Enantioselective Catalysis

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Dual Catalysis: A Combined Enantioselective Brønsted Acid and Metal-Catalyzed Reaction—Metal Catalysis with Chiral Counterions**

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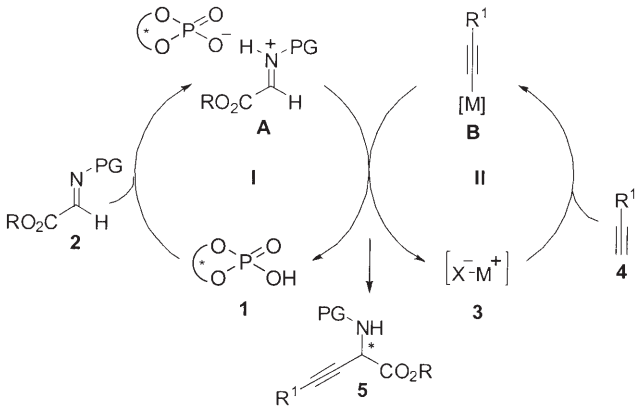
The application of chiral Brønsted acids in asymmetric organocatalysis is continuously increasing.[1–3] Various highly enantioselective, metal-free reactions have been developed, most of which are based on the activation of the electrophile through protonation to form a chiral ion pair. Different nucleophiles have been added to aldemines and ketoimines in an enantioselective fashion by using this approach.[2,3] We were able to demonstrate that the electrophile and nucleophile could be simultaneously activated in a combined process catalyzed by two Brønsted acids. This led to the development of the first enantioselective Mannich and Mannich–Michael reactions catalyzed directly by Brønsted acids.[2g–i] More recently, we developed the first activation of "pure" carbonyl compounds catalyzed by a chiral Brønsted acid which resulted in the first organocatalytic, enantioselective Nazarov cyclization.[2k] We now present a new dual catalysis procedure, which comprises a combined and cooperative enantioselective Brønsted acid and a metal-catalyzed alkynylation.

The enantioselective addition of organometallic compounds to imines is one of the most important reactions for the preparation of chiral amines.[4] This is also valid for the alkynylations of nitrones, enamines, and aldemines, which afford the corresponding propagylamines.[5,6] Although various metal-catalyzed, enantioselective alkyne additions to imines have been reported, the enantioselective alkynylation of α-imino esters has been neglected, even though the resulting amino acids are of great biological interest.[5l] This may be due to the basic reaction conditions employed, which often lead to racemization and loss of enantioselectivity.

In this context we decided to examine the alkynylation of α-imino esters catalyzed by a Brønsted acid. Based on our earlier work[2] on asymmetric ion pair catalysis we wondered whether the combination of a chiral Brønsted acid catalyst and a metal catalyst would lead to the valuable α-alkynylated amino acids. Our new concept is based on two parallel catalytic cycles **I** and **II**, in which the activation of the electrophile **2** by a chiral Brønsted acid (**1**) catalyst and the activation of the nucleophile **4** by a metal salt (**3**) proceed simultaneously (Scheme 1). This approach should lead to the formation of an intermediary chiral ion pair **A** and an achiral metal complex **B**, which after subsequent reaction give the desired amino acid **5** and the regenerated catalysts.



Scheme 1. Combined enantioselective Brønsted acid and metal-catalyzed alkynylation of α-imino esters. PG = protecting group.

In previous work we demonstrated that chiral binol hydrogen phosphates **1** (binol = 1,1′-bi-2-naphthyl) are excellent Brønsted acid catalysts for chiral ion-pair catalysis. Therefore, we decided to initially use these as chiral catalysts for the activation of the α-imino esters **2** (catalysis cycle **I**). As a metal salt (**3**) for the activation of the alkyne **4** (catalysis cycle **II**) we used silver salts, as earlier studies demonstrated that alkynyl–silver derivatives are stable in protic media and hydrolysis can only be achieved in the presence of strong acids, such as hydrochloric acid or trifluoromethane sulfonic acid.[7]

Hence, we carried out the first enantioselective alkynylations of α-imino ester **2a** with phenylacetylene (**4a**) in the presence of 5 mol% silver acetate[8] and different binol phosphates **1a–i** or triflylphosphoramides **1j/k** (5–10 mol%, Table 1). From this survey, the best enantiomeric ratios for amino acid **5a** were obtained when binol phosphates **1g** and **1i** were used (e.r. 91:9; Table 1, entries 8 and 10). The use of the corresponding triflylphosphoramides **1j** and **1k** resulted in considerably lower selectivity (Table 1, entries 11 and 12).

