Oxidative Cross-Coupling

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Significant Enhancement in the Efficiency and Selectivity of Iron-Catalyzed Oxidative Cross-Coupling of Phenols by Fluoroalcohols**

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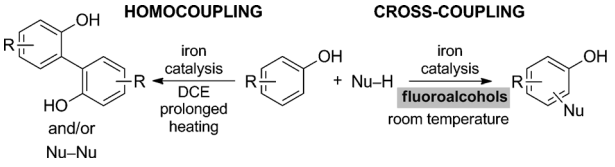
Abstract: *Significant enhancement of both the rate and the chemoselectivity of iron-catalyzed oxidative coupling of phenols can be achieved in fluorinated solvents, such as 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), 2,2,2-trifluoroethanol (TFE), and 1-phenyl-2,2,2-trifluoroethanol. The generality of this effect was examined for the cross-coupling of phenols with arenes and polycyclic aromatic hydrocarbons (PAHs) and of phenol with β-dicarbonyl compounds. The new conditions were utilized in the synthesis of 2‴-dehydroxycalodenin B in only four synthetic steps.*

Synthetic methods based on iron chemistry have gained considerable attention in recent years,[1] partially as a result of the implementation of green chemistry concepts in organic chemistry.[2] Of particular interest is the iron-catalyzed oxidative cross-coupling reaction,[3] also known as cross-dehydrogenative coupling (CDC),[4] which offers a practical and sustainable strategy for the formation of a new carbon–carbon bond directly from two C–H bonds. In these methods, iron complexes with high oxidation states are generated following the oxygen–oxygen bond scission of organic peroxides or molecular oxygen.[5] These high-valent iron species are capable of inducing a single electron transfer (SET) process, generating an active radical cation species that reacts with a nucleophile.

The iron oxidative cross-coupling of phenols is an extremely important synthetic tool for the production of advanced phenol-based materials from readily available building blocks.[6] The development of this chemistry relies on the ability of phenols to stabilize a positive charge either a) during an electrophilic aromatic substitution with an oxidized coupling partner, such as a β-ketoester,[6b,g] an α-hydroxy ketone,[6f] or a cyclic ether,[6a] or b) following the single-electron oxidation of the phenol to an electrophilic phenoxyl radical cation that, in turn, reacts with various carbon–hydrogen nucleophiles, such as a second phenol,[5b,c] an α-substituted β-ketoester,[6e] a nitroalkane,[5a] or a conjugated alkene.[6c,d] The general catalytic system relies on Fe^{III} salts (5–20 mol%) and a terminal oxidant. The most widely used solvents for such reactions are 1,2-dichloroethane (DCE) and toluene. Prolonged heating at an elevated temperature (60–100 °C) is typically required to initiate the oxidation process and to ensure satisfactory conversions. Under these conditions, by-products resulting from over-oxidation,[6d] Friedel–Crafts alkylation,[6b,g] and various homo-coupling processes (Scheme 1)[6e] may affect the selectivity and efficiency of the reaction.



Scheme 1. Chemoselectivity of the iron-catalyzed oxidative cross-coupling of phenols.

1,1,1,3,3,3-Hexafluoropropan-2-ol (HFIP) and 2,2,2-trifluoroethanol (TFE)[7] are polar solvents with low boiling points, high dielectric constants and high ionization power that have a significant stabilizing effect on radical cation intermediates.[8] HFIP was effectively applied by the Kita group as a solvent in the hypervalent iodine oxidative coupling reactions of arenes[8a,9] and by the Waldvogel group in electrochemical oxidative coupling reactions.[10] As part of our group's interest to study the role of additives in the iron-catalyzed oxidative cross-coupling of phenols,[6e] we examined the role of fluorinated alcohols in this chemistry.

Here, we report the significant effect of fluoroalcohols on the iron-catalyzed oxidative coupling of phenols. The use of fluorinated solvents reduces the oxidation potential of the phenols, thereby facilitating coupling reactions under mild conditions. Moreover, we demonstrated that under common CDC conditions, dimerization processes are preferred, whereas under the modified conditions phenols react with high chemoselectivity with arenes and polycyclic aromatic hydrocarbons (PAHs) or β-diketones. The applicability of this chemistry in drug discovery is demonstrated for the synthesis of 2‴-dehydroxycalodenin B.

