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Catalytic, Asymmetric α-Fluorination of Acid Chlorides: Dual Metal−Ketene Enolate Activation

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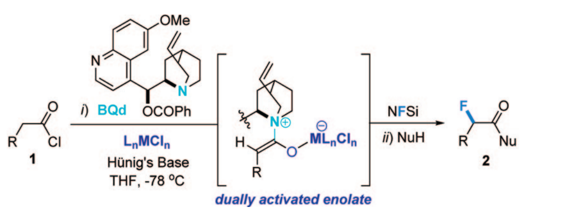
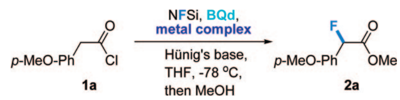
In many ways, medicinal chemistry has entered the "age of fluorine". The number of drugs and drug candidates that contain fluorine has increased exponentially over the past few years, making its installation in a stereoselective (especially an enantioselective) manner of vital importance to the synthetic chemist.[1] Along these lines, several impressive examples of catalytic, enantioselective fluorination have recently appeared in which *β*-keto esters, imides, and aldehydes serve as substrates to produce products in high enantioselectivity and yield.[2] However, one very important complementary piece of the puzzle would be an enantioselective α-fluorination of ketene enolates that could produce simple, optically enriched α-fluorinated carboxylic acid derivatives directly.[3] In this Communication, we report a catalytic, highly enantioselective α-fluorination of acid chlorides to produce products of broad scope and in excellent yield. This new reaction exploits a recently developed "dual activation" strategy from our laboratories in which a chiral nucleophile is combined with a transition metal-based Lewis acid cocatalyst to access metal-coordinated, chiral ketene enolates.[4] In this instance, these catalytically generated, dually activated enolates are efficiently fluorinated with commercially available *N*-fluorodibenzenesulfonimide (NFSi)[5] to produce configurationally stable α-fluorinated carboxylic acid derivatives in high enantiomeric excess (ee) (eq 1). The power of this new method is demonstrated in the broad range of different derivatives that can be synthesized depending on the work up conditions; fluorinated carboxylic acids, amides, esters, and even peptides are all accessible depending on the nucleophile employed to quench the reaction.



(1)

Our interest in catalytic, enantioselective halogenation extends back over several years.[6] We originally reported an enantioselective chlorination and bromination of acid chlorides using cinchona alkaloid derivatives as catalysts and polyhalogenated quinones as mild sources of halogen in conjunction with a variety of stoichiometric bases. Unfortunately, we could never adequately extend this method to an analogous enantioselective fluorination. At best, only low yields of product were observed—the ketene enolate nucleophilicity was seemingly never high enough to allow a smooth reaction with standard fluorinating agents, including NFSi. We returned to the challenge after a lengthy recess upon our discovery that the reactivity of ketene enolates toward *o*-quinones in enantioselective oxygenation reactions could be substantially enhanced by the inclusion of a transition metal cocatalyst, namely $(Ph_3P)_2PdCl_2$.[4] Extensive evidence showed that this metal species binds to the ketene enolate oxygen, thereby enhancing both its reactivity and chemoselectivity. Consequently, whereas the "metal-free" reaction of *p*-methoxyphenylacetyl chloride (**1a**), Hünig's base, 10 mol % benzoylquinidine (BQd), and 1 equiv NFSi in THF at −78 °C (followed by a methanol quench)[7] produces a modest yield of the chiral, α-fluorinated methyl ester **2a**, including 10 mol % *trans*-$(Ph_3P)_2PdCl_2$ as a cocatalyst dramatically increases the yield of product **2a** to 76% (98% ee). Isolation of the initially formed, putative bis(sulfonimide) intermediate (**5**) is difficult owing to its lability; this fact necessitated a quenching reaction that turned out to be a blessing in disguise. A number of middle-transition series-based cocatalysts were then screened, with the results summarized in Table 1. For example, the metal-free reaction (entry 1) optimized at 39% yield of **2a** (97% ee).[8] Wilkinson's catalyst (entry 2) produced a marginal increase, whereas $(PPh_3)_2PtCl_2$ (entries 3 and 4) produces a notable increase in yield. Although the yields for the metal screen vary, the ee's for the test reaction stay consistently high. *trans*-$(PPh_3)_2PdCl_2$ (76%) and the chelating complex (dppp)-$NiCl_2$[9] (83%) performed the best, producing the desired product in 98% and 99% ee, entries 6 and 8, respectively.

