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Rhodium-Catalyzed Enantioselective Defluorinative α-Arylation of Secondary Amides

Young Jin Jang, Daniel Rose, Bijan Mirabi and Mark Lautens*[a]

Abstract: We exploited the reactivity of an electronically biased Michael acceptor to perform a defluorinative α-arylation reaction using a chiral diene(L*)-rhodium catalyst. Through this methodology, we are able to obtain various secondary amides, containing a tertiary α-stereocenter and a β,γ-unsaturated *gem*-difluoro olefin, with excellent enantioselectivities. This methodology addresses the limitations of the previously described α-arylation methods to construct stereo-labile tertiary α-stereocenters. Further investigation of the reaction via *in situ* ^{19}F NMR monitoring suggests that the formation of the product leads to the inhibition of the active rhodium catalyst.

Owing to fluorine's ability to affect lipophilicity, metabolic stability and dipole moments of pharmaceutical agents, the development of methods to incorporate fluorine atoms into an organic molecule has seen remarkable advances over the past decade.[1] As a wider array of fluorinated molecules become available, methods to selectively activate and functionalize carbon-fluorine bonds have become increasingly valuable.[2]

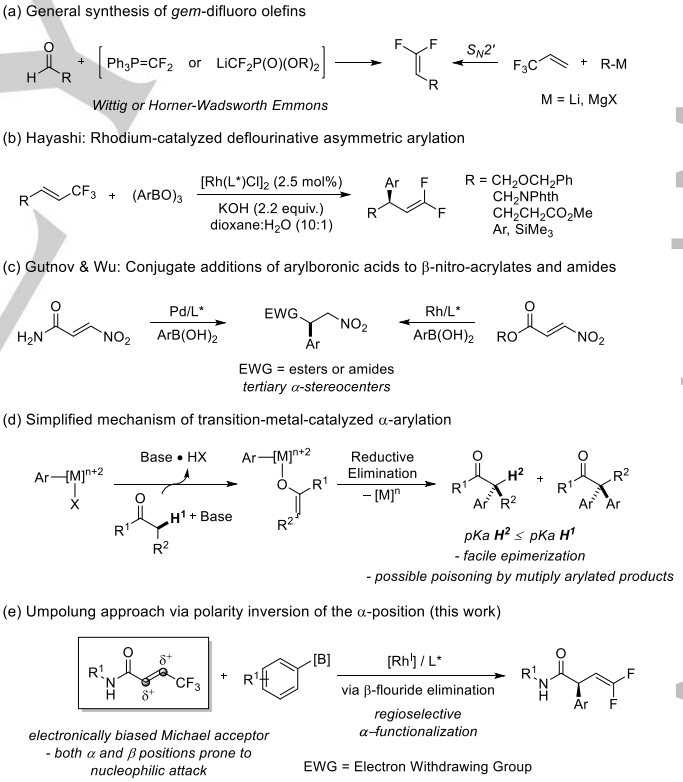
In this regard, *gem*-difluoro olefins have proven to be useful synthetic precursors to a multitude of fluorinated scaffolds. The electron-deficient nature of these olefins has allowed them to participate in various stereoselective functionalizations via transition-metal-catalyzed methodologies.[3] These transformations are versatile methods to access novel classes of fluorinated organic scaffolds that are otherwise difficult to synthesize.

Generally, the syntheses of *gem*-difluoro olefins can be accomplished through Wittig- or Horner-Wadsworth-Emmons-type olefination and S_N2' reactions of vinyl trifluoromethyl compounds (Scheme 1a).[4] Although these methods are efficient in constructing 1,1-*gem*-difluoro olefins, development of methods with milder reaction conditions and broader functional group tolerance would be beneficial.

In 2016, Hayashi's group reported the enantioselective rhodium-catalyzed defluorinative arylation reaction (Scheme 1b). A rhodium-mediated arylative β-fluoride elimination was proposed, leading to enantiomerically enriched *gem*-difluoro olefins.[5] We envisioned exploiting this reactivity to achieve an enantioselective rhodium-catalyzed α-arylation to construct a potentially stereo-labile tertiary α-stereocenter (Scheme 1c).[6]