We first examined the effect of fluorinated alcohols on the iron-mediated oxidative dimerization of 2-naphthol (**1a**). For purposes of comparison, **1a** was self-coupled in DCE at room temperature with $FeCl_3$ (5 mol%), as the catalyst, and *t*BuOO*t*Bu (2.5 equiv), as the terminal oxidant (Figure 1). Under these conditions, only 9% conversion was obtained after 24 h. A high accelerating effect was observed when the

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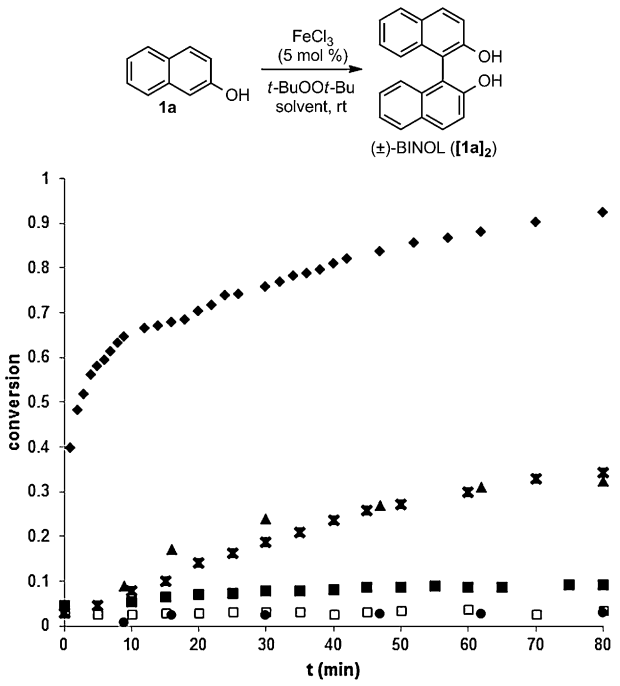
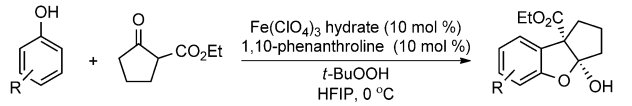


Figure 1. Effect of the solvent on the oxidative coupling of 2-naphthol (**1a**).[a] [a] Conditions: **1a** (1 mmol), $FeCl_3$ (0.05 mmol), *t*BuOO*t*Bu (2.5 mmol), solvent (1 M), room temperature. The following solvents were used: (◆) 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP); (▲) 2,2,2-trifluoroethanol (TFE); (*) 2,2,2-trichloroethanol; (■) 1-phenyl-2,2,2-trifluoroethanol; (□) 1,1,1-trifluoropropan-2-ol; (●) 1,2-dichloroethane. The reaction progress was monitored by HPLC.

reaction was performed in TFE or 2,2,2-trichloroethanol, affording BINOL **2a** with 75% and 97% conversion, respectively, after 24 h. Remarkably, when the reaction was performed in HFIP, almost complete consumption of 2-naphthol was observed within 1 h. 1,1,1-Trifluoropropan-2-ol and 1-phenyl-2,2,2-trifluoroethanol had no impact on the reaction rate, and ethanol and acetic acid were not efficient solvents for this transformation.

