Asymmetric Synthesis

Nucleophile-Catalyzed Asymmetric Acylations of Silyl Ketene Imines: Application to the Enantioselective Synthesis of Verapamil**

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Generating enantiomerically enriched nitriles in which the cyano group is bound to an all-carbon quaternary stereocenter (e.g. **1**) is an important challenge in synthetic organic chemistry and is owed in part to the biological activity of such compounds.[1] We have recently turned our attention to the development of catalytic asymmetric methods that address this challenge[2,3] by focusing on reactions of nitrile anions.[4] Such species are, of course, ambident nucleophiles that are capable of reacting at nitrogen centers to afford an N-substituted ketene imine or at carbon atoms to furnish a C-substituted nitrile [Eq. (1)].[5]

We recently described the application of a new dual-activation strategy to catalytic enantioselective intermolecu-

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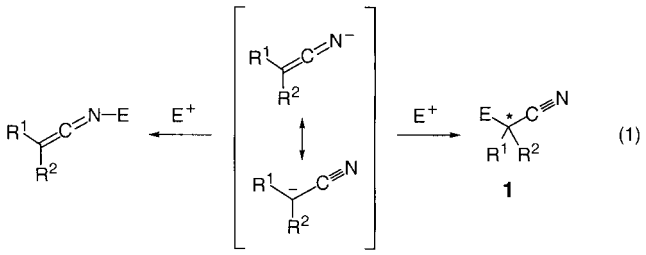
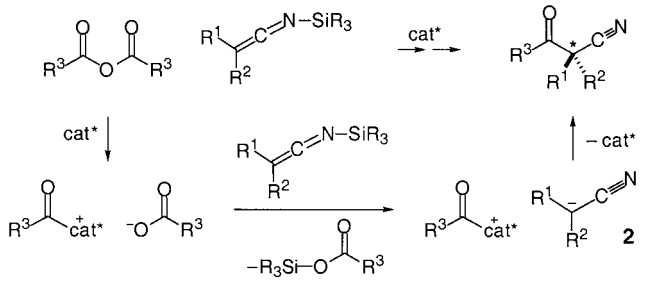


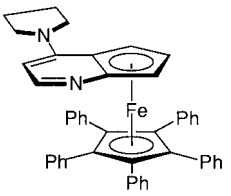
(1)

lar C acylations of silyl ketene acetals.[6] Naturally, we have been interested in determining if this approach is general and can be employed for reaction partners other than silyl ketene acetals. For example, we were intrigued by the possibility of synthesizing enantioenriched target molecules such as **1** through the treatment of silyl ketene imines with anhydrides[7] through the chiral-nucleophile-catalyzed pathway outlined in Scheme 1.



Scheme 1. Proposed pathway for a chiral-nucleophile-catalyzed asymmetric synthesis of all-carbon quaternary stereocenters through the acylation of silyl ketene imines.

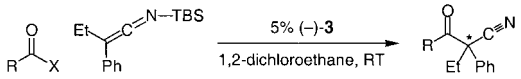
Silyl ketene imines are readily generated through the reaction of a nitrile with a Brønsted base and a silylating agent.[5] At room temperature in the absence of a catalyst, silyl ketene imines are essentially inert to a variety of acylating agents. However, in the presence of the chiral PPY (4-(pyrrolidino)pyridine) derivative **3**[8] (5%), they



undergo C acylation to furnish α-cyano carbonyl compounds (Table 1).[9] Reactions of cyanoformates or chloroformates proceed with low enantioselectivity (Table 1, entries 1 and 2, respectively), whereas acylations by anhydrides can lead to substantial values of *ee* (Table 1, entries 3 and 4). Very bulky anhydrides do not react at room temperature (Table 1, entry 5). To the best of our knowledge, these are the first examples of nucleophile-catalyzed reactions of silyl ketene imines.

