Multicomponent Reactions

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Brønsted Acid Catalyzed Enantioselective Three-Component Reaction Involving the α Addition of Isocyanides to Imines**

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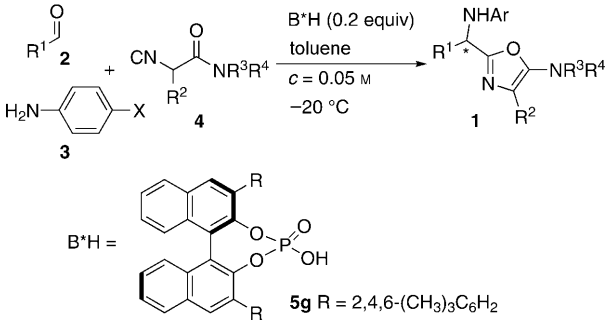
The Passerini three-component reaction (P-3CR)[1] and the Ugi four-component reaction (U-4CR)[2] are two of the most important multicomponent reactions (MCRs) known to date. Because of the mildness of reaction conditions, the wide application scope, and the high variability (four diversity points for U-4CR) they are ideally suited for generating molecular diversity and complexity; they are widely used in the syntheses of natural products and medicinally relevant compounds.[3] In these reactions, one chiral center is created, which results from the α addition of divalent isonitrile carbon atom to polarized double bonds (carbonyl or imine groups), therefore the ability to control the stereochemical outcome would significantly expand their synthetic utility. Although diastereoselective P-3CR[4] and U-4CR[5] using chiral substrates or chiral auxiliaries have been reported,[6] the development of an enantioselective version of these reactions remains a significant challenge. In spite of the great efforts dedicated to this field, only limited success has been made, thereby highlighting the difficulties associated with the development of such a catalyst.[7] In this context, Denmark and Fan developed an elegant Lewis base catalyzed enantioselective two-component Passerini reaction.[8] Dömling and co-workers discovered that a stoichiometric amount of a titanium–taddol (taddol = 1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-D-threitol) complex was capable of promoting the P-3CR reaction to afford the α-acyloxyamides in moderate enantioselectivities.[9] Schreiber and co-workers demonstrated that an indan copper(II)–pybox (pybox = pyridine-2,6-bisoxazoline) complex was able to catalyze the P-3CR; however, the enantioenriched Passerini adducts were obtained only when chelating aldehydes were used as reaction partners.[10] We have recently reported that the chiral aluminum–salen (salen = N,N'-bis(salicylidene)ethylenediamine) complex[11] was an efficient catalyst for the enantioselective Passerini three-component reaction.[12] All these enantioselective catalytic processes involve an α addition of isocyanides to aldehydes as a key step. To the best of our knowledge, there is no single report on Ugi-type reactions which involve the α addition of isocyanides to imines for generating the chiral centers. As a continuation of our interests in developing enantioselective isocyanide-based transformations, we report herein that the chiral phosphoric acid **5g** is able to catalyze the three-component reaction of the aldehydes **2**, anilines **3**, and α-isocyanoacetamides **4**, leading to 2-(1-aminoalkyl)-5-aminoxazoles (**1**) in excellent yields and moderate to good enantioselectivities (Scheme 1).[13]



Scheme 1. Chiral phosphoric acid catalyzed enantioselective α addition of α-isocyanoacetamides to imines: Three-component synthesis of 2-(1-aminoalkyl)-5-aminooxazoles.

Chiral phosphoric acids are now well-established as bifunctional organocatalysts, particularly in catalyzing the addition of nucleophiles to imines/acylimines.[14,15] As a prelude of our work, we examined the reaction of the preformed imine **6a** ($R^1 = t$Bu) and the α-isocyanoacetamide **4a** (R^2 = Bn)[16] in the presence of chiral phosphoric acids.[17] As it can be seen from Table 1, all the phosphoric acids investigated were able to catalyze the oxazole formation, however the enantioselectivity varied significantly with **5g** and **5l** being the most efficient. The *N*-triflyl phosphoramide **5o**,[18] a stronger Brønsted acid than **5l**, efficiently catalyzed the reaction but with reduced asymmetric induction (Table 1, entry 18). Among the solvents screened, toluene was found to be the most appropriate (Table 1, entries 19–21). Overall, the optimum conditions consisted of performing the reaction in toluene ($c = 0.05$ M) at −20 °C in the presence of **5g** or **5l** (0.2 equiv) as a catalyst. Oxazoles synthesized under these