To further investigate this accelerating effect, the oxidation potentials of various phenols in three different solvents were measured (Table 1). The cyclic voltammetry experiments demonstrate the effect of fluorinated alcohols on the oxidation potentials of the phenols. For example, the E_{ox} of 2-naphthol (**1a**) in HFIP (0.48 V, entry 1) was lower than the oxidation potentials measured in TFE (0.51 V) or in acetonitrile (0.61 V). These results support the notion that HFIP stabilizes the aromatic radical cation intermediates generated during the SET process.[5b,8a,9b] This rate accelerating effect may be accounted for in at least two additional ways: 1) Based on the study of Berkessel and others,[7b–f] it is suggested that fluoroalcohols weaken the peroxide bonds by forming multiple H-bond network thereby reducing the activation energy of the peroxide oxygen–oxygen bond cleavage in what is considered to be the rate-determining step of the process[5b] and 2) HFIP may coordinate to the metal, forming iron complexes[11] with improved oxidizing capabilities.[12]

Table 1: Oxidation potentials of phenols in different solvents and their cross-coupling with compound **2**.[a]



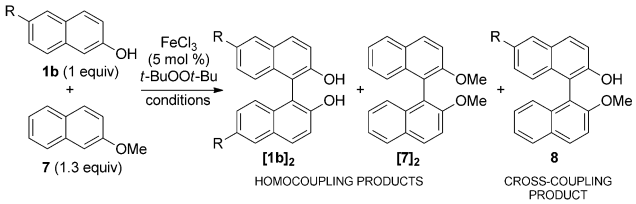
1c–f **2** **3–6**

entry	R	E_{ox} (V)[b]			Product, yield [%][c]	
		CH_3CN	TFE	HFIP	DCE[d]	HFIP
1	2-Nf (**1a**)	0.61	0.52	0.48	95	ND[e]
2[f]	3,5-Me_2 (**1c**)	0.68	0.66	0.62	27	**3**, 63
3	H (**1d**)	0.73	0.68	0.63	NR[g]	**4**, 49
4	4-Br (**1e**)	0.83	0.73	0.67	NR[g]	**5**, 64
5	3-Cl (**1f**)	0.90	0.84	0.76	NR[g]	**6**, 38

[a] Conditions: phenol **1** (1 equiv), ethyl 2-oxocyclopentane-carboxylate (**2**, 1.5 equiv), $Fe(ClO_4)_3$ hydrate (10 mol%), 1,10-phenanthroline (10 mol%), *t*BuOOH (solution in decane, 2 equiv), HFIP (0.5 M), 0°C. [b] Cyclic voltammetry conditions: phenol (3 mM), supporting electrolyte: tetrabutylammonium hexafluorophosphate (50 mM) in solvent (5 mL) versus Ag/0.01 M $AgNO_3$ in 0.1 M TBAP/CH_3CN, 50 mVs^{-1}. [c] Yield of the isolated product. [d] Conditions: $FeCl_3$ (10 mol%), 1,10-phenanthroline (5 mol%), *t*BuOO*t*Bu, DCE, 70°C.[6e] [e] ND = not determined. [f] *t*BuOO*t*Bu (2.5 equiv), HFIP (1 M), room temperature. [g] NR = no reaction.

Next, the effect HFIP has on cross-coupling reactions was studied. The coupling of phenoxyl radicals to α-substituted β-ketoesters was chosen as the benchmark reaction, because it was suitable only for naphthols and electron-rich phenols, while being ineffective for phenols with higher oxidation potentials.[6e] Indeed, when 3,5-dimethylphenol (**1c**) and ethyl 2-oxocyclopentanecarboxylate (**2**) were reacted under our previously reported conditions [FeX_3 (10 mol%), 1,10-phenanthroline (5 mol%), *t*BuOO*t*Bu (2.5 equiv), DCE, 70°C],[6e] the polycyclic hemiacetal **3** was isolated in 27% yield for X = Cl and 34% yield for X = ClO_4. In contrast, when this transformation was performed in HFIP at reduced temperatures under modified conditions [$Fe(ClO_4)_3$ hydrate (10 mol%), 1,10-phenanthroline (10 mol%),[13] and *t*BuOOH (5 M solution in decane, 2 equiv)] the coupling product **3** was isolated with an improved yield of 63%. The novel catalytic system possesses superior oxidizing power and for the first time phenols with higher oxidation potentials, such as **1d** (R = H, 0.63 V), **1e** (R = 4-Br, 0.67 V), and **1f** (R = 3-Cl, 0.76 V), were coupled at temperature as low as 0°C with partner **2** to afford **3–6** in moderates yields.

