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Three-Component, Room Temperature Crotylation Catalyzed by Solid-Supported Brønsted Acid: Enantioselective Synthesis of Homoallylic Carbamates

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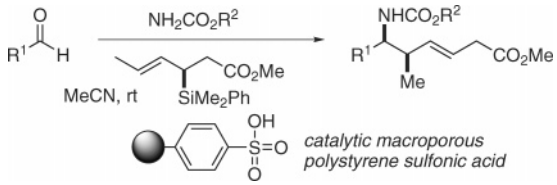
ABSTRACT



A heterogeneous, three-component crotylation of in situ generated *N*-acyl iminium ions has been developed. This reaction proceeds under ambient temperature in MeCN and is catalyzed by macroporous polystyrene-bound sulfonic acid (MP-TsOH). Workup is accomplished by filtration, upon which the catalyst is recoverable. A range of homoallylic amine equivalents have been prepared from the corresponding aldehydes, carbamates, and chiral (*E*)-crotylsilanes in a highly stereoselective manner.

Chiral allyl- and crotylmetal additions to activated C−X π bonds continue to afford the rapid and efficient assembly of synthetic building blocks with increasing structural and stereochemical diversity. Recently we have sought to develop technologies that will streamline the use of our chiral organosilane bond construction methodology. We impose the constraints that such methods would yield useful chiral building blocks with high selectivity in a single step, be stable under ambient temperature, atmosphere, and moisture, produce minimal stoichiometric waste, and require a trivial purification. Reactions of enantioselective additions to imines have attracted the attention of the synthetic community due to the prevalance of medicinally important nitrogen containing compounds.[1] Previous reports from our laboratory have shown that asymmetric chiral (*E*)-crotylsilane additions to in situ generated *N*-tosyl or *N*-acyl iminium ions yield homoallylic carbamates, tosylamines, and pyrrolidines with high selectivity.[2] However, this system was optimized under Lewis acid catalysis, using excess $TiCl_4$ or $BF_3{\cdot}OEt_2$ at low temperatures. The allyl and crotylation of acylhydrazones reported by Leighton[3] accesses homoallylic hydrazides (amine precursors) with useful levels of selectivity. In these examples, preformation of the acylhydrazone is prescribed, and subsequent cleavage of the N−N bond of the hydrazide product may impede its use in the context of parallel synthesis strategies. In that regard, polymer supported organocatalysts have begun to attract attention as convenient, efficient, and environmentally benign promotors of a range

(1) (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438.

(2) (a) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674−2675. (b) Schaus, J. V.; Jain, N. F.; Panek, J. S. *Tetrahedron*. **2000**, *56*, 10263−10274.

(3) (a) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596−9597. (b) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *127*, 2858−2859.

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of useful transformations.[4] For instance, Yamamoto's polystyrene-bound tetrafluorophenylbis(triflyl)methane promotes the addition of allyl TMS to benzaldehyde (Sakurai−Hosomi allylation) in a heterogeneous mixture[5] as well as through a single-pass reaction column.[6] Herein we report a stereoselective crotylation of in situ generated aldimine derivatives catalyzed by macroporous polystyrene-bound sulfonic acid (MP-TsOH). This is a rare example of an allylsilane reagent undergoing addition via Brønsted acid catalysis without intervening protodesilation: high levels of selectivity are achieved even at room temperature. The process results in an operationally simple and economic source of enantioenriched amine precursors that can easily access a range of functionalities due to its multicomponent nature. This work represents a significant operational improvement over our previously reported imine crotylation and a useful application of solid-supported organocatalysis in asymmetric synthesis.

We arrived at our current strategy by considering similar multicomponent catalytic reactions that would proceed at room temperature. Initially, this line of thought led us to examine the use of metal triflates ($M(OTf)_n$) as recyclable, water-stable catalysts of several well-known reactions.[7] Of particular interest was Kobayashi's $Sc(OTf)_3$ catalyzed allylstannylation of aldehydes to yield homoallylic alcohols.[8] Additionally, recent work involving racemic three-component additions of allyl TMS to acyl imines derived from the in situ condensation of aldehydes with benzyl carbamate catalyzed by $Bi(OTf)_3$[9] and $Sc(OTf)_3$[10] invited the development of an asymmetric variant (Figure 1).