Table 1. Metal Complexes Tested for Dual System



entry	metal complex	% yield[a]	% ee
1	no metal	39	97
2	$(PPh_3)_3RhCl$	42	97
3	*trans*-$(PPh_3)_2PtCl_2$[b]	60	98
4	*cis*-$(PPh_3)_2PtCl_2$	62	98
5	*cis*-$(PPh_3)_2PdCl_2$	72	97
6	***trans*-$(PPh_3)_2PdCl_2$[b]**	76	98
7	**$(PPh_3)_2NiCl_2$**	77	97
8	**(dppp)$NiCl_2$[c]**	83	99

[a] Reactions run with 1 equiv acid chloride, base, NFSi, and catalysts: 10 mol % BQd, and 10 mol % metal complex, except where noted; reactions quenched with methanol after 8 h; yield for pure product. [b] Used 1 mol %. [c] Used 3 mol %.

Accordingly, both achiral Pd- and Ni-based phosphine complexes were chosen (interchangeably) for further screening on a range of acid chlorides, as presented in Table 2. Acid halides containing aromatic as well as heterocyclic substituents proved to be good substrates, producing products in very high ee and good to excellent yields.[10] Protected aminoalkyl-substituted acid chlorides also work well, leading to α-fluorinated *β*-amino acid derivatives. Another salient example is shown in the fluorination of readily available acid chloride **3** to provide fluorinated product **4** (84% yield and 95% ee), a derivative of the anti-inflammatory drug indomethacin[11] (eq 2). Other examples, such as the fluorination of an aldol adduct to form **2l**, show that the reaction is also compatible with isomerizable carbon−carbon double bonds.

Additionally, simply by modifying the quench conditions, an array of chiral, α-fluorinated carboxylic acid derivatives can be produced. Along with an alcohol quench that provides esters, a water workup affords α-fluoro carboxylic acids, compounds that should be of potentially broad utility. An amine-based workup

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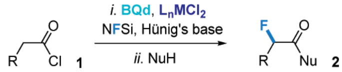
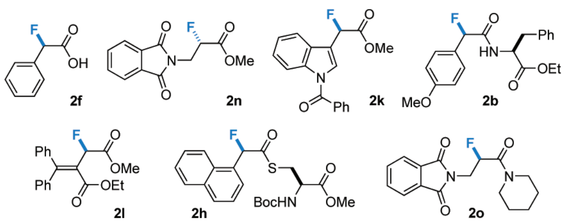
Table 2. Asymmetric, Bifunctional Catalytic α-Fluorination