Oxidative cross-coupling of phenols with electron-rich arenes is a powerful strategy for synthesizing nonsymmetrical biaryls.[5b,9b,10a,b,14] The development of a successful process relies on the ability to selectively oxidize a phenol in the presence of an arene coupling partner. This is a challenging task, because undesired homocoupling pathways must be avoided.[14b] Indeed, when 6-methoxycarbonyl-2-naphthol (**1b**, 1 equiv) and 2-methoxynaphthalene (**7**, 1.3 equiv) were reacted under the common CDC conditions [$FeCl_3$ (5 mol%), *t*BuOO*t*Bu (1.5 equiv), DCE at 70°C], BINOL **[1b]$_2$** was formed exclusively in 96% yield (Scheme 2). However, when the reaction was performed in HFIP at room temperature, the cross-coupling process dominated, and biaryl **8** was isolated in



conditions	yield of [1b]$_2$	yield of [7]$_2$	yield of 8
DCE, 70 °C	96%	--	--
HFIP, rt	10%	traces	56%

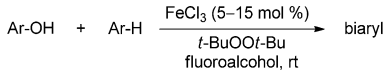
Scheme 2. Oxidative cross-coupling of phenols with arenes.

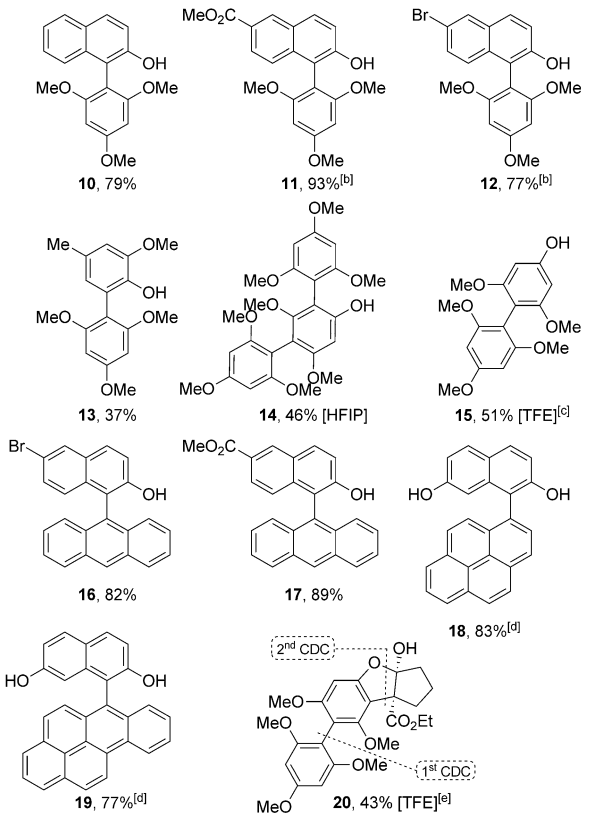
56% yield. The coupling of different phenols with 1,3,5-trimethoxybenzene (**9**) in HFIP afforded nonsymmetrical biaryl products **10**–**14** in good yields (Table 2). PAHs such as anthracene, pyrene,[15] and benzopyrene are excellent coupling partners, and their coupling with naphthol derivatives was highly selective, affording PAH biaryl products **16**–**19** in excellent yields. To the best of our knowledge, this is the first reported example of an iron-catalyzed $Csp^2_{(Ar-OH)}$–$Csp^2_{(Ar-H)}$ CDC reaction.

The efficiency of the iron catalyst and the power of this chemistry in designing multistep processes that rely on a single catalytic system were examined. The coupling of 3,5-dimethoxyphenol (**1g**) with arene **9** in TFE afforded the isolated biaryl **15** in 51% yield (Table 2). In a different experiment β-ketoester **2** was introduced into the reaction mixture after the formation of **15**, and the living iron catalyst mediated a second oxidative coupling reaction, affording hemiacetal **20** in 43% yield. This example emphasizes the generality of the new set of conditions and stresses the versatility of iron catalysis.