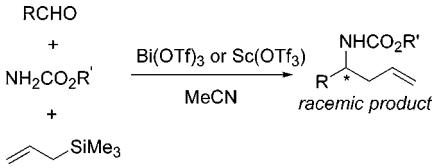
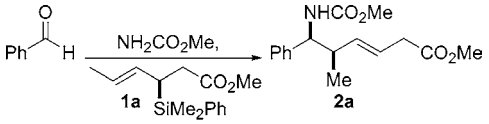


Figure 1. Previous three-component syntheses of homoallylic carbamates under metal trifalte catalysis.

Despite the remarkable efficiency displayed by these catalytic systems, elucidation of the metal triflate−substrate interaction remains a challenge. A recent report[11] describing the in situ formation and allylstannylation of aryl imines has invoked a combined Lewis/Brønsted complex[12] to explain the rate enhancement observed when 1 equiv of benzoic acid is added to 0.02 equiv of $La(OTf)_3$. In another case, TfOH alone has been found to catalyze the allylstannylation of aldehydes in H_2O, though the highest yields were achieved with an excess of acid.[13] We attempted to develop an asymmetric crotylation with $Sc(OTf)_3$, beginning our work with the assumption that the scandium(III) ion was activating the imine in a typical Lewis acid−base interaction. However, given that the initial imine condensation liberates a stoichiometric equivalent of H_2O, we reasoned that subsequent hydrolysis of $Sc(OTf)_3$ and formation of TfOH (which is itself a known catalyst of our [4+2] annulation chemistry[14]) might be the operative catalyst. We compared the results of a pilot experiment under $Sc(OTf)_3$ catalysis to those of the same reaction upon the addition of drying agents ($MgSO_4$ or 4 Å mol sieves) and a poorly chelating amine base (2,6-lutidine) to neutralize any TfOH that may have been liberated (Table 1).[15] Because 4 Å mol sieves and 2,6-lutidine shut down the reaction completely, we were not surprised that TfOH alone was found to be the best catalyst for this system. Accordingly, our evidence supports TfOH (H^+) as the catalytically active species in this crotylation.

Table 1. Asymmetric Crotylation of *N*-Acyl Imines



entry	catalyst	additive	dr syn:anti[a]	% yield of **2a**[b]
1	$Sc(OTf)_3$		>20:1	58
2	$Sc(OTf)_3$	$MgSO_4$ (1 wt equiv)	>20:1	64
3	$Sc(OTf)_3$	4 A M. S. (1 wt equiv)	no conv	
4	$Sc(OTf)_3$	2,6-lutidine (1 equiv)	no conv	
5	TfOH		>20:1	79

[a] Diastereomeric ratios determined by ^1H NMR after removal of silane reagent and unreacted carbamate by SiO_2 chromatography. [b] Yields refer to chromatographically pure material.

Though we were pleased by this outcome, the Brønsted acid TfOH suffers from the same operational difficulties as conventional Lewis acid promoters (instability in air and incompatibility with certain functional groups). Accordingly, we performed a screen of air-stable, solid sulfonic acids ($TsOH\cdot H_2O$ and CSA) in addition to other common and inexpensive proton sources (TFA, $PhCO_2H$, and HCl) (Table 2). Given the success of *p*-$TsOH\cdot H_2O$ in catalyzing the

(4) (a) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401−3429. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4196.

(5) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4077−4079.

(6) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* **2002**, 1296−1298.

(7) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15−27 and references therein.

(8) (a) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1993**, *58*, 6958−6960. (b) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. *Chem. Lett.* **1997**, 831−832.

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(10) Kalita, R. H.; Phukan, P. *Synth. Commun.* **2005**, *35*, 475−481.

(11) Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 323−325.

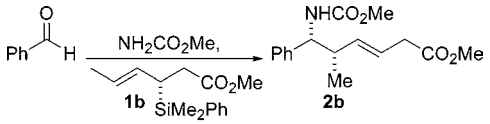
(12) (a) Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron Lett.* **1998**, *39*, 9283−9286. (b) Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 319−321.

(13) Loh, T.; Xu, J. *Tetrahedron Lett.* **1999**, *40*, 2431−2434

(14) Via the in situ condensation of an aldehyde and a secondary TMS ether: (a) Su, Q.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223−1225. (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529−1532. (c) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231−3234.

(15) The use of 1 wt equiv $MgSO_4$ alone did not promote the reaction.