The enantioselective transition-metal-catalyzed α-arylation reaction is well documented, with pioneering studies described by the groups of Hartwig, Kündig, Buchwald and Glorius.[7] Numerous chiral nickel and palladium catalysts have been described to construct quaternary α-stereocenters. Conversely, methods to construct stereo-labile tertiary α-stereocenters has considerably lagged.[8] The origin of this challenge stems from the comparable acidity of the α-protons in the substrate and in the resulting product. The strongly basic reaction conditions promote the epimerization of the α-position, which makes it challenging to construct tertiary α-stereocenters (Scheme 1d). Consequently, only products lacking such α-protons or with a structural bias that inhibits deprotonation can be accessed via the traditional approach.[9]

Herein, we describe the development of the rhodium-catalyzed defluorinative α-arylation reaction, granting access to a novel class of secondary amides containing a tertiary α-stereocenter and a β,γ-unsaturated *gem*-difluoro olefin (Scheme 1e). This may serve as an alternative approach to the traditional palladium- and nickel-catalyzed α-arylation reaction.



Scheme 1. Enantioselective transition-metal-catalyzed α-arylation reactions, and the proposed rhodium-catalyzed defluorinative α-arylation reaction.

At the outset of our investigation, we set out to demonstrate our proof of concept on the acrylamide **1a**, bearing a more acidic N–H group versus the α-proton in the resulting product, in order to minimize epimerization of the α-stereocenter. The resulting secondary amide would represent a novel class of difluorinated organic scaffold.

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Initial screening of typical rhodium conjugate addition conditions quickly led to the optimized conditions for the racemic transformation (Table 1, entry 1). Screening of various classes of chiral ligands such as the (*R*)-BINOL derived phosphoramidite ligand **L1**, led to poor yield with moderate enantioselectivity (Table 1, entry 2). Employing Carreira's diene **L2**, furnished the desired product in comparable enantioselectivity, but with

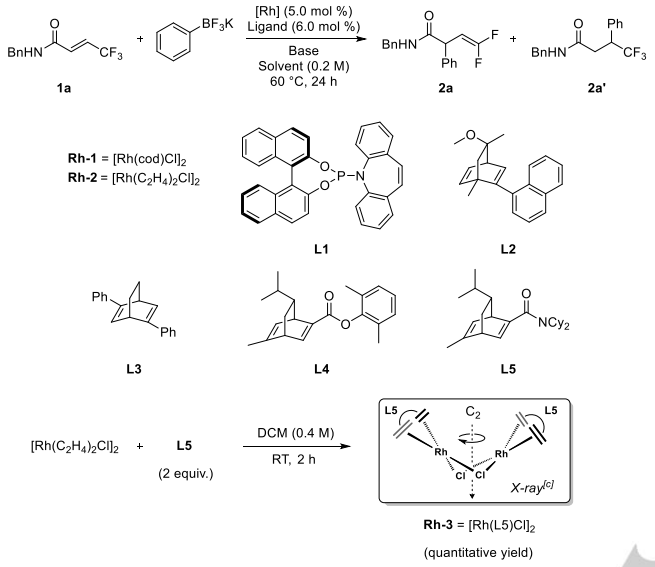


Table 1. Optimization Table

	[Rh]	L	base	solvent (4/1)	S.M. (%)	yield[b] **2a/2a'**	ee **2a**
1	**Rh-1**	-	KOH	diox/H_2O	<5	84 / 13	-
2	**Rh-2**	**L1**	KOH	diox/H_2O	45	15 / 23	56
3	**Rh-2**	**L2**	KOH	diox/H_2O	<5	41 / 27	-50
4	**Rh-2**	**L3**	KOH	diox/H_2O	53	23 / 8	78
5	**Rh-2**	**L4**	KOH	diox/H_2O	17	10 / 67	90
6	**Rh-2**	**L5**	KOH	diox/H_2O	61	31 / <5	90
7	**Rh-2**	**L5**	KOH	DCE/H_2O	41	40 / <5	94
8	**Rh-3**	-	KOH	DCE/H_2O	55	30 / <5	ND
9[a]	**Rh-3**	-	KOH	DCE/H_2O	15	60 / <5	98
10[a]	**Rh-3**	**L5**	KOH	DCE/H_2O	<5	**68** / <10	**98**
11[a]	**Rh-3**	**L5**	Li_2CO_3	DCE/H_2O	<5	**74** / <5	**98**

Enantiomeric excess was determined by HPLC using chiral stationary phase column, and yields, S.M. and ee are reported in percentages. [a] 10 mol % of [Rh] [b] NMR yields determined from crude ^{1}H NMR spectra, using 1,3,5-trimethoxybenzene as the internal standard. [c] See Supporting information for detailed reaction conditions and characterization data.