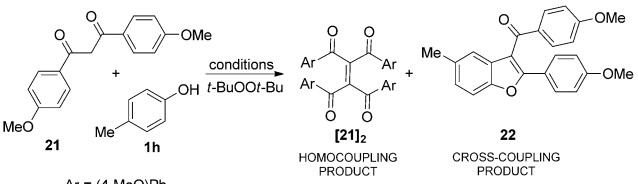
Our final set of experiments was designed to study the effect fluoroalcohols have on different types of iron-catalyzed oxidative cross-coupling of phenols. Despite their structural similarity to β-ketoesters, β-diketones failed to react with phenols under common CDC conditions.[6g] For example, when 1,3-bis(4-methoxyphenyl)-1,3-propanedione (**21**) and *p*-cresol (**1h**) were reacted using $FeCl_3(H_2O)_6$ (10 mol%) as the catalyst and *t*BuOO*t*Bu (2.5 equiv) as the terminal oxidant in DCE at 70°C (Scheme 3), only dimer **[21]$_2$** was isolated in 50% yield. The formation of this dimer provides evidence for the tendency of **21** to transform to electrophilic radical species.

Table 2: Scope of the phenol–arene oxidative cross-coupling.[a]





[a] Conditions: phenol (1 equiv), arene (1–3 equiv), $FeCl_3$ (5–15 mol%), *t*BuOO*t*Bu (1.5–2 equiv), HFIP. [b] $FeCl_3(H_2O)_6$ (5 mol%), *t*BuOO*t*Bu (2 equiv), HFIP. [c] TFE was used as solvent. [d] 1-Phenyl-2,2,2-trifluoroethanol was used as the solvent at 40°C. [e] For the exact coupling conditions see the SI.



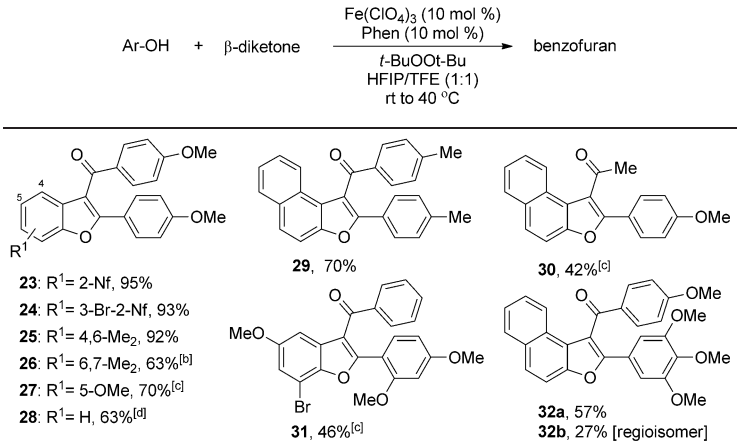
conditions	yield of [21]$_2$	yield of 22
$FeCl_3(H_2O)_6$ (10 mol %), DCE, 50 °C	50%	traces
$Fe(ClO_4)_3$ hydrate (30 mol %), HFIP/TFE (1:1), rt	ND	87%

Scheme 3. Oxidative cross-coupling of *p*-cresol **1h** with **21**.

A comprehensive optimization study (see Table 2S in the Supporting Information, SI) was performed to identify improved catalytic conditions. It was found that a high degree of chemoselectivity was obtained when the reaction was carried out in a HFIP/TFE mixture (1:1), affording the cross-coupling product **22** in 87% yield (Scheme 3). Cyclic voltammetry measurements of β-diketone **21**, performed in acetonitrile ($E_{ox} = 0.995$ V), TFE (1.08 V), and HFIP (1.20 V) displayed an opposite trend to the one recorded for phenols (Table 1). These oxidation potentials imply that the oxidation of β-diketone **21** is much slower in protic fluorinated solvents and as a result, the chemoselectivity of the cross-coupling reaction improves.

