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Direct Catalytic Asymmetric Mannich-Type Reactions of γ-Butenolides: Effectiveness of Brønsted Acid in Chiral Metal Catalysis

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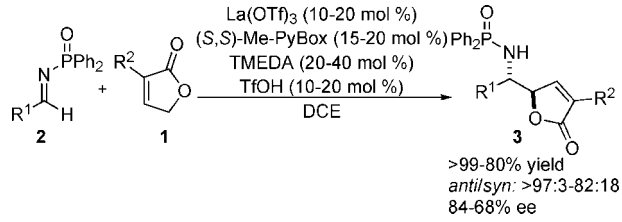
ABSTRACT



Direct catalytic asymmetric Mannich-type reactions of γ-butenolides are described. A chiral Lewis acid/amine base/Brønsted acid combination was used to catalyze a γ-addition of γ-butenolides to *N*-diphenylphosphinoyl imines, affording the products in up to >99% yield, *anti*/*syn* = >97:3, and 84% ee. The use of a catalytic amount of TfOH in addition to La(OTf)$_3$/Me-PyBox/TMEDA was important for improving yield and stereoselectivity.

Catalytic asymmetric Mannich(-type) reactions of aldehydes, ketones, esters, and other donors directed toward the synthesis of β-amino carbonyl compounds have been intensively investigated over the past decade.[1] In contrast, vinylogous asymmetric Mannich-type reactions affording useful chiral δ-amino carbonyl compounds are not as well studied.[2–4] γ-Butenolides and related compounds are important donors for asymmetric vinylogous Mannich(-type) reactions, because the γ-butenolide skeleton appears in many natural products.[5] Only a few asymmetric vinylogous Mannich-type reactions of preformed siloxyfurans, affording Mannich-adducts in high enantioselectivity, have been reported to date.[4] A highly enantioselective aza-Friedel−Crafts reaction with methoxyfuran as a nucleophile has also been reported, but additional oxidation was required to convert the aza-Friedel−Crafts product to γ-butenolide.[6] There are no reports on the direct use of γ-butenolides themselves[7] in

(1) For reviews, see: (a) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis, Supplement I*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 2003;Chapter 29.5. (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

(2) For reviews of vinylogous Mannich-type reactions, see: (a) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.

(3) Catalytic asymmetric γ-selective (vinylogous) Mannich-type reactions: For direct reactions see: (a) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878. (b) Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 1620. For Mukaiyama-type reaction see: (c) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631.

(4) For asymmetric vinylogous Mannich-type reactions of siloxyfurans, see: (a) Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949. (b) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230.

(5) Catalytic asymmetric synthesis of functionalized γ-butenolide skeleton: For a review, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. For selected examples, see: (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (c) Szlosek, M.; Figadère, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1799. (d) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 8. (e) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (f) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203. (g) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. See also ref 7.

(6) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.

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catalytic asymmetric Mannich(-type) reactions,[8] which is a potentially more straightforward and atom-economical process. Here we describe the utility of a chiral Lewis acid/amine base/Brønsted acid combination in direct catalytic asymmetric Mannich-type reactions of γ-butenolides **1** and *N*-diphenylphosphinoyl imines **2**, affording the products in up to >99% yield, *anti*/*syn* = >97:3, and 84% ee. The use of a catalytic amount of TfOH in addition to La(OTf)$_3$/Me-PyBox/TMEDA (Figure 1) was important for improving yield and stereoselectivity.

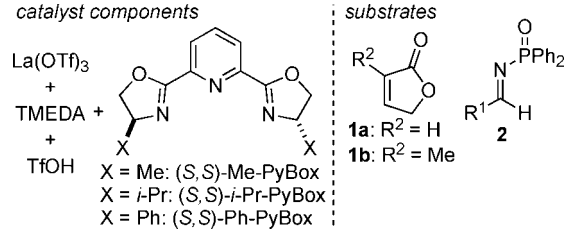
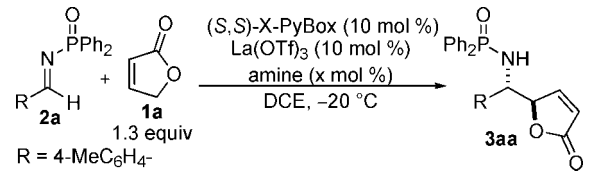


Figure 1. Catalyst components and structures of γ-butenolide donors **1** and *N*-diphenylphosphinoyl imines **2**.

