JOC*Note*

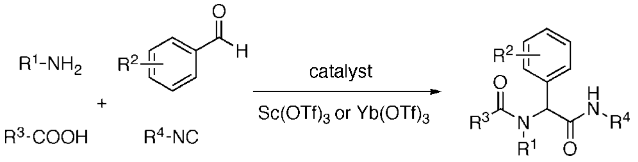
Catalysis of Ugi Four Component Coupling Reactions by Rare Earth Metal Triflates

Babajide O. Okandeji, Jonathan R. Gordon, and
Jason K. Sello*

*Department of Chemistry, Brown University, 324 Brook
Street, Providence, Rhode Island 02912*

jason_sello@brown.edu

Received April 07, 2008

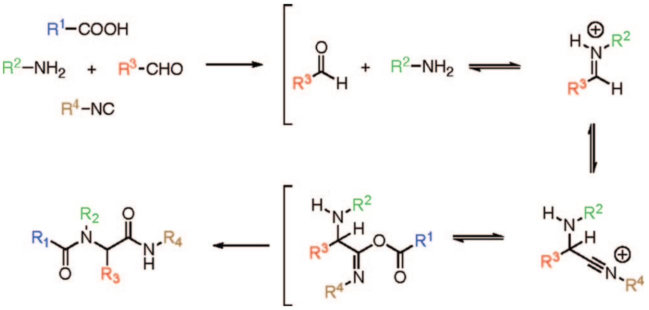


Substoichiometric quantities of scandium and ytterbium triflate increase the yield of Ugi four component coupling reactions of aromatic aldehydes 2- to 7-fold. These rare earth metal triflates enhance the reaction yields primarily via activation of the imine intermediate of this multicomponent reaction.

From a mechanistic perspective, multicomponent reactions are among the most peculiar in organic chemistry. In these reactions, more than two reactants condense with retention of most of their atoms to yield a defined product.[1] In the most preparatively useful multicomponent reactions, a sequence of reversible steps is concluded by an enthalpically driven and irreversible product-forming step.[2] Beyond their mechanistic interest, multicomponent reactions are extensively used in total synthesis, drug discovery, and bioconjugation.[3]

One of the best known multicomponent reactions is the Ugi four component coupling (4CC) reaction (Scheme 1).[2] The substrates for this reaction are an isocyanide, an amine, a carboxylic acid, and either an aldehyde or a ketone. In this reaction, these substrates spontaneously condense to yield an α-acylamino carboxamide. The generally accepted mechanism of the Ugi 4CC reaction involves four elementary steps, the last of which is irreversible.[2] In the first step, the carbonyl compound condenses with an amine to form an imine. Next, the isocyanide adds to the imine to yield a nitrilium ion. Then, a reactive *O*-acylimidate is formed via the α-addition of the carboxylate anion to the nitrilium ion. The fourth and final step is the *O*- to *N*-acyl transfer (Mumm rearrangement) to yield the α-acylamino carboxamide product.

SCHEME 1. Proposed Mechanism of the Ugi Four Component Coupling Reaction



In recent years, there has been much interest in catalysis of isocyanide-based multicomponent reactions.[3,4] Because the Ugi 4CC reaction is generally high yielding (especially in protic solvents like methanol and trifluoroethanol), there has been little interest in catalysis of the Ugi four component reaction. Catalysts for the Ugi 4CC reaction would be valuable in cases where substrates have limited reactivity (e.g., aromatic aldehydes and ketones). Moreover, catalysis is likely to provide the general and much needed strategy that enables asymmetric Ugi 4CC reactions.[5] To the best of our knowledge, there are only two catalysts reported to be useful in Ugi 4CC reactions.[6] First, there are a few examples in which stoichiometric quantities of $ZnCl_2$ are used to both activate and rigidify chiral imines for asymmetric additions of isocyanides.[6a–c] Second, Ciufolini and coworkers reported that $TiCl_4$ is a particularly effective Lewis acid catalyst at 5 mol % for Ugi five center-four component reactions of α-amino acids, aromatic aldehydes, isocyanides, and methanol.[6d] They hypothesized that $TiCl_4$ enhances these reactions by activating the aldehydes for imine formation.

The multistep mechanism of the Ugi 4CC reaction makes it an intriguing and challenging subject for catalysis. Of particular interest is catalytic activation of the reaction's imine intermediate for the addition of the isocyanide. *In situ* Brønsted acid catalysis via protonation of the imine by the carboxylic acid substrate is believed to facilitate the addition of the isocyanide in the Ugi 4CC reaction.[2] A Lewis acid catalyst could activate the imine intermediate in a similar way. Further, a chiral catalyst that activates the imine for isocyanide addition could also provide stereocontrol over this stereogenic step of the Ugi 4CC reaction. In an effort to identify catalysts that could activate the imine intermediate of the Ugi 4CC reaction, we turned our attention to the Lewis-acidic rare earth metals. Rare earth metal triflates, like scandium and ytterbium triflate, are known to catalyze reactions of imines, including allylations, aza Diels–Alder reactions, cyanations, imino-aldol reactions and three-component

---

(1) Zhu, J., Bienayme, H. *Multicomponent Reactions*; Verlag GmbH & Co. KGaA: Weinheim, 2005.