A study of the reaction scope (Table 3) revealed that 2-naphthol derivatives and electron-rich phenols react under catalytic conditions with good to excellent yields (compounds **22**–**26**, **29**, and **32**). However coupling of phenols that are less nucleophilic than the β-diketone coupling partner are better coupled using a stoichiometric amount of iron salts (com-

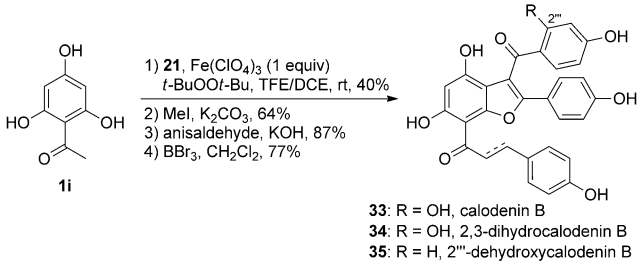
Table 3: Scope of the β-diketone–phenol oxidative coupling.[a]



[a] Conditions: $Fe(ClO_4)_3$ hydrate (10 mol%), 1,10-phenanthroline (10 mol%), *t*BuOO*t*Bu (2 equiv), HFIP/TFE (1:1). For the exact coupling conditions see the SI. [b] $Fe(ClO_4)_3$ hydrate (30 mol%). [c] $FeCl_3(H_2O)_6$ (100 mol%) in DCE. [d] $Fe(ClO_4)_3$ (100 mol%) in HFIP/TFE (1:1). Phen = 1,10-phenanthroline.

pounds **27**, **28**, **30**, and **31**). The reactions of nonsymmetrical β-diketones with phenols produced either a single product (benzofurans **30** and **31**) or a mixture of two constitutional isomers (as in **32a** and **32b**).

Iron-catalyzed phenol oxidative cross-coupling is a powerful synthetic tool for assembling bioactive phenolic natural products in a minimum number of synthetic steps.[6b,e] Calodenin B (**33**, Scheme 4) and 2,3-dihydrocalodenin B



Scheme 4. Total synthesis of 2‴-dehydroxycalodenin B.

(**34**),[16] for example, are two biflavonoids with various biological activities such as antifungal activity,[16e] selective antibacterial activity, and strong cytotoxicity against MCF-7 breast cancer cells.[16d] The coupling of phloroacetophenone (**1i**) with β-diketone **21** under modified conditions [$Fe(ClO_4)_3$ hydrate (1 equiv), TFE/DCE, room temperature] afforded the corresponding benzofurans in 40% yield. Methylation, Claisen–Schmidt condensation with anisaldehyde (K_2CO_3, THF/MeOH), and deprotection using BBr_3 (excess) furnished 2‴-dehydroxycalodenin B (**35**) in as little as four synthetic steps, paving the way for a structure–activity relationship study of this important class of natural products.

In summary, we have demonstrated a simple means to extend the reactivity of iron-catalyzed oxidative cross-coupling reactions of phenols by introducing fluorinated alcohols as solvents. The reduction in the oxidation potentials of the phenols in these solvents affects both the efficiency and the selectivity of the processes, promoting the coupling of phenols with various nucleophiles under mild catalytic conditions (even at 0 °C rather than 70 °C). Under our modified conditions, arenes, including PAHs, and β-diketones, which failed to react with phenols under catalytic conditions in common organic solvents, have become legitimate coupling partners for phenols. The new conditions were utilized, for the first time, for the synthesis of 2‴-dehydroxycalodenin B.