Although the pK_a values of γ-butenolides are low enough for in situ generation of dienolate,[9] other obstacles must be overcome to achieve the desired Mannich-type reactions of imines with γ-butenolide donors. (1) Both γ-butenolides themselves and the γ-butenolide units in Mannich-adducts have high reactivity as *electrophiles*,[10] and serve as conjugate addition acceptors to give undesirable side products. Therefore, selective activation of γ-butenolides as donors and imines as electrophiles is required. (2) The enantioselectivity, diastereoselectivity, and α/γ-selectivity of dienolate must be controlled.

In the initial screening, various chiral metal aryloxide catalysts developed for direct Mannich-type reactions of other donors in our group[11] produced unsatisfactory results. Additional studies revealed that a La(OTf)$_3$/PyBox/amine base combination[12–14] was promising for the direct Mannich-type reaction of γ-crotonolactone (**1a**) and *N*-diphenylphosphinoyl imine[15] **2a**. The optimization studies are summarized in Tables 1 and 2. The combined use of La(OTf)$_3$/Me-PyBox/

Table 1. Conditions Screening



entry	(*S*,*S*)-PyBox	amine (mol %)	time (h)	yield (%)	*anti*/*syn*[a]	% ee[b] (*anti*)
1	Me-PyBox	Et_3N (20)	35	53	81:19	1
2	Me-PyBox	Et_3N (40)	35	62	82:18	10
3	Me-PyBox	none	24	NR		
4	Me-PyBox	pyridine (20)	24	NR		
5	Me-PyBox	DBU (20)	35	0		
6	Me-PyBox	TMEDA (20)	35	56	93:7	66
7	*i*-Pr-PyBox	TMEDA (20)	39	17	70:30	11
8	Ph-PyBox	TMEDA (20)	35	8	60:40	2

[a] Determined by crude ^{1}H NMR analysis. [b] Determined by chiral HPLC analysis.

Et_3N in 1,2-dichloroethane (DCE) at −20 °C afforded γ-addition product **3aa** in 53% yield, albeit in poor enantioselectivity and modest diastereoselectivity (Table 1, entries 1 and 2).[16] No reaction proceeded without an amine base (entry 3) or with pyridine (entry 4). On the other hand, imine **2a** was consumed completely with DBU, but desired product **3aa** was not obtained. Complex mixtures of side products

(7) Direct use of γ-butenolides in racemic aldol reactions was reported: (a) Franck, X.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 1449. (b) Sarma, K. D.; Zhang, J.; Curran, T. T. *J. Org. Chem.* **2007**, *72*, 3311.

(8) For recent reviews on direct catalytic Mannich(-type) reactions affording β-amino carbonyl compounds, see: (a) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348. (b) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089. (c) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. (d) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797.

(9) The pK_a value of γ-crotonolactone (**1a**) was estimated to be 17.7 in DMSO. Calculations were performed by using the B3LYP level of the density functional theory. See the Supporting Information for details.

(10) For example, treatment of **1a** with La(OTf)$_3$, Me-PyBox, and Et_3N in the absence of imine **2a** gave oligomers of **1a**.

(11) (a) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. J. *Am. Chem. Soc.* **2007**, *129*, 9588. (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (c) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365. (d) Yamaguchi, A.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 3387. (e) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. (f) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.

(12) Rare earth-PyBox complexes in asymmetric catalysis: For a review, see: (a) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119. (b) For selected examples, see: Keith, J. M.; Jacobsen, E. N. *Org. Lett.* **2004**, *6*, 153. (c) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. (d) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029. (e) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351. (f) Aspinall, H. C.; Bickley, J. F.; Greeves, N.; Kelly, R. V.; Smith, P. M. *Organometallics* **2005**, *24*, 3458. (g) Comelles, J.; Pericas, A.; Moreno-Manas, M.; Vallribera, A.; Drudis-Sole, G.; Lledos, A.; Parella, T.; Roglans, A.; Garcia-Granda, S.; Roces-Fernandez, L. *J. Org. Chem.* **2007**, *72*, 2077. (h) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem. Eur. J.* **2007**, *13*, 9478.