Table 2. Brønsted Acid Screen



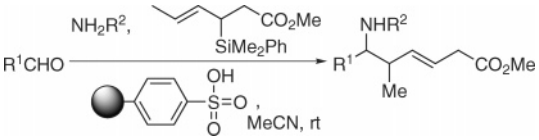
entry	catalyst	dr syn:anti[a]	% yield of **2b**[b]
1	*p*-TsOH·H_2O	>20:1	41
2	CSA	>20:1	22
3	TFA	no conv	
4	$PhCO_2H$	no conv	
5	HCl	no conv	

[a,b] See Table 1.

reaction (Table 2, entry 1), we reasoned that macropourous polystyrene-bound sulfonic acid (MP-TsOH) might also be effective. In addition, the process would be considerably simplified by eliminating the need for basic quench and extractive isolation sequence.[16]

With 35 mol % of MP-TsOH and a reaction time of 24 h (Table 3, entry 1), we were able to surpass the isolated yield

Table 3. Substrate Screen[a]



entry	R^1	(*E*)-crotylsilane	R^2	mol % of MP-TsOH/ time	product (yield,[b] syn:anti[c])
1	Ph	**1a**	CO_2Me	35/24 h	**2a** (75, >20:1)
2	Ph	**1a**	CO_2Et	35/24 h	**2b**(80, >20:1)
3[d]	Ph	**1a**	Cbz	35/24 h	**2c** (73, >20:1)
4[e]	Ph	**1b**	Ts	100/48 h	**2d** (32, >20:1)
5	*m*-$MeOC_6H_4$	**1a**	CO_2Me	35/24 h	**2e** (83, >20:1)
6	*p*-$MeOC_6H_4$	**1a**	CO_2Me	35/24 h	**2f** (78,[f] 4:1)
7	*p*-ClC_6H_4	**1a**	CO_2Me	35/24 h	**2g** (77, >20:1)
8[e]	*p*-BrC_6H_4	**1b**	CO_2Me	35/24 h	**2h** (62, >20:1)
9	Cy	**1a**	CO_2Me	65/24 h	**2i** (57, >20:1)
10	$BnOCH_2$	**1a**	CO_2Me	100/48 h	**2j** (32, >20:1)

[a] Typical reaction proceeded under ambient conditions at 1 M in aldehyde. MP-TsOH (average particle size 67 μm, 4.40 mmol/g) was employed for all entries except 2, 3, and 10 (534 μm, 3.31 mmol/g). Generally, reactions were slower with the larger MP-TsOH beads, presumably due to decreased catalytic surface area. [b] Yields refer to chromatographically pure material. [c] Diastereomeric ratios determined by ^{1}H NMR after removal of silane and unreacted carbamate by SiO_2 chromatography. [d] Concentration of 0.5 M to facilitate dissolution of NH_2Cbz. [e] Concentration of 0.67 M. [f] Mixture of diastereomers.

of the reaction promoted by $Sc(OTf)_3$ (Table 1, entry 1) with a significantly less expensive catalyst for which the workup requires a simple filtration. To investigate substrate compatibility of this three-component reaction, a range of aromatic and aliphatic aldehydes were condensed with methyl, ethyl, benzyl carbamate, and *p*-toluenesulfonamide, followed immediately by crotylation by our reported (*E*)-crotylsilane **1a**.[17] In a typical experiment, aldehyde (1 mmol) was added to a solution of carbamate or sulfonamide (1 mmol) dissolved in 0.5 mL of MeCN in a test tube equipped with a magnetic stirbar.[18] The solution was then treated with MP-TsOH (35 mol %) followed by **1a** or **1b** (1.3 mmol in 0.5 mL of MeCN). The reaction was covered and stirred for 24 h at room temperature. The reaction mixture was then passed through a cotton plug that was rinsed with MeCN (3 × 1 mL). The solution was concentrated followed by a short chromatography (silica, 10 to 30% EtOAc/hexanes) to separate nonpolar silicon-containing elimination products from the homoallylic carbamate or tosylamine. Although less reactive than TfOH, the sheer operational simplicity of the heterogeneous reaction makes it an inviting tool for streamlined synthesis. A substrate screen yielded interesting results, which are summarized in Table 3.