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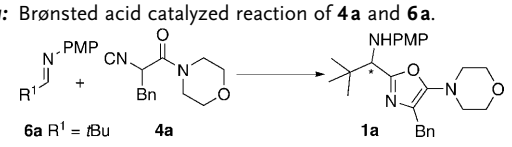
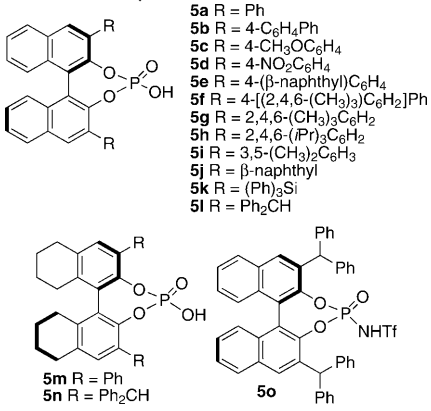
Table 1: Brønsted acid catalyzed reaction of **4a** and **6a**.



6a R^1 = *t*Bu **4a** **1a**

Entry	Catalyst	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**5a**	toluene	RT	99	38
2	**5a**	toluene	−7	97	39
3	**5a**	toluene	−20	96	52
4	**5a**	toluene	−40	87	32
5	**5b**	toluene	−20	77	26
6	**5c**	toluene	−20	99	12
7	**5d**	toluene	−20	92	7
8	**5e**	toluene	−20	93	6
9	**5f**	toluene	−20	47	25
10	**5g**	toluene	−20	99	54
11	**5h**	toluene	−20	21	53
12	**5i**	toluene	−20	99	18
13	**5j**	toluene	−20	76	23
14	**5k**	toluene	−20	89	19
15	**5l**	toluene	−20	99	58
16	**5m**	toluene	−20	99	40
17	**5n**	toluene	−20	74	33
18	**5o**	toluene	−20	99	25
19	**5l**	iPr_2O	−20	94	52
20	**5l**	CH_2Cl_2	−20	97	35
21	**5l**	MeCN	−20	99	3

[a] Reaction conditions: **6a**/**4a** = 1:1, in toluene *c* = 0.05 M, **5** (0.2 equiv). [b] Yield of chromatographically pure material. [c] Determined by chiral HPLC analysis. Bn = benzyl, PMP = *para*-methoxyphenyl, Tf = trifluoromethanesulfonyl.



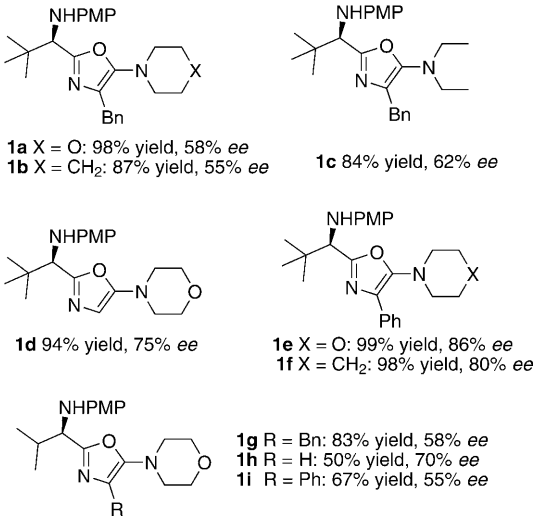
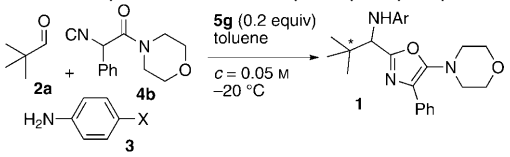


Figure 1. General reaction conditions: preformed imine **6**/**4** = 1:1 (**6** not shown), in toluene *c* = 0.05 M, **5** (0.2 equiv). Yield refers to chromatographically pure material; *ee* value was determined by chiral HPLC analysis. Catalyst **5l** was used for the preparation of **1a**–**1c** and catalyst **5g** was used for the preparation of **1d**–**1i**.