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[1] a) S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317 – 3321; *Angew. Chem.* **2008**, *120*, 3363 – 3367; b) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217 – 6254.
[2] J. A. Linthorst, *Found. Chem.* **2010**, *12*, 55 – 68.
[3] a) F. Jia, Z. Li, *Org. Chem. Front.* **2014**, *1*, 194 – 214; b) Q. Liu, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 13871 – 13873; *Angew. Chem.* **2013**, *125*, 14115 – 14117.
[4] a) C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335 – 344; b) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436 – 451; c) S. A. Girard, T. Knauber, C. J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74 – 100; *Angew. Chem.* **2014**, *126*, 76 – 103; d) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672 – 3673; e) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810 – 11811; f) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215 – 1292; g) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928 – 8933.
[5] a) T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2012**, *134*, 20017 – 20020; b) H. Egami, K. Matsumoto, T. Oguma, T. Kunisu, T. Katsuki, *J. Am. Chem. Soc.* **2010**, *132*, 13633 – 13635; c) H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2009**, *131*, 6082 – 6083.
[6] a) B. D. Barve, Y.-C. Wu, M. El-Shazly, M. Korinek, Y.-B. Cheng, J.-J. Wang, F.-R. Chang, *Org. Lett.* **2014**, *16*, 1912 – 1915; b) U. A. Kshirsagar, R. Parnes, H. Goldshtein, R. Ofir, R. Zarivach, D. Pappo, *Chem. Eur. J.* **2013**, *19*, 13575 – 13583; c) Z. Huang, L. Jin, Y. Feng, P. Peng, H. Yi, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 7151 – 7155; *Angew. Chem.* **2013**, *125*, 7292 – 7296; d) U. A. Kshirsagar, C. Regev, R. Parnes, D. Pappo, *Org. Lett.* **2013**, *15*, 3174 – 3177; e) R. Parnes, U. A. Kshirsagar, A. Werbeloff, C. Regev, D. Pappo, *Org. Lett.* **2012**, *14*, 3324 – 3327; f) X. Guo, W. Li, Z. Li, *Eur. J. Org. Chem.* **2010**, *2010*, 5787 – 5790; g) X. Guo, R. Yu, H. Li, Z. Li, *J. Am. Chem. Soc.* **2009**, *131*, 17387 – 17393.
[7] a) D. Vuluga, J. Legros, B. Crousse, A. M. Z. Slawin, C. Laurence, P. Nicolet, D. L. Bonnet-Delpon, *J. Org. Chem.* **2011**, *76*, 1126 – 1133; b) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, *2007*, 2925 – 2943; c) A. Berkessel, J. A. Adrio, D. Hüttenhain, J. M. Neudörfl, *J. Am. Chem. Soc.* **2006**, *128*, 8421 – 8426; d) A. Berkessel, J. A. Adrio, *J. Am. Chem. Soc.* **2006**, *128*, 13412 – 13420; e) J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, *2004*, 18 – 29; f) S. P. de Visser, J. Kaneti, R. Neumann, S. Shaik, *J. Org. Chem.* **2003**, *68*, 2903 – 2912.

[8] a) T. Dohi, N. Yamaoka, Y. Kita, *Tetrahedron* **2010**, *66*, 5775 – 5785; b) H. Hamamoto, G. Anilkumar, H. Tohma, Y. Kita, *Chem. Eur. J.* **2002**, *8*, 5377 – 5383; c) L. Eberson, M. P. Hartshorn, O. Persson, F. Radner, *Chem. Commun.* **1996**, 2105 – 2112.

[9] a) M. Ito, H. Kubo, I. Itani, K. Morimoto, T. Dohi, Y. Kita, *J. Am. Chem. Soc.* **2013**, *135*, 14078 – 14081; b) K. Morimoto, K. Sakamoto, Y. Ohnishi, T. Miyamoto, M. Ito, T. Dohi, Y. Kita, *Chem. Eur. J.* **2013**, *19*, 8726 – 8731; c) A. Jean, J. Cantat, D. Bérard, D. Bouchu, S. Canesi, *Org. Lett.* **2007**, *9*, 2553 – 2556.

[10] a) B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2014**, *53*, 5210 – 5213; *Angew. Chem.* **2014**, *126*, 5311 – 5314; b) A. Kirste, G. Schnakenburg, F. Stecker, A. Fischer, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2010**, *49*, 971 – 975; *Angew. Chem.* **2010**, *122*, 983 – 987; c) A. Kirste, M. Nieger, I. M. Malkowsky, F. Stecker, A. Fischer, S. R. Waldvogel, *Chem. Eur. J.* **2009**, *15*, 2273 – 2277.