In further experiments, the solvent as well as the protecting group were varied (Table 2). The combined Brønsted acid and silver-catalyzed alkyne addition can be performed in different aromatic and halogenated solvents (Table 2, entries 1–6), with the best selectivities being obtained when toluene was used (Table 2, entry 2). Varying the protecting group and the use of sterically more demanding residues in

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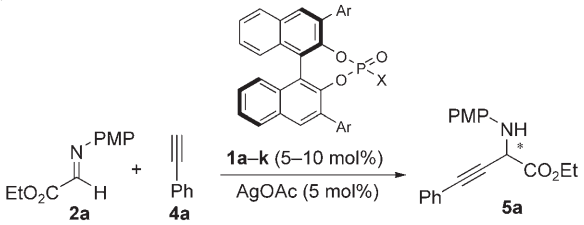
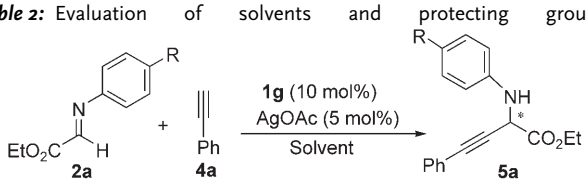
Table 1: Chiral Brønsted acids in the enantioselective silver-catalyzed alkyne addition.



Entry[a]	1	Ar	X	1 [mol%]	e.r.[b]
1	**1a**	phenyl[c]	OH	10	57:14
2	**1b**	4-biphenyl	OH	5	55:45
3	**1c**	1-naphthyl[c]	OH	10	55:45
4	**1d**	2-naphthyl	OH	10	54:46
5	**1e**	3,5-$(CF_3)_2$-C_6H_3	OH	5	62:38
6	**1f**	3,5-tBu$_2$-PMP	OH	5	49:51
7	**1g**	9-phenanthryl	OH	5	86:14
8	**1g**	9-phenanthryl	OH	10	91:9
9	**1h**	$[H]_8Ph_3Si$	OH	5	69:31
10	**1i**	9-anthracenyl	OH	10	91:9
11	**1j**	9-phenanthryl[d]	NHTf	10	41:59
12	**1k**	9-anthracenyl[d]	NHTf	10	31:69

[a] Reaction conditions: **2a**, **4a**, 5–10 mol% **1**, 5 mol% AgOAc at room temperature in toluene. [b] Enantioselectivities were determined by HPLC analysis. [c] Reaction performed at 45°C. [d] In $CHCl_3$. PMP = *p*-methoxyphenyl, Tf = triflate, $[H]_8Ph_3Si$ = (R)-3,3′-bis(triphenylsilyl)octahydrobinol phosphate.

Table 2: Evaluation of solvents and protecting groups.



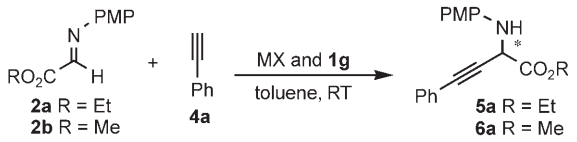
Entry[a]	Solvent	R	e.r.[b]
1	benzene	OMe	86:14
2	toluene	OMe	91:9
3	p-xylene	OMe	84:16
4	CH_2Cl_2	OMe	76:24
5	$CHCl_3$	OMe	53:47
6	$(n$Bu$)_2O$	OMe	73:27
7	toluene	OEt	82:18
8	toluene	Opentyl	88:12
9	toluene	OCF_3	58:42
10	toluene	OPh	76:24

[a] Reaction conditions: **2a**, **4a** 10 mol% **1g**, 5 mol% AgOAc at room temperature. [b] Enantioselectivities were determined by HPLC analysis.

the 4-position resulted in lower enantiomeric ratios (Table 2, entries 7–10).

Having established the best conditions with respect to the solvents, temperature, protecting group, and chiral Brønsted acids, we decided to further optimize the reaction by examining different metal salts and catalyst loadings (Table 3). While the alkynylation could be successfully performed with various silver salts (Table 3, entries 7–14) as well as copper salts (Table 3, entries 15 and 16), the combination of 5 mol% silver acetate and 10 mol% **1g** gave **5a** with an enantiomeric ratio of 91:9 (Table 3, entry 5)[9] The use of larger or smaller amounts of Brønsted acid **1g** resulted in a loss of enantioselectivity (Table 3, entries 3, 4, and 7). No product formation was observed if only Brønsted acid **1g** or the silver acetate were used (Table 3, entries 1 and 2). Copper acetates could also be employed, however the reactivities were considerably reduced compared with the silver salts (Table 3, entries 15 and 16). The best enantiomeric ratios (e.r. 94:6) were obtained by changing to the α-imino methyl ester **2b** in the presence of **1g** and silver acetate (Table 3, entry 6). We examined a variety of aryl-substituted alkynes in the combined catalysis procedure under these optimized conditions. In general the amino acid products **6a–h** were obtained in good yields and enantiomeric ratios (Table 4).[10]

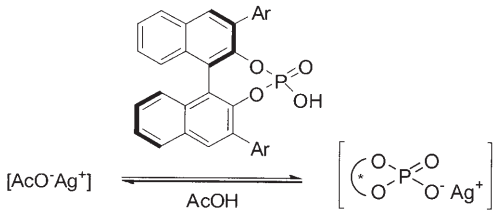
Table 3: Variation of the metal salts, catalyst loading, and *N*-PMP-imino ester.