(2) Dömling, A. *Angew. Chem., Intl. Ed.* **2000**, *39*, 3168–3210.

(3) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

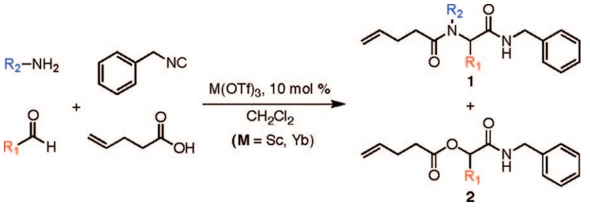
(4) (a) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825. (b) Andreana, P. R.; Liu, C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231. (c) Henkel, B.; Beck, B.; Westner, B.; Mejat, B.; Dömling, A. *Tetrahedron Lett.* **2003**, *44*, 8947. (d) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew.Chem., Int. Ed.* **2008**, *47*, 388–391.

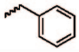
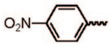
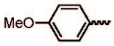
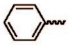
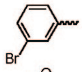
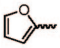
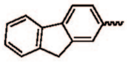
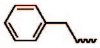
(5) Ramón, D. J.; Yus, M. *Angew. Chem., Intl. Ed.* **2005**, *44*, 1602.

(6) (a) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651–652. (b) Oertel, K.; Zech, G.; Kunz, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1431–4333. (c) Ross, G. F.; Herdtweck, E.; Ugi, I. *Tetrahedron* **2002**, *58*, 6127–6133. (d) Godet, T.; Bonvin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M. A. *Org. Lett.* **2004**, *6*, 3281.

10.1021/jo800745a CCC: $40.75

TABLE 1. Metal Triflate Catalyzed Ugi 4CC Reactions[a]



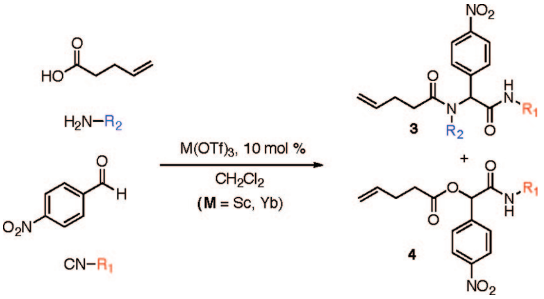
Entry	R_1	Isolated yield (**1**/**2**)					
		R_2: 			R_2: 		
		-	Sc	Yb	-	Sc	Yb
a		13/13	50/14	45/13	20/12	71/10	62/7
b		5/trace	24/trace	22/trace	16/trace	52/trace	49/trace
c		19/0	59/0	46/0	29/0	66/0	55/0
d		15/6	53/5	53/5	28/4	67/trace	66/trace
e		5/0	18/0	15/0	14/0	41/0	27/0
f		8/trace	31/trace	20/trace	27/trace	63/trace	58/4
g		88/trace	81/6	72/12	93/trace	62/12	62/11
h		42/0	38/0	35/0	56/0	38/0	39/0

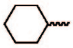
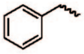
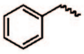
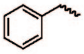
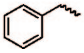
[a] All reactions were performed in CH_2Cl_2 (0.5 M) for 15 h at room temperature, preceded by a 30 min precondensation of the aldehydes and amines.

reactions of aldehydes, amines, and various nucleophiles.[7,8] Several recent reports of chiral scandium (III) complexes that catalyze asymmetric reactions further piqued our interest in rare-earth metal triflates for catalysis of the Ugi 4CC reaction.[9] We report here that $Sc(OTf)_3$ and $Yb(OTf)_3$ are effective catalysts for Ugi 4CC reactions.