improved yield (Table 1, entry 3). Upon switching to Hayashi's diene **L3**, Ph-bod* (Table 1, entry 4), we observed superior enantioselectivity, albeit in low yield. Further screening of chiral diene ligands derived from α-phellandrene (**L4**, **L5**) gave improved results (Table 1, entries 5,6), with the best outcome achieved in a dichloroethane and water mixture as the solvent (Table 1, entry 7). Subsequent efforts to increase the yield were challenging, but the use of the preformed rhodium-complex (**Rh-3**) (Table 1, entry 8), and increased catalyst loading (Table 1, entry 9), with additional chiral diene ligand **L5** gave better results (Table 1, entry 10). The use of lithium carbonate led to slightly higher yield without the erosion of enantioselectivity (Table 1, entry 11).

With the optimized conditions in hand, we examined the applicability of our reaction on various substrates. The benzyl-substituted **2a**, the phenyl-substituted **2b**, as well as bulky aliphatic amides **2c** and **2d** were well tolerated, furnishing the corresponding products in modest yields and excellent enantioselectivities. The absolute configuration of **2c** was unambiguously determined through X-ray crystallography, and the configuration of other substrates is assumed by analogy. Moreover, heterocycle containing amide **2e** was generated in good yield and excellent enantioselectivity. The tri-substituted amide **2f** was also synthesized, but in lower yield and enantioselectivity. Conversely, cyclopropyl amide **2g** was obtained in excellent yield and enantioselectivity. Furthermore, a diverse array of potassium aryl-trifluoroborate salts were subjected to the reaction conditions. Substitutions on the *meta*- and *para*- positions were well tolerated (**2h-n, 2p-q, 2s-2z)**, giving modest yields and comparable enantioselectivities. Interestingly, reactions with cyclopropylamide gave consistently higher yields compared to other amides. In comparison, the

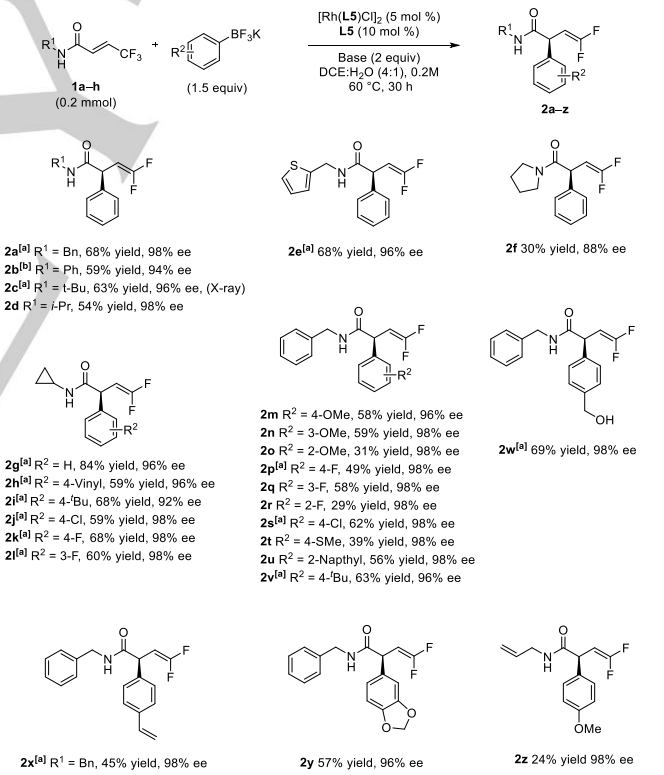
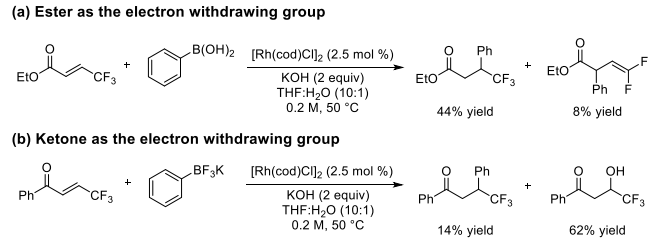