Table 2: Three-component reaction catalyzed by the phosphoric acid **5g**.



Entry	**3**	Additive	**1**	Yield [%]	*ee* [%]
1	X = OMe	none	**1e**	95	84
2	X = OMe	3 Å M.S.	**1e**	92	77
3	X = OMe	4 Å M.S.	**1e**	90	67
4	X = OMe	5 Å M.S.	**1e**	80	66
5	X = F	none	**1j**	91	84
6	X = Cl	none	**1k**	89	88
7	X = Br	none	**1l**	92	88
8	X = CF_3	none	**1m**	82	90

M.S. = molecular sieves.

conditions are listed in Figure 1. A simple recrystallization of **1d** from diethyl ether increased the *ee* value of the product to 90%.

Whereas these results represented the first examples of enantioselective α addition of isocyanides to imines, the use of a preformed imine as a reactant limited its application scope. Indeed imines derived from aliphatic aldehydes are generally unstable and difficult to access, therefore we set out to examine the more challenging three-component version. Reasoning that the basicity of aniline might influence the catalytic efficiency of the process, the reaction of the 4-substituted aniline **3**, having different electronic properties, with pivalaldehyde (**2a**) and α-isocyano-α-phenylacetamide (**4b**) in the presence of **5g** was investigated and the results are summarized in Table 2. Gratefully, the three-component reaction proceeded smoothly to afford the enantioenriched adduct in excellent yield and enantioselectivity. The best result was obtained when 4-trifluoroaniline was used as an amine, which led to **1m** in 82% yield and 90% *ee* (Table 2, entry 8). The addition of molecular sieves reduced the *ee* value of the products (Table 2, entries 2–4). In contrast, by using 2-hydroxyaniline, the corresponding oxazole was obtained in 54% yield with only 13% *ee*.

The generality of this chiral phosphoric acid catalyzed three-component reaction was next examined and the results are summarized in Figure 2. The reaction was applicable to representative aliphatic aldehydes including linear heptaldehyde, α-branched cyclohexanecarbaldehyde, isobutyraldehyde, and highly hindered pivalaldehyde, with the latter being the best substrate in terms of the *ee* value of the product. The aromatic aldehydes also participated in the reaction to provide the corresponding adducts, albeit with

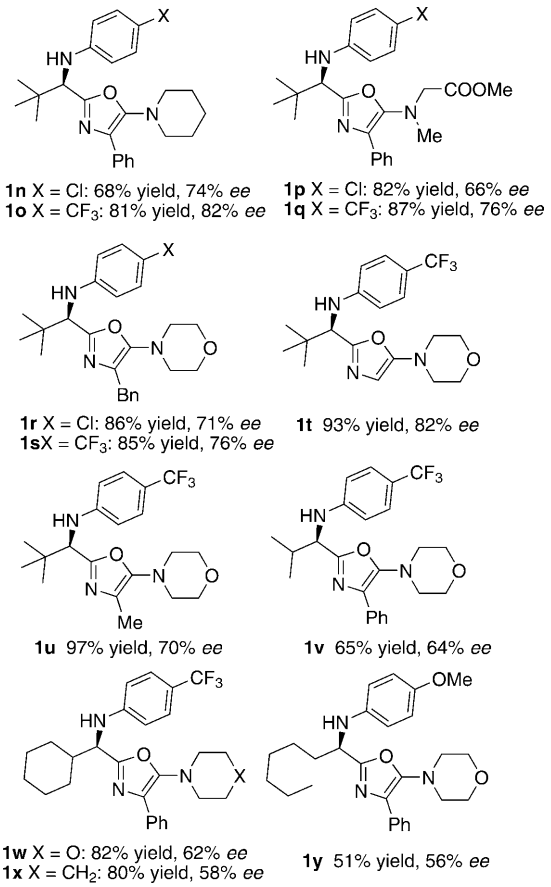
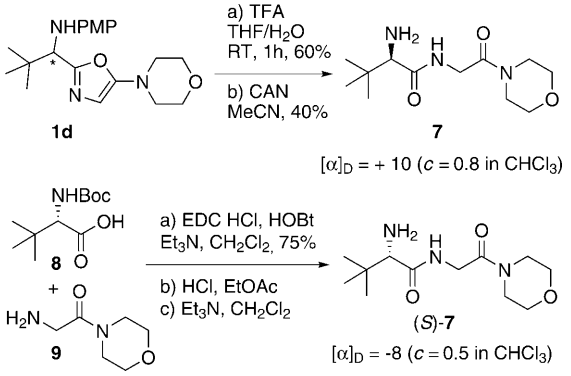