With an interesting new catalytic and enantioselective C–C bond-forming process in hand, we turned our attention to the determination of the scope of the reaction. With respect to the alkyl substituent on the ketene imine, the acylations proceed with good *ee* values for a variety of groups (Table 2, entries 1–4), although the sterically demanding cyclopentyl-substituted compound reacts with somewhat diminished stereoselectivity (Table 2, entry 5).[10]

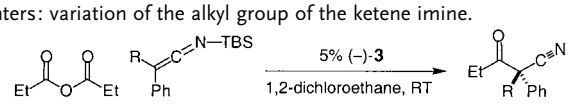
Table 1: Reaction of acylating agents with a silyl ketene imine in the presence of a chiral PPY derivative.



Entry	RCOX	*ee* [%][a]	Yield [%][a]
1	$MeO_2C(CN)$	< 5	81
2	$tBuCH_2O_2CCl$	7	61
3	Ac_2O	72	64
4	$(EtCO)_2O$	81	85
5	$(iPrCO)_2O$	–	< 5

[a] Average of two runs. TBS = *tert*-butyldimethylsilyl.

Table 2: Catalytic asymmetric synthesis of all-carbon quaternary stereocenters: variation of the alkyl group of the ketene imine.

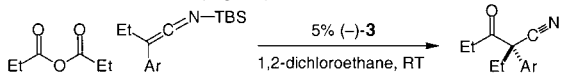


Entry	R	*ee* [%][a]	Yield [%][a]
1	Me	81	89
2	Et	81	85
3	CH_2CHMe_2	83	93
4	CH_2CMe_3	81	52
5	cyclopentyl	69	53

[a] Average of two runs.

We have also examined the scope of this process with respect to the aryl substituent on the ketene imine.[11] Increasing the electron-rich nature of the aromatic ring has no effect on the values of the *ee* (Table 3, entry 1 versus entry 2), whereas the introduction of an electron-withdrawing group leads to a loss in enantioselectivity (Table 3, entry 1 versus entry 3). Reactions of more-hindered aryl or heteroaryl (Table 3, entries 4 and 5) ketene imines furnish values for *ee* that are comparable to the phenyl-substituted substrate (Table 3, entry 1).

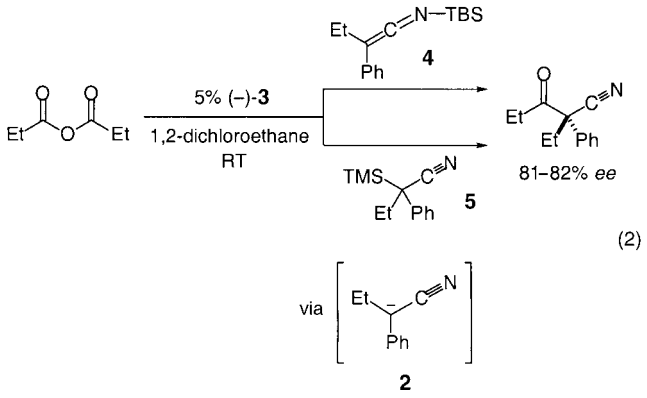
Table 3: Catalytic asymmetric synthesis of all-carbon quaternary stereocenters: variation of the aryl group of the ketene imine.



Entry	Ar	*ee* [%][a]	Yield [%][a]
1	Ph	81	85
2	4-$(MeO)C_6H_4$	81	65
3	4-$(F_3C)C_6H_4$	53	50
4	1-naphthyl	80	78
5	3-thienyl	77	72

[a] Average of two runs.

In analogy with the chemistry of silyl ketene acetals,[6] we believe that these acylations of silyl ketene imines proceed through the pathway depicted in Scheme 1, wherein the carboxylate ion desilylates the imine to generate a nitrile anion **2** as the key reactive nucleophile.[12] On the basis of this mechanistic hypothesis, we predicted that **4** and **5** [Eq. (2),



(2)

TMS = trimethylsilyl] should react with an anhydride in the presence of catalyst **3** to furnish the target α-cyano carbonyl compound with the same sense and level of enantioselectivity. As illustrated in Equation (2) this prediction has indeed been borne out experimentally and is consistent with a common intermediate, that is, a silicon-free nitrile anion **2**, for the two acylation processes.

