Synthetic Methods

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Highly Enantioselective Pictet–Spengler Reactions with α-Ketoamide-Derived Ketimines: Access to an Unusual Class of Quaternary α-Amino Amides**

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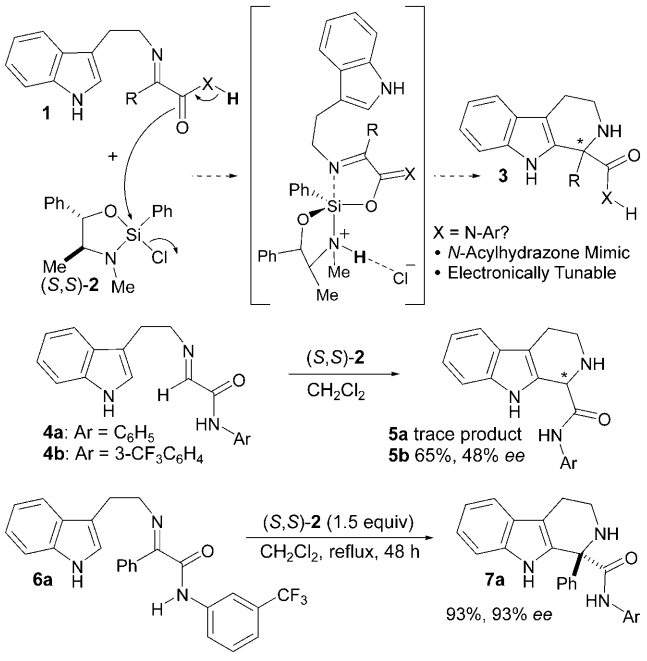
The Pictet–Spengler reaction[1] provides access to tetrahydro-β-carbolines and tetrahydroisoquinolines, which are heterocyclic ring systems of considerable importance to natural products and medicinal chemistry. Asymmetric variants would be expected to find utility, especially to the extent that they reliably provide access to complex and highly enantioenriched products from simple starting materials by employing only straightforward experimental techniques. While many Pictet–Spengler reactions controlled by chiral auxiliaries have been reported,[2] it is only more recently that the first reports of highly enantioselective variants (external asymmetric induction) have appeared.[3] Notably, all of these methods require prior modification of the amino group of the tryptamine from which the active iminium species is prepared,[3a,d,e] or derivatization of the imine nitrogen prior to cyclization,[3b] or the use of a substituted tryptamine precursor.[3c] In terms of scope, most of these reports described the reactions of aldimine derivatives; only very recently have Jacobsen and co-workers reported the first examples of highly enantioselective Pictet–Spengler reactions (and related reactions with pyrroles) of ketimine derivatives.[4] Owing partly to the fact that 1,1-disubstituted tetrahydro-β-carbolines appear in important natural products (e.g. ecteinascidins 722 and 736)[5] and have been the subject of screening library development,[6] and partly to the fundamental synthetic challenge, the development of a highly enantioselective ketimine Pictet–Spengler reaction—wherein tryptamine itself and the ketone are simply condensed with no further modification required—seemed a worthy goal.

We have developed Lewis acidic chiral chlorosilanes for a range of highly enantioselective imine addition reactions that requires activation by protic nucleophiles within the imine substrate. Effective activators include the NHCOR fragment of *N*-acylhydrazones,[7] the OH group of phenols,[8] and the NH group of imidazoles.[9] In a projected enantioselective ketimine Pictet–Spengler reaction, the activating group cannot be a part of the imine *N*-substituent (as in *N*-acylhydrazones) and must therefore be a part of the ketone from which the imine is derived. Carboxyl derivatives that possess an acidic proton (e.g. carboxylic acid, secondary amide) seemed attractive in this regard both because of their general synthetic versatility and because the products would represent an interesting class of quaternary α-amino acid derivatives. Mechanistically, it was envisioned that *O*-silylation of compounds of the general structure **1** with silane (*S*,*S*)-**2**[7b,c,d] would give, by way of the illustrated complex, products **3** (Scheme 1). Owing to a resemblance to the "amide" fragment of *N*-acylhydrazones, and to the expectation that they would be readily electronically tunable, secondary *N*-aryl amides became the subject of our exploratory studies (X = N–Ar).

