8	**8**[f]	0	100/85	A	Ph_3As (20 mol%)
9	**8**[f]	−15[g]	30/90	A	Ph_3As (20 mol%)
10	**8**[f]	−15[g]	52/90	B	Ph_3As (20 mol%)
11	**8**[f]	−15[g]	79/90	B	Ph_3As (20 mol%)[h]
12	**8**[e]	−15[g]	100/90	B	Ph_3As (20 mol%)[h]

[a] General procedure: 5 or 10 mol% catalyst, alkene (0.22 mmol, 1 equiv), $F_3CCH_2NH_3Cl$ (3 equiv), 10 mol% NMI or 20 mol% Ph_3As, 1.8 mL H_2O, $NaNO_2$ (1.8 or 3.6 equiv). [b] Determined by supercritical fluid chromatography (SFC). [c] Determined by enantioselective SFC. [d] A: Syringe pump addition of aqueous $NaNO_2$. B: One-portion addition of solid $NaNO_2$. [e] 10 mol% catalyst. [f] 5 mol% catalyst. [g] Performed in 20% NaCl solution. [h] In H_2SO_4/NaOAc buffer.

well as **3** were examined (Table 1, entry 2).[6] Interestingly, the use of either resulted in full recovery of starting material, indicating that Co^{III} was not suitable for the reaction under the examined conditions. Examination of complexes derived from other diamine backbones only led to poor results (see Supporting Information for compilation). We also screened a number of ligand variants differing in the substitution pattern on the salicyl groups. Examination of the latter set of ligand analogs revealed the importance of a bulky alkoxy group at the C-3/C-3′ positions (compare entries 3–5 in Table 1), from which the corresponding cobalt catalysts resulted in increased conversion and afforded products with enhanced selectivity. It is interesting to note that steric congestion alone is not determinant for enantioselectivity, as the complex derived from the ligand incorporating isopropoxy groups at C-3 and C-3′ (Table 1, entry 6) furnished product with inferior *ee* and conversion, making evident the existence of a steric "sweet spot" at these positions. The screening also revealed that the substituents at C-5/C-5′ positions were critical to the generation of catalysts affording products with improved enantioselectivity, with a preference for electron-withdrawing groups. Particularly noteworthy were the results obtained with complex **8**, which includes the C-3/C-3′ di-*i*BuO and C-5/C-5′/C-6/C-6′ tetrachlorinated ligand (Table 1, entry 7). These observations are interesting when considered in light of the reported electronic effects for metal–salen catalysts in a variety of transformations.[6f,10] In the asymmetric epoxidation of Jacobsen et al. a clear preference for electron-rich ligands has been noted with respect to the enantioselectivity of the process.[10a,b] Similarly, in the cyclopropanation reaction of styrene with diazoacetates and Co^{III}–salen complexes Katsuki et al. have reported greater selectivity with electron-rich complexes.[6f] The electronic effects have been suggested to correlate to the position of the transition state along the reaction coordinate. However, a mechanistic study by Gronert et al. on the reaction of Co^{III}–salen complexes with diazoacetates indicates that reactions are faster with ligands bearing substituents with positive σ values.[10c] Consequently, the combination of electron donating and withdrawing group in the optimal ligand scaffold in **8** is unique.

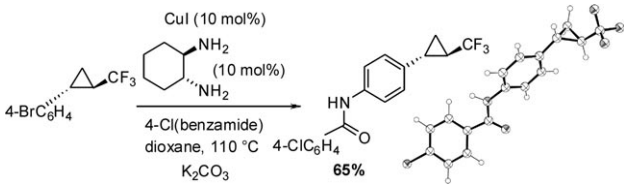
The preparation of optimal catalyst **8** is conveniently carried out in three steps from 2,3-dihydroxybenzaldehyde (Scheme 2). These include alkylation with *i*BuBr in DMSO (68%), chlorination with NCS in acetic acid (89%), and condensation with (*S*,*S*)-1,2-cyclohexyldiamine in the presence of $Co(OAc)_2$ (80%). As shown in Scheme 2, we have obtained an X-ray structure of the catalyst as the methanol/water solvate (see **9**) by recrystallization from CH_2Cl_2/MeOH.