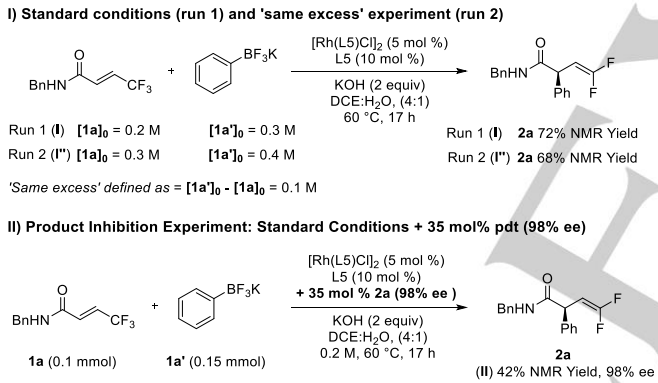
Figure 1. Substrate scope of the enantioselective defluorinative α-arylation reaction. KOH (2 equiv) was used as base and the reaction was conducted for 30 h unless otherwise indicated. See supporting information for detailed reaction conditions. Enantiomeric excess was determined by HPLC. [a] 2 equivalents of Li_2CO_3 was used and the reaction was carried out for 24 h. [b] 2 equivalents of K_2CO_3 was used and the reaction was carried out for 24 h.

reaction of *ortho*-substituted aryl trifluoroborate salts (**2o**, **2r**), independent of their electronic properties, led to lower yields, but with excellent enantioselectivities. Functional groups such as primary alcohol (**2w**) and mono-substituted olefin (**2x**) were well tolerated with excellent enantioselectivities.



Scheme 2. Probing the effects of different electron withdrawing groups.

To probe the effects of the electron withdrawing group on the reaction outcome, β-trifluoromethyl substituted acrylates and acrylones were also investigated. Using the acrylate (Scheme 2a), minimal amounts of the desired α-arylated product were observed accompanied by a significant amount of the 1,4-conjugate adduct. Similarly, acrylone was shown to be too reactive towards 1,4-addition with the hydration of the double bond being observed as the major product (Scheme 2b).[10] Overall, less electron withdrawing amides are favoured in the defluorinative α-arylation reaction.



Scheme 3. Product inhibition experiments monitored via ^{19}F NMR.

Incomplete conversion leading to low yields was observed in our studies. This led us to speculate the potential for catalyst deactivation. To gain additional insight, the 'same excess' protocol developed by Blackmond was conducted (Scheme 3-I).[11] Two experiments **I** (Run 1) and **I''** (Run 2) have different initial concentrations of **1a** and **1a'**, but the difference in their temporal concentrations are identical ('same excess' defined as $[1a']_0 - [1a]_0$). A comparison of the reaction rates of the two runs at the time point indicated by the dotted arrows, where the concentrations of **1a** and **1a'** are identical in both runs 1 and 2, supports the proposal that the accumulation of product leads to catalyst deactivation (Figure 2a). This may be due to either catalyst decomposition over time or the catalyst could be sensitive to product inhibition.[11] Conversely, in the absence of catalyst deactivation, the observed reaction rate at the time point

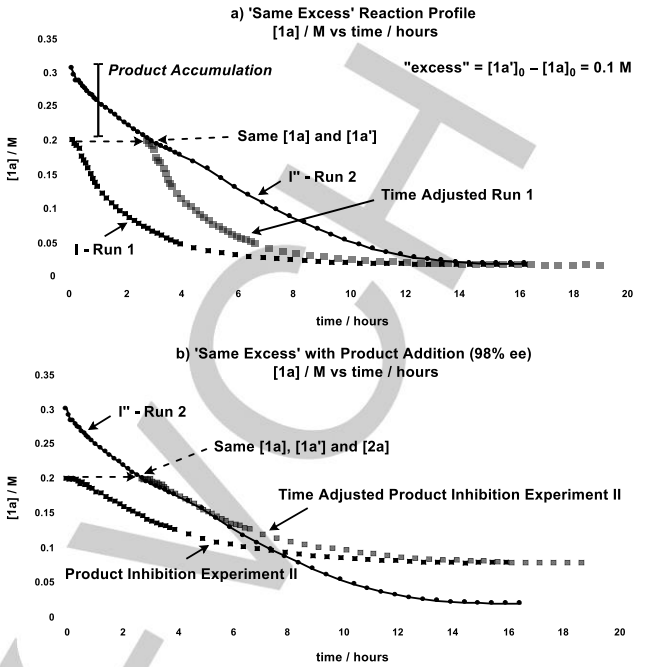
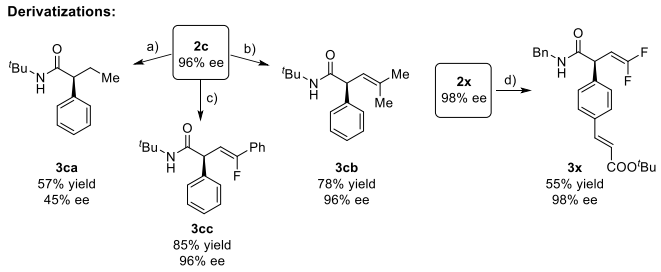


Figure 2. Fluorobenzene was used as the internal standard, see supporting information for additional plots and detailed reaction procedures.

indicated by the dotted arrows, should be identical, and complete overlay of the two graphs of time adjusted run 1 and run 2 should be observed.