In our initial experiments, we explored the efficacy of $Sc(OTf)_3$ and $Yb(OTf)_3$ as catalysts for the reaction of benzyl isocyanide, 4-pentenoic acid, two amines (benzyl amine and *n*-butyl amine) and a variety of aldehydes in CH_2Cl_2.[10] At a 10 mol % catalyst loading,[11] $Sc(OTf)_3$ and $Yb(OTf)_3$ increased the yield of the desired α-acylamino carboxamides (**1**) from 2- to 5-fold (Table 1). In all cases, $Sc(OTf)_3$ proved to be a better promoter than $Yb(OTf)_3$. While the yields of the catalyzed reactions are consistently greater than those of the uncatalyzed reactions, the yields of the catalyzed reactions are modest. In some cases, the modest yield of the desired α-acylamino carboxamides (**1**) is a consequence of the competing Passerini reaction of aldehydes, carboxylic acids, and isocyanides to yield α-acyloxycarboxamides (**2**) (Table 1, entries a and d).[12] However, in all cases, the remainder of material recovered from the reactions was unreacted substrates. The reaction yields may be limited by catalyst coordination to the secondary amine in the product of the isocyanide addition (the nitrilium intermediate), which could interfere with the reaction's *O*- to *N*-acyl shift.[7] This possibility is consistent with our observation that reaction yields are lower at catalyst loadings greater than 10 mol %.[11]

TABLE 2. Metal Catalysis of Ugi 4CC with Various Isocyanides[a]



Entry	R_1	R_2	Isolated yield (**3**/**4**)		
			-	Sc	Yb
a			7/trace	47/trace	42/trace
b			20/12	71/10	62/7
c			10/16	48/13	43/15
d			13/13	50/14	45/18

[a] All reactions were performed in CH_2Cl_2 (0.5 M) for 15 h at room temperature, preceded by a 30 min precondensation of the aldehydes and amines.

In examining the substrate scope of these metal triflate-catalyzed reactions, we note that the catalysts are effective in reactions with aromatic aldehydes. In contrast, $Sc(OTf)_3$ and $Yb(OTf)_3$ suppressed Ugi 4CC reactions with aliphatic aldehydes under these conditions (Table 1, entries g and h). The suppression of these reactions by the metal triflates is again ascribed to inhibitory coordination of the metals to the secondary amine of the nitrilium intermediate.[7]

Whereas the identity of the amine had subtle effects on the degree of catalysis, the identity of the isocyanide component proved more significant in the yields of $Sc(OTf)_3$ and $Yb(OTf)_3$-catalyzed reactions (Table 2). For reasons that are not clear, the influence of the catalysts was significantly higher in the reaction with cyclohexyl isocyanide than with benzyl isocyanide (Table 2, entries a and b).[13]

As Lewis acidic metals, $Sc(OTf)_3$ and $Yb(OTf)_3$ can be expected to activate the aldehyde for imine formation and the imine for addition of the isocyanide in the Ugi 4CC reaction. We performed a series of experiments to determine which mode

---

(7) Kobayshi, S. *Eur. J. Org. Chem.* **1999**, *1*, 15–27.

(8) (a) Scandium triflate has also been used to catalyze a number of other isocyanide-based multicomponent reactions Keung, W.; Bakir, F.; Patron, A. P.; Rogers, D.; Priest, C. D. *Tetrahedron Lett.* **2004**, *45*, 733. (b) Ireland, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369. (c) Schwerkoske, J.; Masquelin, T.; Perun, T.; Hulme, C. *Tetrahedron Lett.* **2005**, *46*, 8355.

(9) (a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (b) Fukuzawa, S.; Komuro, Y.; Nakano, N.; Obara, S. *Tetrahedron Lett.* **2003**, *44*, 3671. (c) Schneider, C.; Sreekanth, A. R.; Mai, E. *Angew. Chem., Int. Ed.* **2004**, *42*, 5691. (d) Kobayashi, S.; Hachiya, I; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535.

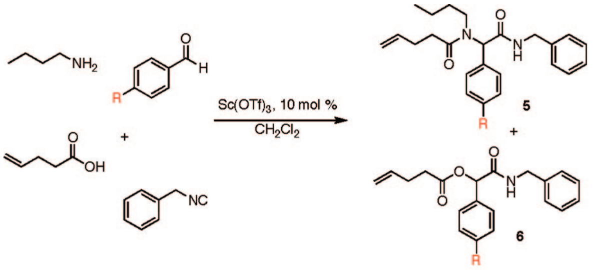
(10) $Sc(OTf)_3$ and $Yb(OTf)_3$ facilitate unproductive reaction of aldehydes with nucleophilic solvents like methanol and trifluoroethanol.

(11) A survey of catalyst loadings revealed that 10 mol% is optimal (see Supporting Information).

(12) In separate experiments, it was found that $Sc(OTf)_3$ and $Yb(OTf)_3$ did not catalyze the Passerini reaction at 0.5 M in CH_2Cl_2.

(13) Cyclohexylisocyanide is reported to be slightly more reactive than benzyl isocyanide in Ugi 4CC reactions: Portal, C.; Launay, D.; Merritt, A.; Bradley, M. *J. Comb. Chem.* **2005**, *7*, 554.