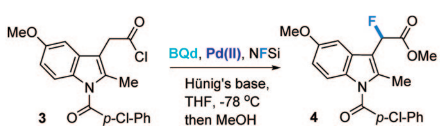


entry	R	cocatalyst [M][a]	NuH	product	% yield[a]	% ee [de][g]
1	*p*-MeOPh	Ni(II)	MeOH	**2a**	83	99
2	*p*-MeOPh	Pd(II)	L-NH_2-Phe-OEt[b]	**2b***	68	>99[g]
3	*p*-MeOPh	Pd(II)	PhSH[b]	**2c**	67	98
4	*p*-MeOPh	Ni(II)	*N*-Boc-L-prolinol[b]	**2d**	90	>99[g]
5	Ph	Ni(II)	MeOH	**2e**	61	99[d]
6	Ph	Ni(II)	H_2O	**2f***	60	99[d]
7	1-Np	Ni(II)	MeOH	**2g**	68	98
8	1-Np	Ni(II)	*N*-Boc-L-Cys-OMe[b]	**2h***	80	>99[g]
9	2-Np	Pd(II)	MeOH	**2i**	63	>99
10	2-thiophene	Pd(II)	MeOH	**2j**	69	99
11	3-(*N*-benzoylindolyl)	Pd(II)	MeOH	**2k***	58	94
12	2-(3-Ph-(ethylcinnamate))	Ni(II)	MeOH	**2l***	71	99
13	phthalimido-CH_2	Pd(II)	MeOH	**2m**	72	>99
14	phthalimido-CH_2[e]	Pd(II)	MeOH	**2n***	74	99
15	phthalimido-CH_2	Pd(II)	$NH(CH_2)_5$[b]	**2o***	79	>99
16	indo[f]	Pd(II)	MeOH	**4***	84	95
17	phthalimido-CH_2	Pd(II)	(+)-emetine[c]	**7***	91	>99[g]



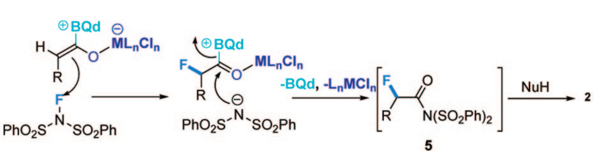
[a] Reactions run with 1 equiv acid chloride, Hünig's base, NFSi, and catalysts: 10 mol % BQd, and 3 mol % (1,3-dppp)$NiCl_2$ or *trans*-$(PPh_3)_2PdCl_2$ in THF at −78 °C, and were quenched with nucleophile after 6−15 h; yield for pure product based on limiting reagent. An excess of NuH was used except: [b] Run using 1.1 equiv NuH; [c] Run using 0.8 equiv NuH. [d] Correlation confirmed sense of induction, see Supporting Information. [e] BQ was used instead of BQd and yields the (*S*)-enantiomer. [f] 3-[*N*-(*p*-Cl-Benzoyl)-(5-MeO-2-Me-indol)]. [g] Diastereomeric excess (de) is measured. *Product is depicted.

affords amides; accordingly, thioesters can be readily accessed. In a representative example, work up with L-phenylalanine ethyl ester produces the fluorinated peptide **2b** in 68% yield (>99% diastereomeric excess [de]).



(2)

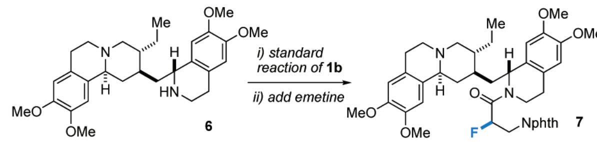
From a mechanistic standpoint, the absence of observable concentrations of free, protonated dibenzenesulfonimide during the course of the reaction suggests that it indeed reacts to form intermediate **5**. This leads us to propose a mechanism (eq 3), which is also based on our previous data on metal-bound zwitterionic ketene enolates.[4] Fluorination of the dually activated enolate leads to an acyl ammonium



(3)

salt that reacts with the liberated dibenzenesulfonimide anion to form the active amide intermediate **5**. As established, this species effects a transacylation with added nucleophiles to generate the final products in high ee and excellent yields.

Finally, one of the prime advantages of generating chiral, α-fluorinated reactive intermediates "in a flask" is the ability to quench them with drugs, natural products, and other exotic nucleophiles to produce interesting and potentially useful derivatives. For example, work up of a standard fluorination of 3-phthalimidopropionyl chloride (**1b**) with the antiprotozoal isoquinoline alkaloid[12] natural product (+)-emetine produces the diastereomerically pure fluorinated derivative **7** in 91% yield (eq 4).



(4)

Along these lines, one can imagine a wide range of fluorinated intermediates coupled with a vast array of natural nucleophiles to produce a virtually limitless number of derivatives. Future work on enantioselective fluorination will concentrate on the synthesis of other medicinally significant intermediates and on a detailed mechanistic investigation of this new method.

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

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