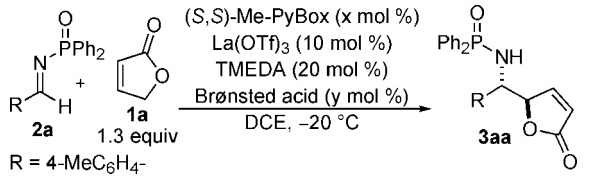
(13) Combination of metal triflate and amine base in asymmetric catalysis: For reviews, see: (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. (b) Kanemasa, S.; Ito, K. *Eur. J. Org. Chem.* **2004**, 4741. For selected examples, see: (c) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (d) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979. (e) Itoh, K.; Oderaotoshi, Y.; Kanemasa, S. *Tetrahedron: Asymmetry* **2003**, *14*, 635. (f) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (g) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (h) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760. (i) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Commun.* **2000**, 2211. (j) Gathergood, N.; Juhl, K.; Poulsen, T. B.; Thordrup, K.; Jørgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 1077. (k) Kjærsgaard, A.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 804. (l) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117. (m) Tur, F.; Saa, J. M. *Org. Lett.* **2007**, *9*, 5079.

(14) Other metal triflates gave less satisfactory results. No reaction proceeded with Cu(OTf)$_2$, In(OTf)$_3$, and Zn(OTf)$_2$. Some of other rare earth metal triflates promoted the reaction of imine **2a** with donor **1a**, but enantioselectivity was lower than La(OTf)$_3$ or comparable to La(OTf)$_3$.

(15) Weinreb, A. M.; Orr, R. K. *Synthesis* **2005**, 1205.

(16) Stereochemistry was determined by conversion to known compounds. See the Supporting Information for details.

Table 2. Conditions Screening



entry	Brønsted acid (mol %)	Me-PyBox (mol %)	time (h)	yield (%)	*anti*/*syn*[a]	% ee[b] (*anti*)
1	none	10	35	56	93:7	66
2	PMPOH[c] (10)	10	35	16	76:24	40
3	AcOH (10)	10	35	81	52:48	65
4	MsOH (10)	10	35	43	88:12	68
5	TfOH (10)	10	39	86	96:4	79
6	TfOH (15)	10	24	22	97:3	85
7	TfOH (10)	15	72	89	96:4	84
8[d]	TfOH (10)	10	39	NR		

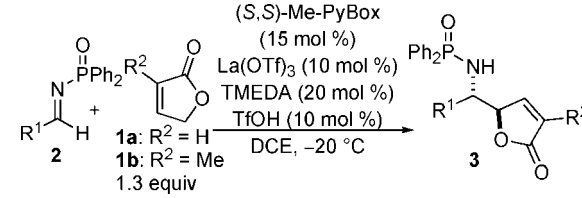
[a] Determined by crude ^{1}H NMR analysis. [b] Determined by chiral HPLC analysis. [c] 4-MeOC$_6$H$_4$OH. [d] Without La(OTf)$_3$.

were observed, possibly due to undesirable conjugate additions to γ-butenolide units (entry 5). TMEDA was the most promising in terms of diastereo- and enantioselectivity (*anti*/*syn* = 93:7 and 66% ee), giving **3aa** in 56% yield (entry 6). PyBox ligands with bulkier substituents than those in the Me-PyBox, such as *i*-Pr-PyBox and Ph-PyBox, afforded **3aa** in low yield and stereoselectivity (entries 7 and 8).

At the beginning of the initial screening, the reactions had low reproducibility. For example, the conditions of entry 5 in Table 1 afforded **3aa** in variable yield (38−76%) and enantioselectivity (44−79% ee). Detailed studies to overcome the reproducibility problem revealed that a small amount of TfOH contaminated in La(OTf)$_3$ was important. Therefore, La(OTf)$_3$ was carefully flame-dried under reduced pressure to remove TfOH prior to use in all experiments described in this paper to obtain good reproducibility, and the accurate amount of Brønsted acid was added in Table 2. The effects of additional Brønsted acid are shown in Table 2. The addition of 10 mol % of 4-MeOC$_6$H$_4$OH to a mixture of La(OTf)$_3$/Me-PyBox/TMEDA = 1:1:2 (La = 10 mol %) had adverse effects on both reactivity and stereoselectivity (entry 2). An AcOH additive afforded **3aa** in 81% yield, but the diastereoselectivity was low (*anti*/*syn* = 52:48, entry 3). MsOH diminished the yield and diastereoselectivity, although the enantioselectivity was comparable to that of entry 1 (entry 4). Among Brønsted acids investigated, TfOH was the best, giving 86% yield and 79% ee (entry 5). Increasing TfOH loading to 15 mol % gave **3aa** in 85% ee, albeit in poor yield (entry 6). 15 mol % of Me-PyBox in the presence of 10 mol % of TfOH gave **3aa** in 89% yield, *anti*/*syn* = 96:4, and 84% ee (entry 7). No reaction proceeded in the absence of La(OTf)$_3$, implying that neither Me-PyBox/TfOH nor TMEDA/TfOH is an effective catalyst species in the present system (entry 8).