As a proof of concept experiment, *N*-phenylglyoxamide-derived imine **4a** was prepared and treated with silane (*S*,*S*)-**2** (Scheme 1). The desired product **5a** was produced, but in only trace quantities (< 10%). However, it was found that electron-withdrawing groups on the *N*-aryl ring dramatically enhanced the reaction rate. Among the aryl amides screened,



Scheme 1. Reaction design, discovery, and optimization.

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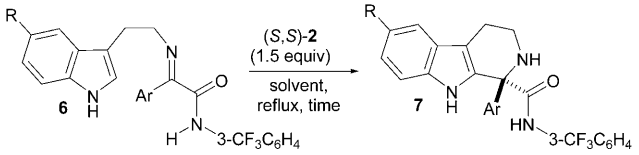
the *N*-3-(trifluoromethyl)phenyl amide **4b** provided superior reactivity giving **5b** in (an unoptimized) 65% yield and 48% *ee*. Having established the feasibility of the process, we next prepared phenylketone-derived amide **6a** and subjected it to reactions with silane (*S*,*S*)-**2**. Although an elevated reaction temperature and extended reaction time was required, this reaction proceeded smoothly and gave **7a** in good yield and with an improved enantioselectivity relative to **5b**. Optimization of the reaction conditions to maximize efficiency and enantioselectivity was straightforward, and using the illustrated conditions[10] **7a** was isolated in 93% yield and 93% *ee*.

A series of *N*-3-(trifluoromethyl)phenyl amides **6** were prepared and subjected to the Pictet–Spengler reaction with silane (*S*,*S*)-**2** (Table 1). As compared to parent substrate **6a** (Table 1, entry 1), bromine substitution at the 5-position of the indole (**6b**) resulted in a relatively sluggish reaction that nevertheless produced **7b** in 68% yield and 89% *ee* (Table 1, entry 2), whereas the corresponding methoxy substitution (**6c**) resulted in a highly efficient (93% yield), albeit less selective (82% *ee*) reaction (Table 1, entry 3). Substitution of the aryl group (Ar) was well tolerated (Table 1, entries 4–7), as was the heteroaromatic (3-pyridyl) group (Table 1, entry 8). While *ortho* substitution on the aryl group may be tolerated (Table 1, entries 9 and 10), the reactions were significantly more sluggish, and required both increased loadings of the silane Lewis acid and higher reaction temperatures (1,2-dichloroethane (DCE) at reflux). Despite this, the highly sterically hindered products **7h** and **7i** were obtained with high levels of enantioselectivity (87 and 90% *ee*, respectively).

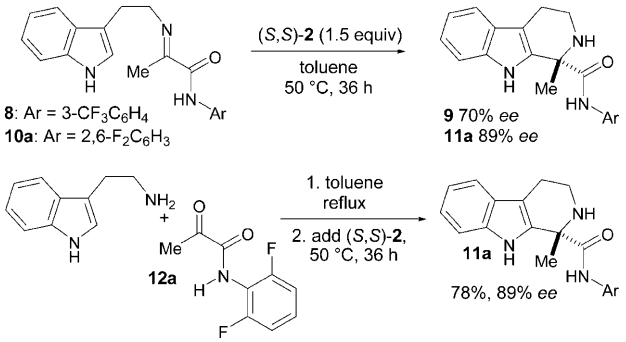
Table 1: Highly enantioselective Pictet–Spengler reactions of ketimines derived from alkyl ketones.