To demonstrate the utility of our catalytic asymmetric method for the generation of cyano-substituted, all-carbon quaternary stereocenters, we applied the method to the enantioselective synthesis of the drug verapamil (Scheme 2), the enantiomers of which have significantly different biological activity.[1,13,14] Alkylation of nitrile **6** with 2-(2-bromoethyl)-1,3-dioxolane, both of which are commercially available, followed by formation of the silyl ketene imine, furnishes **7** in 80% yield (over two steps). Asymmetric C acylation catalyzed by (–)-**3** generates **8**, which bears the target quaternary stereocenter, in 81% *ee*.[15] A two-step olefination reaction followed by a hydrogenation reaction affords intermediate **9**. The aldehyde is deprotected and then subjected to reductive amination, which provides (*S*)-verapamil in 25% overall yield from **6**.

In conclusion, we have described a new nucleophile-catalyzed reaction, the acylation of silyl ketene imines, and we have established that it can produce all-carbon quaternary stereocenters with good enantioselectivity. Our mechanistic data are consistent with a dual-activation pathway in which a nitrile anion intermediate undergoes asymmetric acylation. We have applied our method to the first catalytic asymmetric synthesis of the drug verapamil.[16] Ongoing studies are directed at providing further evidence for the generality of this dual-activation strategy in asymmetric catalysis.

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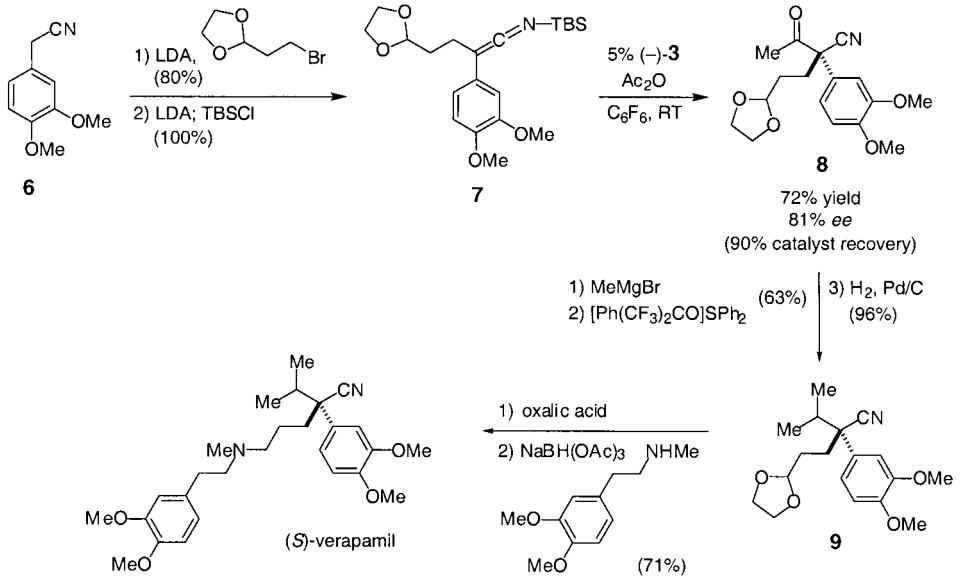

Scheme 2. Catalytic asymmetric synthesis of (*S*)-verapamil. LDA = lithium diisopropylamide.

[1] As an example, the drug verapamil, which is the oldest known calcium-channel blocker, belongs to this category. For reviews of verapamil, see: a) L. M. Prisant, *Heart Dis.* **2001**, *3*, 55–62; b) R. N. Brogden, P. Benfield, *Drugs* **1996**, *51*, 792–819.

[2] As noted in a recent review, "only a few catalytic asymmetric C–C bond-forming reactions have been shown to be useful for constructing all-carbon quaternary stereocenters." See: C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367.

[3] For examples of catalytic asymmetric methods for the synthesis of cyano-substituted, all-carbon quaternary stereocenters, see:

a) M. Sawamura, H. Hamashima, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 8295 – 8296; b) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11 204 – 11 205.