The relative configurations of the products were determined by comparison of the analytical data (^{1}H NMR, ^{13}C NMR, IR, HRMS, and optical rotation) of known compounds **2a**, **2d**, and **2j** to the previously published data.[19] In all but one case (Table 3, entry 6[20]) a single diastereomer was detectable by crude ^{1}H NMR analysis (denoted as >20:1). Compound **2a** was recovered in 89% ee[21] from a batch of **1a** prepared in 97% ee. The stereochemical outcome of the

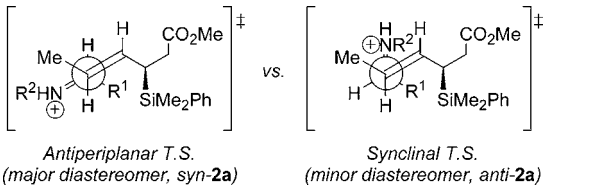


Figure 2. Transition state analysis for major and minor diastereomers.

condensation is rationalized by way of the open transition state[2b] (Figure 2) in which the respective π systems of the activated imine and the (*E*)-crotylsilane adopt an antiperiplanar relationship when viewed down the developing C−C bond. In our experience, facial bias is consistent across a range of substrates.[22]

(16) Basic workup was accomplished with equal efficacy through normal saturated aqueous $NaHCO_3$ quench or by filtration through basic solid-phase extraction cartridges.

(17) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1998**, *75*, 78−88.

(18) Although glassware was oven dried prior to use, all results shown were obtained without Ar or N_2 purge.

(19) As described in ref 2b, relative stereochemical assignment was originally made by ^{1}H NMR coupling constant studies of the oxazolidinone derivatives of such products.

(20) 4-Anisaldehyde is a poor substrate for generating useful levels of diastereoselectivity in crotylsilane additions. See: Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594−6600.

(21) As determined by chiral HPLC analysis (Chiralcel OD), hexanes/*i*-PrOH: 9/1, flow rate of 0.5 mL/min. t_R major = 16.9 min, t_R minor = 31.9 min.

This one-pot reaction provides access to homoallylic amine synthons that are isolated in protected form as carbamates or sulfonamides.[23] It should be possible to extend this methodology to the inclusion of other amine derivatives of attenuated basicity. Although aromatic aldehydes are more reactive than aliphatics, we believe that a useful level of substrate generality has been achieved under these mild conditions.[24] The catalyst recovery is also an improvement over the $Sc(OTf)_3$ reaction, which in our experience requires an aqueous quench and exhaustive organic washings of the aqueous layer, which must then be concentrated and thoroughly dried.

In summary, our initial studies on Brønsted acid catalysis of allylation reactions yielded an MP-TsOH promoted addition of organosilanes to in situ generated aldimine derivatives that shows considerable synthetic potential. Stereoselectivity of the (*E*)-crotylsilane is high at room temperature and atmosphere in this system. Additionally, these chiral reagents have stable shelf lives of years and are trivial to prepare up to 100 g.[25] Application of this multicomponent protocol toward other heteroatom nucleophiles should enable the flexible synthesis of chiral building blocks of greater complexity and elemental composition.[26,27] Additionally, this system opposes the notion that powerful external Lewis acids are necessary for substrate activation in type-II allylmetal addition chemistry.[1b] Further investigation of such room temperature organosilane additions, particularly as they apply to streamlined synthesis strategies, are currently under investigation in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) A synclinal transition state has also been invoked for the formation of the syn product; see ref 2b. For a more complete discussion of the acyclic stereocontrol elements of (*E*)-crotylsilane additions, see: Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1326.

(23) *tert*-Butyl carbamate did not participate in the reaction; only starting material was found by ^{1}H NMR analysis of the crude reaction mixture.

(24) The relatively low isolated yields of entries 4 and 9 are the result of incomplete conversion: unreacted starting materials, rather than decomposition products, were determined by crude ^{1}H NMR analysis.

(25) Preparations of **1a** and **1b** that were stored as neat liquids on the order of 1 year at room temperature were used in this paper and produced results indistinguishable with those of freshly prepared reagents.

(26) Three-component synthesis of homoallylic ethers: (a) Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755−5758. (b) Panek, J. S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790−5792.

(27) Synthesis of homoallylic thioethers: Liu, P.; Binnun, E. D.; Schaus, J. V.; Valentino, N. M.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 1705−1707.