Entry	R	Ar	Solvent	*t* [h]	Yield [%]	*ee* [%]
1	H	C_6H_5 (**7a**)	CH_2Cl_2	48	93	93
2	Br	C_6H_5 (**7b**)	$CHCl_3$	70	68	89
3	OMe	C_6H_5 (**7c**)	CH_2Cl_2	27	93	82
4	H	*p*-BrC_6H_4 (**7d**)	CH_2Cl_2	48	85	90
5	H	*p*-$CF_3C_6H_4$ (**7e**)	CH_2Cl_2	48	89	90
6	H	*p*-$MeOC_6H_4$ (**7f**)	$CHCl_3$	20	94	87
7	H	2-naphthyl (**7g**)	CH_2Cl_2	46	82	91
8	H	3-pyridyl (**7h**)	CH_2Cl_2	42	77	87
9[a]	H	1-naphthyl (**7i**)	DCE	60	50	87
10[a]	H	2,4-$Cl_2C_6H_3$ (**7j**)	DCE	60	86	90

[a] These reactions were performed with 2 equivalents of (*S*,*S*)-**2**.

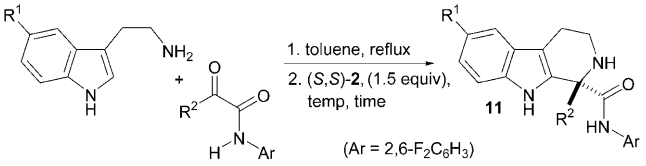
To establish greater generality and scope for the process we next examined the performance of imines derived from alkyl ketones (**1**, R = alkyl). Exploratory studies with pyruvate-derived amide **8** revealed that the 3-(trifluoromethyl)-phenyl amide provided product **9** with insufficiently high enantioselectivity (70% *ee*; Scheme 2). A brief survey of other aryl amides led to the discovery that the 2,6-difluorophenyl group provided good results and upon optimization it was found that treatment of imine **10a** with 1.5 equivalents of (*S*,*S*)-**2** in toluene at 50 °C led to **11a** in 89% *ee*. As toluene proved to be an effective solvent for this reaction and is a convenient and effective solvent for the imine formation, we have developed a one-pot procedure wherein tryptamine and the ketone are condensed in toluene at reflux (with a Dean–Stark trap), and upon completion of the imine formation the reaction mixture was cooled to 50 °C and the silane Lewis acid was added. By using this convenient procedure, **11a** may be produced in 78% yield (from ketone **12a**) and 89% *ee*.



Scheme 2. Optimization of the Pictet–Spengler reactions of ketimines derived from alkyl ketones.

The results of a brief survey of the scope and generality of this one-pot process with tryptamines and alkyl ketones are summarized in Table 2. As with the aryl ketone-derived substrates, 5-bromo and 5-methoxy substitution of the tryptamine are tolerated, albeit with a similar moderate drop in enantioselectivity (compare Table 2, entry 1 with entries 2 and 3). Importantly, a significant degree of steric hindrance may be tolerated, as demonstrated by the isobutyl and isopropyl ketone substrates (Table 2, entries 4 and 5), and indeed these reactions proceed with improved enantioselectivity.

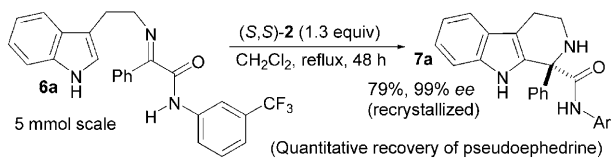
Table 2: Highly enantioselective one-pot Pictet–Spengler reactions of tryptamines and α-(alkyl)ketoamides.



Entry	R^1	R^2	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	H	Me (**11a**)	50	36	78	89
2	Br	Me (**11b**)	75	48	67	86
3	OMe	Me (**11c**)	50	48	86	81
4	H	*i*Bu (**11d**)	50	26	81	90
5	H	*i*Pr (**11e**)	55	25	83	94

To demonstrate that this process is readily scalable, the reaction of **6a** was carried out on a 5 mmol scale (with the silane loading reduced to 1.3 equiv[11]). Tetrahydro-β-carbo-

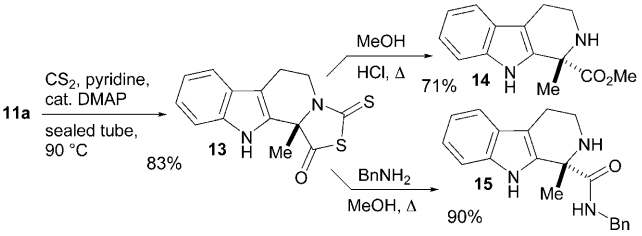
line **7a** was isolated by recrystallization in 79% yield and 99% *ee* (Scheme 3). In addition, the pseudoephedrine was quantitatively recovered by simple basification and extraction



Scheme 3. Larger scale reaction without the need for chromatography and quantitative recovery of the pseudoephedrine.