Substrate scopes and limitations were investigated under the optimized reaction conditions (Table 3). Nonisomerizable

Table 3. Direct Catalytic Asymmetric Mannich-Type Reactions of γ-Butenolides **1** and Imines **2**



entry	R^1	**2**	**1**	time (h)	yield[a] (%)	**3**	*anti*/*syn*[b]	% ee[c] (*anti*)
1	Ph	**2b**	**1a**	72	83	**3ba**	96:4	83
2	4-MeC$_6$H$_4$−	**2a**	**1a**	72	89	**3aa**	96:4	84
3	2-MeC$_6$H$_4$−	**2c**	**1a**	69	85	**3ca**	91:9	79
4	4-MeOC$_6$H$_4$−	**2d**	**1a**	69	80	**3da**	96:4	83
5	4-ClC$_6$H$_4$−	**2e**	**1a**	45	99	**3ea**	95:5	83
6	2-thienyl	**2f**	**1a**	50	>99	**3fa**	97:3	84
7[d]	(CH$_3$)$_2$CHCH$_2$−	**2g**	**1a**	31	84	**3ga**	86:14	78
8[d]	CH$_3$(CH$_2$)$_3$−	**2h**	**1a**	43	86	**3ha**	82:18	72
9[e]	Ph	**2b**	**1b**	62	82	**3bb**	>97:3	68

[a] Isolated yield after column chromatography. [b] Determined by crude ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis. [d] 2.5 equiv of **1a** was used. [e] Reaction was performed at rt. 20 mol % of La(OTf)$_3$, (*S*,*S*)-Me-PyBox, TfOH, and 40 mol % of TMEDA were used.

aryl imines **2a**−**e** with various substituents on the aromatic ring, as well as heteroaryl imine **2f**, gave Mannich adducts in >99−80% yield, 97:3−91:9 *anti*-selectivity, and 84−79% ee (entries 1−6). Imine **2c** with ortho-substituent **3ca** somewhat diminished both the diastereo- and enantioselectivity (*anti*/*syn* = 91:9, 79% ee, entry 3). It is noteworthy that readily isomerizable alkyl imines **2g** and **2h**[17] were also applicable, giving **3ga** and **3ha** in 84% and 86% yield, respectively. Enantio- and diastereoselectivity, however, both had room for improvement (entries 7 and 8). A Mannich-type reaction of 3-methyl-(*5H*)-furan-2-one (**1b**) was performed at room temperature because no reaction proceeded at −20 or 0 °C (entry 9). With donor **1b**, 20 mol % of La(OTf)$_3$ was required for good yield and moderate enantioselectivity (entry 9).

In the present reaction, the catalytic amount of TfOH was key to achieving the optimized enantioselectivity. To glean insight on the role of TfOH, we obtained ^{1}H NMR spectra of the La(OTf)$_3$/Me-PyBox/TMEDA mixture at a ratio of 1:1:2 in CDCl$_3$ with and without TfOH (Figure 2). In the absence of TfOH, metal-free Me-PyBox was the major constituent and Me-PyBox complexed with La metal was the minor constituent (Figure 2A), suggesting that (tmeda)$_2$La(OTf)$_3$ would be the major La species. In the presence of TfOH, the ratio of metal-free Me-PyBox/metal-bound Me-PyBox changed, and Me-PyBox complexed with La metal was observed as the major species (Figure 2B). We speculate that La(OTf)$_3$/Me-PyBox/TMEDA = 1:1:1 would be the active species[18,19] in the present reaction, and

(17) For synthesis of alkyl *N*-diphenylphosphinoyl imines, see: (a) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (b) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 3985.