Figure 2. **5g**-catalyzed three-component reaction of aldehyde, aniline, and α-isocyanoacetamide.

reduced *ee* values (results not shown). The parent α-isocyanoacetamide, having a phenyl, benzyl, and methyl substituent at the α-position, as well as a dipeptide isocyanide participated in this reaction to provide the corresponding oxazoles in excellent yields and moderate to good *ee* values (56–90%).

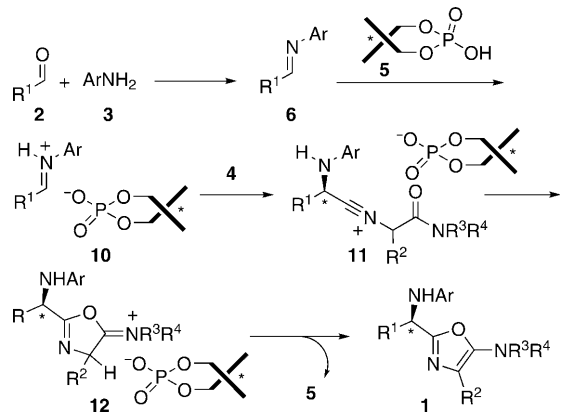
The absolute configuration of oxazole **1d** was determined as shown in Scheme 2. Hydrolysis of **1d** under acidic conditions and subsequent removal of the PMP group under



Scheme 2. Determination of the absolute configuration of **1d**. TFA = trifluoroacetic acid, THF = tetrahydrofuran, CAN = ceric ammonium nitrate, Boc = *tert*-butoxycarbonyl, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxybenzotriazole.

oxidative conditions furnished dipeptide **7**. Alternatively, the authentic amide (*S*)-**7** was synthesized from (*S*)-*N*-Boc-*tert*-leucine (**8**) and the glycine amide **9** by using a standard three-step sequence. Comparison of the sign of the optical rotation allowed the assignment of the *R* configuration to the oxazole **1d**.

We have previously demonstrated that Ugi-type reactions can be performed in toluene in the presence of weak Brønsted acid such as ammonium chloride.[19] Hence, a possible reaction scenario is proposed in Scheme 3. Protonation of



Scheme 3. Reaction pathway of phosphoric acid catalyzed three-component synthesis of 5-aminooxazoles.

imine **6** by the phosphoric acid would lead to the formation of the iminium salt **10**. The nucleophilic addition of the divalent carbon atom of isonitrile **4** onto the *Si* face of the iminium group would afford the nitrilium intermediate **11,** which could undergo cyclization to afford **12**. Deprotonation of the proton on C4 of **12** by the phosphate anion would afford the 5-aminooxazole **1** with concurrent regeneration of the phosphoric acid. The 5-aminooxazole is apparently stable under the reaction conditions as no hydrolysis product was observed.[20]

By using the silver salt of the phosphoric acid **5a** as a catalyst, the reaction of **6a** and **4a** afforded the racemic oxazole **1a** in only 20% yield. This result indicated that the reaction is indeed catalyzed by the Brønsted acid. A control experiment showed that asymmetric induction depended only on the chirality of the phosphoric acids. Therefore, the reaction of (*S*)-**4a** or (±)-**4a** with imine **6a** in the presence of catalyst (*R*)-**5l** afforded the oxazole **1a** with identical enantiofacial selectivity and enantiomeric excess.