[11] a) C. Willis, *Coord. Chem. Rev.* **1988**, *88*, 133 – 202; b) S. A. Cantalupo, J. S. Lum, M. C. Buzzeo, C. Moore, A. G. DiPasquale, A. L. Rheingold, L. H. Doerrer, *Dalton Trans.* **2010**, *39*, 374 – 383.

[12] a) M. Schubert, J. Leppin, K. Wehming, D. Schollmeyer, K. Heinze, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2014**, *53*, 2494 – 2497; *Angew. Chem.* **2014**, *126*, 2527 – 2530; b) L. Tahsini, S. E. Specht, J. S. Lum, J. J. M. Nelson, A. F. Long, J. A. Golen, A. L. Rheingold, L. H. Doerrer, *Inorg. Chem.* **2013**, *52*, 14050 – 14063; c) S. A. Cantalupo, S. R. Fiedler, M. P. Shores, A. L. Rheingold, L. H. Doerrer, *Angew. Chem. Int. Ed.* **2012**, *51*, 1000 – 1005; *Angew. Chem.* **2012**, *124*, 1024 – 1029; d) M. Allan, C. J. Willis, *J. Am. Chem. Soc.* **1968**, *90*, 5343 – 5344.

[13] The addition of 1,10-phenanthroline or 2,2′-bipyridine to the coupling between phenols and β-ketoesters (in DCE as a solvent) is affecting both the efficiency and selectivity of the reaction. However, at a 1:1 ratio of iron to ligand a determinal effect was observed, and the concentrations of these additives had to be kept low with respect to the iron salt. In the mild acidic fluorinated solvents, this determinal effect was cancelled and higher loading of basic ligands can be used.

[14] a) Y. E. Lee, T. Cao, C. Torruellas, M. C. Kozlowski, *J. Am. Chem. Soc.* **2014**, *136*, 6782 – 6785; b) J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540 – 548; c) A. A. Sarhan, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 2730 – 2744.

[15] J. M. Casas-Solvas, J. D. Howgego, A. P. Davis, *Org. Biomol. Chem.* **2014**, *12*, 212 – 232.

[16] a) A. K. R. Bandi, D. U. Lee, R. G. Tih, D. Gunasekar, B. Bodo, *Chem. Biodiversity* **2012**, *9*, 251 – 271; b) M. Möller, U. Suschke, S. Nolkemper, J. Schneele, M. Distl, F. Sporer, J. Reichling, M. Wink, *J. Pharm. Pharmacol.* **2006**, *58*, 1131 – 1138; c) D. E. Pegnyemb, R. G. Tih, B. L. Sondengam, A. Blond, B. Bodo, *Phytochemistry* **2003**, *64*, 661 – 665; d) S. Tang, P. Bremner, A. Kortenkamp, C. Schlage, A. I. Gray, S. Gibbons, M. Heinrich, *Planta Med.* **2003**, *69*, 247 – 253; e) A. Marston, M. G. Zagorski, K. Hostettmann, *Helv. Chim. Acta* **1988**, *71*, 1210 – 1219.

Communications

Oxidative Cross-Coupling

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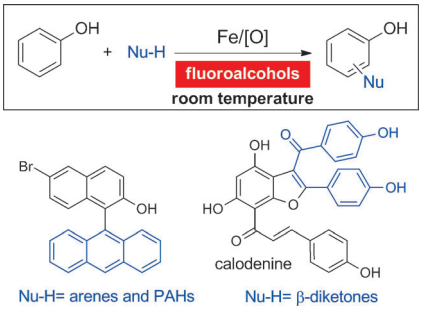
Significant Enhancement in the Efficiency and Selectivity of Iron-Catalyzed Oxidative Cross-Coupling of Phenols by Fluoroalcohols



Not just a solvent: The use of fluorinated solvents leads to a significant rate acceleration and enhancement of the chemoselectivity of the iron-catalyzed oxidative coupling of phenols. This method was used for the synthesis of 2‴-dehydroxycalodenin B.