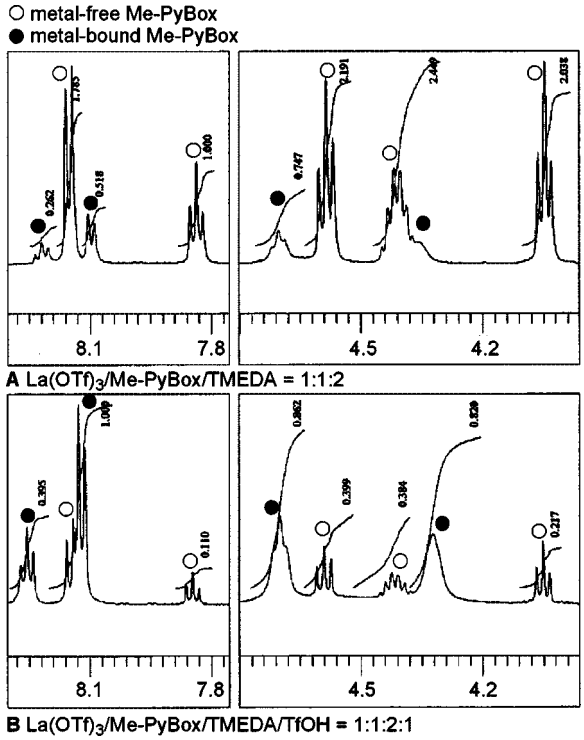


Figure 2. ^{1}H NMR spectra of La(OTf)$_3$/Me-PyBox/TMEDA mixture (A) without TfOH and (B) with TfOH [3.95−4.80 and 7.75−8.20 ppm regions].

that TfOH would support the generation of the desirable active species. In the reaction without TfOH, a racemic reaction promoted by the predominant (tmeda)$_2$La(OTf)$_3$ complex[20] competed with the enantioselective reaction promoted by a minor chiral La complex, resulting in only moderate yield and enantioselectivity (Table 2, entry 1). Reducing (tmeda)$_2$La(OTf)$_3$ by the addition of TfOH improved both the yield and enantioselectivity (Table 2, entry 5). 15 mol % of Me-PyBox gave better enantioselectivity than 10 mol % of Me-PyBox (Table 2, entry 7 vs entry 5), possibly due to the decreased amount of undesirable (tmeda)$_2$La(OTf)$_3$ in the presence of a slight excess of Me-PyBox. (Table 2, entry 7).

The postulated catalytic cycle is shown in Figure 3. TMEDA/TfOH would deprotonate γ-butenolide **1**, which is

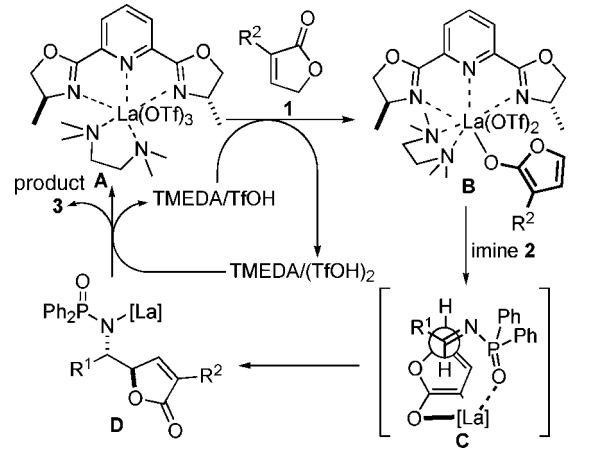


Figure 3. The postulated catalytic cycle of the Mannich-type reaction.

activated by Lewis acidic (pybox)(tmeda)La(OTf)$_3$ **A** to give La-dienolate **B** and TMEDA/(TfOH)$_2$. **B** would react with imine **2** to give **D** via transition state **C** to minimize steric repulsion. **D** would be protonated by TMEDA/(TfOH)$_2$ to give product **3** and regenerate complex **A**.

In conclusion, we developed direct catalytic asymmetric Mannich-type reactions of γ-butenolides using a chiral Lewis acid/amine base/Brønsted acid combination. La(OTf)$_3$/Me-PyBox/TMEDA/TfOH afforded Mannich adducts **3** in up to >99% yield, *anti*/*syn* = >97:3, and 84% ee. The addition of TfOH was important for achieving good yield and stereoselectivity. Further investigations on extending Lewis acid/amine base/Brønsted acid combinations to other catalytic enantioselective reactions are ongoing.

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Supporting Information Available: Experimental procedures, spectral data of products, NMR charts of catalyst mixtures, and determination of stereochemistry of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) We speculate that the active catalyst may contain TMEDA as a ligand, because enantioselectivity strongly depended on amines in Table 1.

(19) La(OTf)$_3$/Me-PyBox/TMEDA = 1:1:1 without TfOH (La = 10 mol %) gave **3aa** in 56% yield, *anti*/*syn* = 93:7, and 73% ee from **2a** and **1a**. Thus, the use of TfOH is essential to obtain optimum results.

(20) La(OTf)$_3$/TMEDA = 1:2 (La = 10 mol %, without Me-PyBox) with and without 10 mol % of TfOH catalyzed the Mannich-type reaction of imine **2a** and donor **1a**, affording **3aa** in 15% yield (35 h, *anti*/*syn* = 84:16, without TfOH) and 18% yield (35 h, *anti*/*syn* = 94:6, with TfOH).