We next investigated the effect of other experimental parameters including temperature, solvent, and additives (Table 1). This included the conditions under which the diazoalkane is generated in situ, such as addition of an aqueous solution of $NaNO_2$ employing a syringe pump (Table 1, entries 1–9) versus addition of solid $NaNO_2$ in one portion (Table 1, entries 10–12). In contrast to what we had reported for the Fe-catalyzed process, addition of $NaNO_2$ in one portion proved optimal for conversion. Additional benefits were noted when the reaction was conducted at −15 °C in the presence of 20 mol% Ph_3As and H_2SO_4/NaOAc buffer with excess $NaNO_2$ (3.6 equiv) (Table 1, entries 11 and 12). It is important to note that in order to carry out the reaction at −15 °C (Table 1, entries 9–12), it was necessary to use 20% aqueous NaCl solution as solvent to prevent freezing of the aqueous reaction media. Interestingly, although NMI is commonly employed in related processes and has been suggested to exert its influence on the catalyst as an axial auxiliary ligand, Ph_3As has not been previously examined in this capacity.[12] The use of a co-solvent (DCM or toluene) resulted in decreased conversion, consistent with our previous suggestion that the transformation proceeds on water.[13]



Scheme 2. Preparation of **8** and the X-ray crystal structure of the solvate, **9**.[11] NCS = *N*-chlorosuccinimide.

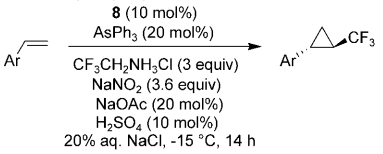
Having identified the optimal catalyst and conditions, we examined the scope of the reaction (Table 2). The method is widely applicable to a range of styrenes, including electron-rich and -poor as well as *o*-substituted substrates. Electron-rich substrates proved to be the best, leading to excellent enantioselectivity (up to 94% *ee*), diastereoselectivity (up to 180:1 d.r.) and yield (up to 95%). Electron-poor substrates were slightly inferior but nonetheless afforded products in up to 90% *ee*. The diastereoselectivity is in most cases excellent, with impressive preference for the *trans* isomer (up to 180:1). It was possible to convert the product of 4-bromostyrene to a crystalline derivative by its subjection to Cu-catalyzed amidation (Scheme 3), allowing determination of the absolute configuration by X-ray analysis.[14]

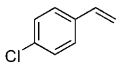
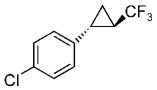
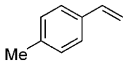
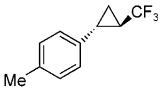
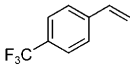
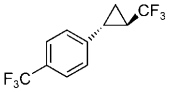
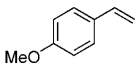
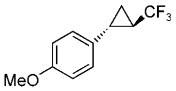
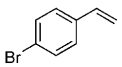
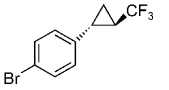
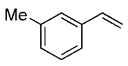
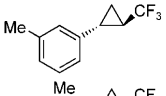
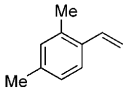
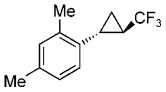
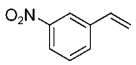
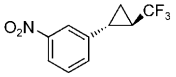
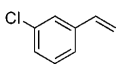
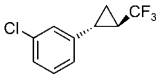
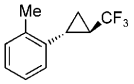


Scheme 3. Determination of the absolute configuration by X-ray analysis of an amide derivative.