[4] a) For a review of cyclization reactions of nitrile anions, see: F. F. Fleming, B. C. Shook, *Tetrahedron* **2002**, *58*, 1 – 23; b) For a recent example of a catalytic asymmetric acylation process that involves a nitrile anion intermediate, see: D. A. Nicewicz, C. M. Yates, J. S. Johnson, *Angew. Chem.* **2004**, *116*, 2706 – 2709; *Angew. Chem. Int. Ed.* **2004**, *43*, 2652 – 2655.

[5] For early studies of the silylation of nitrile anions, see: a) G. A. Gornowicz, R. West, *J. Am. Chem. Soc.* **1971**, *93*, 1714 – 1720; b) D. S. Watt, *Synth. Commun.* **1974**, *4*, 127 – 132.

[6] A. H. Mermerian, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 4050 – 4051.

[7] We are aware of very few studies of reactions of silyl ketene imines with electrophiles. See: a) P. Cazeau, J.-P. Llonch, F. Simonin-Dabescat, E. Frainnet, *J. Organomet. Chem.* **1976**, *105*, 145 – 156; b) P. Cazeau, J.-P. Llonch, F. Simonin-Dabescat, E. Frainnet, *J. Organomet. Chem.* **1976**, *105*, 157 – 160; c) S. Meier, E.-U. Würthwein, *Chem. Ber.* **1990**, *123*, 2339 – 2347.

[8] For leading references, see: G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542 – 547.

[9] For a few examples of total syntheses that employ such α-cyano carbonyl compounds (wherein the α position is an all-carbon quaternary stereocenter) as intermediates, see: a) F. E. Ziegler, C. A. Metcalf III, A. Nangia, G. Schulte, *J. Am. Chem. Soc.* **1993**, *115*, 2581 – 2589; b) D. G. Batt, N. Takamura, B. Ganem, *J. Am. Chem. Soc.* **1984**, *106*, 3353 – 3354; c) R. V. Stevens, F. C. A. Gaeta, D. S. Lawrence, *J. Am. Chem. Soc.* **1983**, *105*, 7713 – 7719; d) R. M. Coates, S. K. Shah, R. W. Mason, *J. Am. Chem. Soc.* **1982**, *104*, 2198 – 2208.

[10] Notes: a) Solvents such as Et_2O, CH_2Cl_2, and toluene furnish 5–10% lower *ee* values; b) A decrease in reaction temperature results in a decrease in enantioselectivity; c) After an extended reaction time, the *ee* value of the product is unchanged, which is consistent with irreversible C–C bond formation.

[11] If both substituents on the silyl ketene imine are alkyl groups, no acylation is observed under our standard conditions. We believe that the key reactive intermediate in processes catalyzed by **3** is a nitrile anion (intermediate **2** in Scheme 1), the formation of which is facilitated by the presence of an anion-stabilizing aromatic substituent on the silyl ketene imine.

[12] For recent discussions of acylation reactions of nitrile anions, see: a) F. F. Fleming, Z. Zhang, P. Knochel, *Org. Lett.* **2004**, *6*, 501 – 503; b) A. R. Katritzky, A. A. A. Abdel-Fattah, M. Wang, *J. Org. Chem.* **2003**, *68*, 4932 – 4934.

[13] a) J. A. Longstreth in *Clinical Pharmacology*, Dekker, New York, **1993**, pp. 315 – 336; b) *The Merck Index*, *13th ed.*, Merck, Whitehouse Station, **2001**, pp. 1771 – 1772.

[14] For leading references regarding the synthesis of nonracemic verapamil, see: R. M. Bannister, M. H. Brookes, G. R. Evans, R. B. Katz, N. D. Tyrrell, *Org. Process Res. Dev.* **2000**, *4*, 467 – 472.

[15] Use of C_6F_6 rather than 1,2-dichloroethane as the solvent leads to improved enantioselectivity. This solvent effect on *ee* values appears to be general. For example, for the reaction illustrated in entry 1 of Table 2, the product is generated in 90% *ee* when C_6F_6 is employed as the solvent.

[16] Brunner reported a method that furnishes a precursor to verapamil in up to 11% *ee*: H. Brunner, H. Zintl, *Monatsh. Chem.* **1991**, *122*, 841 – 848.