The aminooxazole **1** bearing three basic nitrogen atoms can potentially compete with the imine **6** to form a salt or a hydrogen bond with the phosphoric acid, which is detrimental to the desired catalytic cycle. To gain mechanistic insight, we did the following NMR titration experiments. When one equivalent each of the imine **6a** and the phosphoric acid **5g** was mixed in C_6D_6 at room temperature, the imine was completely protonated as indicated by the downfield shift of imine proton ($\Delta\delta = 1.57$ ppm). In contrast, the ^{1}H NMR spectrum of **1e** was almost unchanged upon addition of one equivalent of the phosphoric acid **5g**. Finally, when an NMR

spectrum of a mixture of **1e**, **6a**, and **5g** in C_6D_6 was recorded, only the spectrum of imine **6a** was shifted (see the Supporting Information). These experiments demonstrated that the phosphoric acid was capable of activating selectively the imine and that the product inhibition was minimum.

In summary, we have reported a chiral phosphoric acid catalyzed three-component synthesis of enantioenriched 2-(1-aminoalkyl)-5-aminooxazoles. This represented the first example of enantioselective α-addition of α-isocyanides to imines for the creation of chiral molecules and may lay the foundation for the development of long-awaited enantioselective Ugi four-component reaction.[21]

Experimental Section

General procedure: Aldehyde (0.25 mmol), aniline (0.25 mmol), and dry toluene (2.0 mL), were added to a flame-dried round-bottom flask equipped with a stir bar. The solution was stirred at room temperature for about 0.5–1 h. The phosphoric acid **5g** (0.05 mmol) was then introduced and the resulting mixture was cooled to −20 °C. A solution of α-isocyano acetamide (0.25 mmol) in toluene (3.0 mL) was added slowly via a syringe pump (addition time 1.5 h). After being stirred at −20 °C for 20–24 h, the reaction mixture was purified by flash column chromatography (SiO_2, petroleum ether/EtOAc = 4:1) to give the corresponding oxazole.

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[1] L. Banfi, R. Riva in *Organic Reactions*, *Vol. 65* (Ed.: A. B. Charette), Wiley, New York, **2005**, pp. 1 – 140.

[2] a) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300 – 3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168 – 3210; b) S. Marcaccini, T. Torroba, *Nat. Protoc.* **2007**, *2*, 632 – 639.

[3] a) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51 – 80; b) R. V. A. Orru, M. De Greef, *Synthesis* **2003**, 1471 – 1499; c) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899 – 907; d) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133 – 1144; e) A. Dömling, *Chem. Rev.* **2006**, *106*, 17 – 89; f) I. Akritopoulou-Zane, S. W. Djuric, *Heterocycles* **2007**, *73*, 125 – 147; g) N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, *14*, 8444 – 8454; h) L. El Kaim, L. Grimaud, *Tetrahedron* **2009**, *65*, 2153 – 2171; i) L. A. Wessjohann, D. G. Rivera, O. E. Vercillo, *Chem. Rev.* **2009**, *109*, 796 – 814.

[4] a) S. Marcaccini, D. Miguel, T. Torroba, M. Garcia-Valverde, *J. Org. Chem.* **2003**, *68*, 3315 – 3318; b) R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth, M. Zeller, *Synlett* **2003**, 1536 – 1538; c) G. Cuny, R. Gamez-Montano, J. Zhu, *Tetrahedron* **2004**, *60*, 4879 – 4885; d) P. R. Krishna, G. Dayaker, P. V. N. Reddy, *Tetrahedron Lett.* **2006**, *47*, 5977 – 5980.