Additionally, a product inhibition experiment was conducted (Scheme 3-II). In this experiment, 35 mol % of product **2a** (98% ee) was added at time 0, and the reaction rate was compared to the 'same excess' experiment (Figure 2b). At the time point indicated by the dotted arrows, not only are the temporal concentrations of **1a**, **1a'** identical, but also the temporal concentration of **2a** is matched in both experiments. Comparing the rates of both runs at this time point and onwards, indicates that the catalyst is sensitive to product inhibition. Furthermore, clear deviation of the two plots is observed with time (t > 5 h), suggesting that the byproducts generated, excluding **2a**, help to alleviate product inhibition of the active catalyst (indicated by higher consumption of starting material in run 2). Although the exact nature of this phenomenon is unclear, the different reaction rates observed between the two runs (figure 2b), suggests that the product **2a** chelates to the rhodium catalyst, potentially leading to the formation of an off-cycle ML^1L^2 (L^1 = L5, L^2 = product*) species that is in equilibrium with the active catalyst.[12] We speculate that the boron salts generated from the hydrolysis/transmetalation of potassium aryltrifluoroborate salt,[13] help to shift the equilibrium towards the active catalyst leading to a more efficient reaction.

To demonstrate the utility of the products, derivatization studies were conducted as shown in Scheme 4. Employing the nickel-catalyzed hydrodefluorination methodology developed by Cao,[14] the *gem*-difluoro olefin was fully reduced to afford **3ca** in good yields. Furthermore, the coupling of *gem*-difluorides with simple Grignard reagent was realized under nickel catalysis,[15] furnishing the desired product **3cb** in good yield with no loss in



Scheme 4. a) $Ni(PCy)_3Cl_2$ (5 mol %), $LiAl(OtBu)_3H$ (3 equiv), THF, 40 °C b) $Ni(dppp)Cl_2$ (10 mol %), MeMgBr (10 equiv), C_6H_6, reflux. c) $Pd(TFA)_2$ (10 mol %), 4,4'-Di-tert-butyl-2,2'-dipyridyl (11 mol %), $PhB(OH)_2$ (2 equiv), DMF, 50 °C d) tert-butyl-acrylate (2 equiv), Grubb's 2nd Generation Catalyst (10 mol %), DCM, 40 °C. All reported yields are isolated yields. See supporting information for detailed reaction conditions.

stereochemical information. Stereoselective palladium-catalyzed mono-functionalization of the vinyl fluorides was also accomplished, using the protocol developed by Toste,[16] furnishing the desired product **3cc** in excellent yield and stereoselectivity. Harnessing the lack of reactivity of *gem*-difluoro olefins allows chemo-selective olefin metathesis affording **3x** in modest yield with no loss in enantiomeric purity.[17]

In conclusion, we have developed an enantioselective rhodium-catalyzed defluorinative α-arylation reaction. Through the development of our methodology, we are able to access various secondary amides, containing a tertiary α-stereocenter and a β,γ-unsaturated *gem*-difluoro olefin. The products obtained exhibit thermodynamic stability towards isomerization and are a novel class of fluorinated molecules. Further derivatization studies are underway to access enantiomerically enriched fluorinated compounds.

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Keywords: Defluorinative Arylation • Asymmetric Catalysis • Rhodium Catalysis

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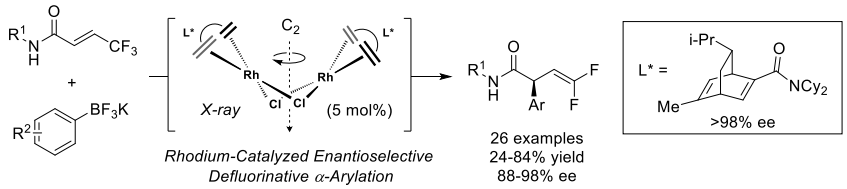

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