TABLE 3. Evidence for Imine Activation by Sc(OTf)$_3$ in Ugi 4CC Reactions[a]



		Isolated Yield (**5/6**)			
		R: ∿H		R: ∿NO$_2$	
Entry	Conditions	-	Sc	-	Sc
a	30 min. precondensation	19/0	59/0	13/13	50/14
b	3 h. precondensation with Sc(OTf)$_3$	16/0	58/0	12/14	50/11
c	3 h. precondensation followed by Sc(OTf)$_3$ addition		55/0		46/8

[a] All reactions were performed in CH$_2$Cl$_2$ at 0.5 M for 15 h at room temperature.

of activation was relevant in the enhanced yields of the metal-catalyzed reactions. Initially, we used ^{1}H NMR to establish that condensation of *n*-butyl amine with either *p*-nitrobenzaldehyde or benzaldehyde to form an imine is complete within 1 h in the absence of the Sc(OTf)$_3$.[14] Accordingly, we observed that condensation of these aldehydes and *n*-butyl amine for 3 h prior to the addition of the 4-pentenoic acid and benzyl isocyanide had no influence on the yield of the Ugi 4CC reactions (Table 3).[15] These observations suggest that under these conditions imine formation is rapid, but the addition of the isocyanide to the imine is relatively slow. Because imine formation is rapid in the absence of Sc(OTf)$_3$ and the timing of Sc(OTf)$_3$ addition had little influence over the degree to which the reaction yields were enhanced (Table 3, entries b and c), we propose that in the present case imine activation by Sc(OTf)$_3$ is primarily responsible for its enhancement of Ugi 4CC reaction yields.

In summary, catalytic quantities of Sc(OTf)$_3$ and Yb(OTf)$_3$ catalyze the Ugi four component coupling reactions. These rare earth metal triflates most likely enhance the yield of this reaction via activation of its imine intermediate. The apparent mechanism of catalysis, the remarkable differences in yield between the uncatalyzed and catalyzed reactions, and the availability of chiral Sc(III) complexes bode well for realization of catalytic asymmetric Ugi 4CC reactions. Studies toward this goal are in progress.

Experimental Section

General Procedure for the Ugi 4CC Reactions. The amine (0.25 mmol, 1 equiv), aldehyde (0.25 mmol, 1 equiv) and metal triflate (0.025 mmol, 0.1 equiv) were added to 400 μL of CH$_2$Cl$_2$ in a 1/2 dram glass vial and mixed for 30 min by rotation. The isocyanide (0.2375 mmol, 0.95 equiv) and the carboxylic acid (0.25 mmol, 1 equiv) were added and the resulting solution (0.5 M) was allowed to rotate for 15 h. The solution was diluted to 2 mL with CH$_2$Cl$_2$ and washed six times with 2 mL of a saturated NaHCO$_3$ solution. The organic layer was dried over MgSO$_4$, and the reaction products were purified by flash column chromatography.

Isolation and characterization of compound **1a**−**i** (Table 1). Flash chromatography conditions: CH$_2$Cl$_2$ until isocyanide and aldehyde eluted then 20:1 (CH$_2$Cl$_2$:ethyl acetate). ^{1}H NMR (400 MHz; CDCl$_3$): δ 8.20 (d, J = 8.8, 2H), 7.56 (d, J = 8.6, 2H), 7.36−7.24 (m, 5H), 6.84 (br, 1H), 5.88−5.79 (m, 2H), 4.48 (d, J = 5.7, 2H), 3.36 (t, J = 7.8, 2H), 2.54−2.50 (m, 2H), 2.45−2.39 (m, 2H), 1.54−1.48 (m, 1H), 1.26−1.14 (m, 3H), 0.83 (t, J = 7.1, 3H).^{13}C NMR (101 MHz; CDCl$_3$): δ 173.7, 169.0, 147.5, 143.2, 137.8, 136.93 129.6, 128.7, 127.7, 127.5, 123.6, 115.7, 62.2, 47.6, 43.7, 32.7, 31.9, 29.2, 20.0, 13.6. LRMS: calcd 423.5 for $C_{24}H_{29}N_3O_4$, observed 446 [M + Na]$^+$.

Acknowledgment. We thank Dr. Tun-Li Shen for mass spectrometric analyses. This work was generously supported by funds from Brown University and a Career Award at the Scientific Interface from the Burroughs Wellcome Fund to J.K.S.

Supporting Information Available: Detailed experimental procedures, compound characterization data, spectra, and expanded discussion of peripheral findings. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800745A

---

(14) We observed that the imine formation within minutes of mixing the aldehydes and *n*-butyl amine at 0.5 M in CDCl$_3$. Sc(OTf)$_3$ enhanced the rate of imine formation under these conditions. See Supporting Information.

(15) Precondensation of the aldehyde and the imine is reported to improve the yield of Ugi 4CC reactions. See ref 2.