[5] a) H. Kunz, W. Pfrengle, *J. Am. Chem. Soc.* **1988**, *110*, 651 – 652; b) R. J. Linderman, S. Binet, S. R. Petrich, *J. Org. Chem.* **1999**, *64*, 336 – 337; c) G. F. Ross, E. Herdtweck, I. Ugi, *Tetrahedron* **2002**, *58*, 6127 – 6133; d) A. Basso, L. Banfi, R. Riva, G. Guanti, *J. Org. Chem.* **2005**, *70*, 576 – 580; e) L. Banfi, A. Basso, G. Guanti, S. Merlo, C. Repetto, R. Riva, *Tetrahedron* **2008**, *64*, 1114 – 1134; f) K. M. Bonger, T. Wennekes, D. V. Filippov, G. Lodder, G. A. van de Marel, H. S. Overkleeft, *Eur. J. Org. Chem.* **2008**, 3678 – 3688.

[6] "Asymmetric Isocyanide-based MCRs": L. Banfi, A. Basso, G. Guanti, L. Banfi in *Multicomponent reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**, pp. 1 – 32.

[7] a) "Catalytic Asymmetric Multicomponent Reactions": J. Seayad, B. List in *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**, pp. 227 – 299; b) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628 – 1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602 – 1634; c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590 – 1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570 – 1581; d) L.-Z. Gong, X.-H. Chen, X.-Y. Xu, *Chem. Eur. J.* **2007**, *13*, 8920 – 8926.

[8] a) S. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2003**, *125*, 7824 – 7825; b) S. Denmark, Y. Fan, *J. Org. Chem.* **2005**, *70*, 9667 – 9676.

[9] U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Dömling, *Org. Lett.* **2003**, *5*, 4021 – 4024.

[10] P. R. Andreana, C. C. Liu, S. L. Schreiber, *Org. Lett.* **2004**, *6*, 4231 – 4234.

[11] For reviews, see: a) J. F. Larrow, E. N. Jacobsen, *Top. Organomet. Chem.* **2004**, *6*, 123 – 152; b) T. Katsuki, *Chem. Soc. Rev.* **2004**, *33*, 437 – 444; c) Structure of group 13 compounds incorporating salen ligands: D. A. Atwood, M. J. Harvey, *Chem. Rev.* **2001**, *101*, 37 – 52.

[12] a) S. X. Wang, M. X. Wang, D. X. Wang, J. Zhu, *Eur. J. Org. Chem.* **2007**, 4076 – 4080; b) S. X. Wang, M. X. Wang, D. X. Wang, J. Zhu, *Org. Lett.* **2007**, *9*, 3615 – 3618; c) S. X. Wang, M. X. Wang, D. X. Wang, J. Zhu, *Angew. Chem.* **2008**, *120*, 394 – 397; *Angew. Chem. Int. Ed.* **2008**, *47*, 388 – 391; d) T. Yue, M. X. Wang, D. X. Wang, J. Zhu, *Angew. Chem.* **2008**, *120*, 9596 – 9599; *Angew. Chem. Int. Ed.* **2008**, *47*, 9454 – 9457.

[13] Synthesis of oxazoles from α-isocyanoacetamides: a) X. Sun, J. Janvier, H. Bienaymé, J. Zhu, *Org. Lett.* **2001**, *3*, 877 – 880; b) P. Janvier, M. Bois-Choussy, H. Bienaymé, J. Zhu, *Angew. Chem.* **2003**, *115*, 835 – 838; *Angew. Chem. Int. Ed.* **2003**, *42*, 811 – 814; c) G. Cuny, R. Gamez-Montano, J. Zhu, *Tetrahedron* **2004**, *60*, 4879 – 4885; d) T. Pirali, G. C. Tron, J. Zhu, *Org. Lett.* **2006**, *8*, 4145 – 4148; e) T. Pirali, G. C. Tron, G. Masson, J. Zhu, *Org. Lett.* **2007**, *9*, 5275 – 5278; f) D. Bonne, M. Dekhane, J. Zhu, *Angew. Chem.* **2007**, *119*, 2537 – 2540; *Angew. Chem. Int. Ed.* **2007**, *46*, 2485 – 2488; g) N. Elders, R. Ruijter, F. J. J. de Kanter, M. B. Groen, R. V. A. Orru, *Chem. Eur. J.* **2008**, *14*, 4961 – 4973; h) R. Scheffelaar, M. Paravidino, D. Muilwijk, A. L. Spek, F. J. J. de Kanter, R. V. A. Orru, R. Ruijter, *Org. Lett.* **2009**, *11*, 125 – 128.