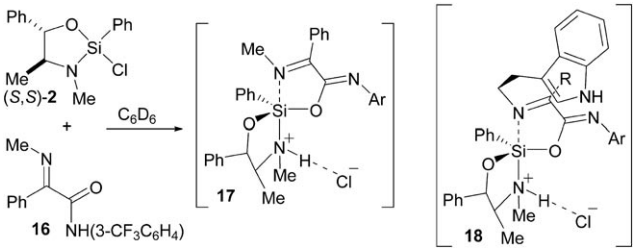
of the aqueous phase that was recovered from the work-up procedure. Thus, neither the isolation of **7a** nor the recovery of the pseudoephedrine required any chromatography, and despite the requirement for a stoichiometric amount of the (extraordinarily simple to prepare in one step and inexpensive) silane Lewis acid (*S*,*S*)-**2**, this is a process that may lay a strong claim to a high degree of economic practicality and scalability.

In principle, and as briefly discussed above, the amide group of the products can serve as a versatile entry to many other functional groups. In practice, however, attempts to carry out alcoholysis and transamination reactions on amide **11a** were unsuccessful. It was found, however, that treatment of **11a** with CS_2 in the presence of pyridine and 4-dimethylaminopyridine (DMAP) in a sealed tube at 90 °C led to **13** in 83% yield (Scheme 4). Compound **13** ably serves as an *N*-protected active ester derivative as shown by the illustrated alcoholysis and aminolysis reactions to give ester **14** and amide **15** in 71% and 90% yields, respectively.



Scheme 4. Transformation of the amide products into other carboxyl derivatives without the use of protecting groups. Bn = benzyl.

To gain mechanistic insight into this reaction, *N*-methyl imine **16** was treated with silane (*S*,*S*)-**2** in C_6D_6 (Scheme 5). As judged by ^1H NMR spectroscopy, this reaction principally resulted in the formation of a single silane–amide complex (≥12:1 with respect to a minor, uncharacterized compound), assigned as structure **17**. Further analysis by NMR spectroscopy (^1H–^{15}N HMBC, COSY, ROESY, ^{29}Si) corroborated this assignment,[12] and it is noteworthy that this structure closely resembles the complex formed from the reaction of (*S*,*S*)-**2** with the *N*-benzoylhydrazone of benzaldehyde.[7b] Based on this assignment it is straightforward to propose a plausible stereochemical model for the reaction: the indole, prevented from attacking the back face of the imine by a steric



Scheme 5. A plausible reaction mechanism and model for absolute stereochemical induction. Ar = alkyl, aryl.

interaction with the relatively large phenyl group attached to silicon, attacks the exposed front face as in structure **18**, which is consistent with the observed sense of induction.

We have developed a highly enantioselective Pictet–Spengler reaction with ketimines derived from α-ketoamides that provides access to an interesting and hitherto inaccessible class of optically active quaternary α-amino acid derivatives. The chiral silane Lewis acid (*S*,*S*)-**2** is extraordinarily simple to prepare and inexpensive, and the method—uniquely—does not require any modification or derivatization of the tryptamine precursor or tryptamine-derived imines. Along the way we have established a highly effective new activating group for our silane Lewis acids (secondary *N*-aryl amides) that may have implications in other reactions, and we have expanded the list of reactions for which silane (*S*,*S*)-**2** is a highly effective and enantioselective promoter.

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[10] On this scale (0.15 mmol), reactions run with lowered silane loadings often proceeded with loss in enantioselectivity. We attribute this outcome to a Brønsted acid catalyzed reaction, likely owing to trace moisture.
[11] On this larger scale, the problem described in Ref. [10] is mitigated, and the silane loading may be lowered with no loss in enantioselectivity.
[12] Full details are provided in the Supporting Information file.