Entry[a]	MX	MX [mol%]	**1g** [mol%]	R	e.r.[b]
1	–	–	10	Et	n.d.[c]
2	AcOAc	10	–	Et	n.d.
3	AgOAc	5	2	Et	76:24
4	AgOAc	5	5	Et	86:14
5	AgOAc	5	10	Et	91:9
6	AgOAc	5	10	Me	94:6
7	AgOAc	5	20	Et	87:13
8	AgOBz	5	5	Et	65:35
9	Ag_2O	2.5	5	Et	55:45
10	Ag_2CO_3	2.5	5	Et	73:27
11	$AgCO_2CF_3$	5	10	Et	85:15
12	$AgSO_3CF_3$	5	10	Et	72:28
13	$AgNO_3$	5	10	Et	81:19
14	$AgBF_4$	5	10	Et	79:21
15	CuOAc	5	10	Et	92:8
16	$Cu(OAc)_2$	5	10	Et	93:7

[a] Reaction conditions: **2a**, **4a**, **1g**, AgOAc in toluene at room temperature. [b] Enantioselectivities were determined by HPLC analysis. [c] Not determined. Bz = benzyl.

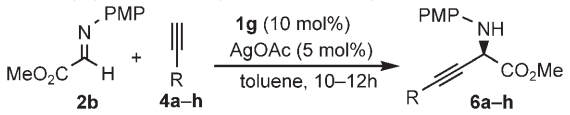
With regard to the reaction mechanism, we can not exclude an exchange of the metal counterion, which leads to the formation of a chiral silver complex [Eq. (1)]. This would

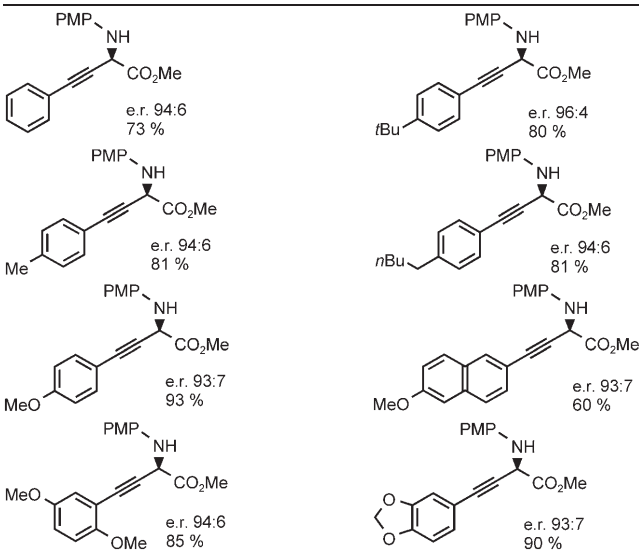


(1)

lead to the first example of a reaction catalyzed by a chiral metal complex[11] in combination with a chiral Brønsted acid catalyst.[12]

Table 4: Products (with e.r. values and yields) of the catalytic enantioselective alkynylation with aryl-substituted alkynes.[a,b]





[a] Reaction conditions: **2b**, **4a–h** (2 equiv), 10 mol% **1g**, 5 mol% AgOAc at 30°C in toluene. [b] Yield after chromatography. Enantioselectivities were determined by HPLC analysis using a chiral stationary phase.[13]

In summary, we have reported a new dual catalysis procedure, in which an enantioselective activation catalyzed by a Brønsted acid is combined with a metal-catalyzed alkynylation. The special features are the mild reaction conditions and the operational simplicity and practicability, which even negate the need to preform the catalyst. The new amino acids obtained have been isolated in good yields and with excellent enantiomeric ratios (up to e.r. 96:4). Furthermore, this unprecedented dual catalysis procedure represents not only the first addition of an organometallic compound to a aldimine activated with a binol phosphate, but more importantly, in this process both the metal salt and the Brønsted acid can be employed in catalytic amounts. We assume the reaction mechanism involves the formation of a chiral silver–binol phosphate complex, which results in a new metal-catalyzed reaction, in which the chiral counterion induces the enantioselectivity.

Further work will be directed toward a more detailed examination and application of the dual catalysis procedure as well as asymmetric metal catalysis with chiral counterions.