[14] Selected examples: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592 – 1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566 – 1568; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804 – 11805; c) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696 – 15697; d) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590 – 7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424 – 7427; e) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679 – 2681; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617 – 2619; f) R. I. Storer, D. E. Carrera, D. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84 – 86; g) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802 – 14803; h) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484 – 1485; i) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang, Q. L. Zhou, *Angew. Chem.* **2007**, *119*, 5661 – 5663; *Angew. Chem. Int. Ed.* **2007**, *46*, 5565 – 5567; j) M. J. Wanner, R. N. S. van der Haas, K. R. de Cuba, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2007**, *119*, 7629 – 7631; *Angew. Chem. Int. Ed.* **2007**, *46*, 7485 – 7487; k) C. Baudequin, A. Zamfir, S. B. Tsogoeva, *Chem. Commun.* **2008**, 4637 – 4639; l) M. Sickert, C. Schneider, *Angew. Chem.* **2008**, *120*, 3687 – 3690; *Angew. Chem. Int. Ed.* **2008**, *47*, 3631 – 3634; m) D. Enders, A. A. Narine, F. Toulgoat, T. Bisschops, *Angew. Chem.* **2008**, *120*, 5744 – 5748; *Angew.*

Chem. Int. Ed. **2008**, *47*, 5661 – 5665; n) H. Liu, G. Dagousset, G. Masson, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598 – 4599.

[15] a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; b) M. Terada, *Chem. Commun.* **2008**, 4097 – 4112; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713 – 5743.

[16] The α-isocyanoacetamides are easily available, see: a) A. Fayol, C. Housseman, X. Sun, P. Janvier, H. Bienaymé, J. Zhu, *Synthesis* **2005**, 161 – 165; b) C. Housseman, J. Zhu, *Synlett* **2006**, 1777 – 1779; c) A. Dömling, B. Beck, T. Fuchs, A. Yazbak, *J. Comb. Chem.* **2006**, *8*, 872 – 880.

[17] Phosphinic acid catalyzed Ugi-type reaction: S. C. Pan, B. List, *Angew. Chem.* **2008**, *120*, 3678 – 3681; *Angew. Chem. Int. Ed.* **2008**, *47*, 3622 – 3625. Chiral Phosphoric acid and phosphinic acid catalyzed Ugi-type reaction afforded essentially the racemic adducts (footnote 12 of this paper).

[18] D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626 – 9627.

[19] a) P. Cristau, J. P. Vors, J. Zhu, *Org. Lett.* **2001**, *3*, 4079 – 4082; b) P. Janvier, X. Sun, H. Bienaymé, J. Zhu, *J. Am. Chem. Soc.* **2002**, *124*, 2560 – 2567; c) P. Cristau, J. P. Vors, J. Zhu, *Tetrahedron* **2003**, *59*, 7859 – 7870.

[20] 5-aminooxazoles were readily hydrolyzed in the presence of trifluoroacetic acid: a) G. Zhao, X. Sun, H. Bienaymé, J. Zhu, *J. Am. Chem. Soc.* **2001**, *123*, 6700 – 6701; b) C. Bughin, G. Zhao, H. Bienaymé, J. Zhu, *Chem. Eur. J.* **2006**, *12*, 1174 – 1184; c) C. Bughin, G. Masson, J. Zhu, *J. Org. Chem.* **2007**, *72*, 1826 – 1829.

[21] Recent developments on the enantioselective α-addition of α-isocyano acetamides to aldehydes: H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 8384 – 8385.