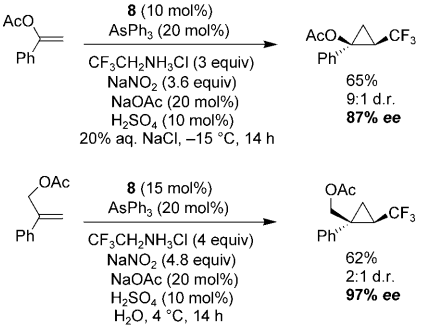
The novel transformation we have described can be extended to 1,1-disubstituted styrene derivatives with additional functional groups.[15] For example, the cyclopropanation reaction proceeded smoothly for the acetophenone-derived enolacetate to afford adduct in 65% yield, 9:1 d.r., and 87% *ee* (Scheme 4). We could also show that an allylic acetate was smoothly converted into the trifluoromethyl-substituted cyclopropane in 2:1 d.r. and excellent enantiose-

Table 2: Scope of the cyclopropanation.[a]



Alkene	Product	Yield[b]	d.r.[c]	*ee* [%][d,e]
		81	56:1	91
		82	66:1	86
		91	38:1	91
		73	22:1	84
		95	35:1	90
		84	37:1	87
		91	57:1	94
		93	63:1	88
		49	11:1	86
		78	27:1	90
		77	180:1	92

[a] General procedure: Catalyst **8** (0.022 mmol, 10 mol%), $AsPh_3$ (0.044 mmol, 20 mol%), alkene (0.22 mmol, 1 equiv), $CF_3CH_2NH_3Cl$ (0.66 mmol, 3 equiv), $NaNO_2$ (0.8 mmol, 3.6 equiv), NaOAc (0.044 mmol, 20 mol%), H_2SO_4 (0.022 mmol, 10 mol%), 1.8 mL 20% NaCl solution, −15 °C, 14 h. [b] Isolated yield in %. [c] Determined by ^{19}F NMR analysis of the crude mixture. [d] Determined by enantioselective HPLC or SFC of the pure product. [e] Absolute configuration established by analogy to that observed for the derivative shown in Scheme 3.



Scheme 4. Enantioselective preparation of functionalized trifluoromethyl cyclopropanes. Yields refer to pure, isolated *trans* isomers.[16]

lectivity (97% *ee*). These results showcase the ability of the method to generate cyclopropanes substituted with trifluoromethyl groups as well as additional reactive sites for further elaboration. In combination with the diversity of arene substituents shown for the styrenes in Table 2, the adducts are amenable to manipulation in a number of different modes.

In summary, we have described the first useful enantioselective preparation of disubstituted cyclopropanes incorporating a trifluoromethyl group. The reaction proceeds with trifluoromethyl diazomethane generated in situ with the alkene as the limiting reagent. These products offer new access to enantioenriched CF_3 building blocks for drug discovery. The catalyst used in this transformation is easily accessible in both enantiomeric forms over three steps and constitutes the first of its kind that is active in asymmetric cyclopropanantion with an in situ generated diazoalkane under extreme conditions (aqueous acidic, oxidative media). The observation that the incorporation of electron-donating and -withdrawing substituents on the same ligand scaffold is beneficial may have broader implications for catalyst design in enantioselective transformations. Further studies and applications of catalysts similar to **8** are currently ongoing and will be reported as they become available.

Experimental Section

General procedure for cyclopropanation: Catalyst **8** (14 mg, 22 μmol), $AsPh_3$ (13 mg, 44 μmol), NaOAc (3.6 mg, 44 μmol), and trifluoroethylamine hydrochloride (90 mg, 0.66 mmol) were dissolved in degassed, 20% brine solution (1.8 mL). Then H_2SO_4 (1.2 μL, 22 μmol) was added. The alkene (0.22 mmol) was subsequently added, and $NaNO_2$ (54 mg, 0.70 mmol) was added in one portion. After 14 h, CH_2Cl_2 and water were added, and the water phase was extracted with CH_2Cl_2 (3×), dried with $MgSO_4$ and evaporated under reduced pressure. After analysis of the crude NMR spectrum (to determine the diastereoselectivity), the crude mixture was chromatographed on silica gel (pentane/diethyl ether) to afford product.

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[11] CCDC 783661 (**9**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[16] Absolute configuration established by analogy to that observed for the derivative shown in Scheme 3.