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[1] Reviews: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; c) C. Bolm, T. Rantanen, I. Schiffers, L. Zani, *Angew. Chem.* **2005**, *117*, 1788; *Angew. Chem. Int. Ed.* **2005**, *44*, 1758; d) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; e) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

[2] a) M. Rueping, C. Azap, E. Sugiono, T. Theissmann, *Synlett* **2005**, 2367; b) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781; c) M. Rueping, T. Theissmann, A. P. Antonchick, *Synlett* **2006**, 1071; d) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; e) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751; f) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; g) M. Rueping, C. Azap, *Angew. Chem.* **2006**, *118*, 7996; *Angew. Chem. Int. Ed.* **2006**, *45*, 7832; h) M. Rueping, E. Sugiono, T. Theissmann, A. Kuenkel, A. Köckritz, A. Pews Davtyan, N. Nemati, M. Beller, *Org. Lett.* **2007**, *9*, 1065; i) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2007**, 144; j) M. Rueping, E. Sugiono, S. A. Moreth, *Adv. Synth. Catal.* **2007**, *349*, 759; k) M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem.* **2007**, *119*, 2143; *Angew. Chem. Int. Ed.* **2007**, *46*, 2097; l) M. Rueping, A. P. Antonchick *Angew. Chem.* **2007**, *119*, 4646; *Angew. Chem. Int. Ed.* **2007**, *46*, 4562.

[3] Review: T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; c) M. Terada, K. Sorimachi, D. Uraguchi, *Synlett* **2006**, 13; d) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254; e) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193; f) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; g) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626; h) A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 3175; i) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074; j) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368; k) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070; l) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802; m) H. Liu, L.-F. Cun, A. Q. Mi, Y. Z. Jiang, L. Z. Gong, *Org. Lett.* **2006**, *8*, 6023; n) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292; o) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484; p) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830.

[4] D. Enders, U. Reinhold, *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

[5] a) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **1999**, *121*, 11245; b) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373; c) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 2651; *Angew. Chem. Int. Ed.* **2002**, *41*, 2535; d) R. Fässler, D. E. Frantz, J. Oetiker, E. M. Carreira, *Angew. Chem.* **2002**, *114*, 3180; *Angew. Chem. Int. Ed.* **2002**, *41*, 3054; e) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638; f) T. F. Knöpfel, E. M. Carreira, *J. Am. Chem. Soc.* **2003**, *125*, 6054; g) N. Gommermann, X. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; h) C. Koradin, N. Gommermann, K. Polborn, P. Knochel, *Chem. Eur. J.* **2003**, *9*, 2797; i) C. Fischer, E. M. Carreira, *Org. Lett.* **2004**, *6*, 1497; j) N. Gommermann, P. Knochel, *Chem. Commun.* **2004**, 2324; k) N. Gommermann, P. Knochel, *Chem. Commun.* **2005**, 4175; l) J. X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196; m) T. F.

Knöpfel, P. Zarotti, T. Ichikawa, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 9682; n) P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, *8*, 2437; o) L. Zani, T. Eichhorn, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 2587.

[6] Recent review: L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263.

[7] U. Halbes-Letinois, J. M. Weibel, P. Pale, *Chem. Soc. Rev.* **2007**, *36*, 759.

[8] The application of silver acetate in the alkynylation of α-imino esters resulted in low conversion even after prolonged reaction times: G. Lu, X. S. Li, Y. M. Li, F. Y. Kwong, A. S. C. Chan, *Adv. Synth. Catal.* **2006**, *348*, 1926.

[9] The reduced enantioselectivities can be explained by the ability of $AgNO_3$ or AgOTf to catalyze the reaction without the addition of Brønsted acids (see Refs. [6–8]).

[10] This represents the first example of an enantioselective alkynylation with phenylacetylene and its derivatives. The use of alkyl-substituted alkynes have been reported in Ref. [5l].

[11] a) H. Alper, N. Hamel, *J. Am. Chem. Soc.* **1990**, *112*, 2803; b) M. C. Pirrung, J. Zhang, *Tetrahedron Lett.* **1992**, *33*, 5987; c) J. Inanaga, H. Furuno, T. Hayano, *Chem. Rev.* **2002**, *102*, 2211; d) J. Lacour, V. Hebbe-Viton, *Chem. Soc. Rev.* **2003**, *32*, 373; e) M. C. Lacasse, C. Poulard, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 12440; f) V. Komanduri, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 16448.

[12] Experiments with chiral silver–binol complexes in combination with the achiral Brønsted acid diphenyl hydrogen phosphates resulted in racemic product.

[13] Experiments for the determination of the absolute configuration are given in the Supporting Information.

[14] **Note added in proof** (July 31, 2007): After the acceptance of our manuscript a further article on metal catalysis with chiral counterions appeared: G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496.

