Asymmetric Catalysis

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Catalytic Asymmetric Alkynylation of C1-Substituted C,N-Cyclic Azomethine Imines by Cu^{I}/Chiral Brønsted Acid Co-Catalyst**

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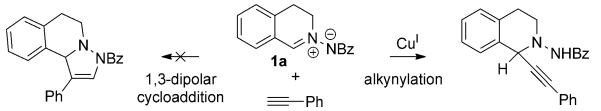
Biologically active tetrahydroisoquinolines having a chiral stereocenter at the C1-position are commonly found in nature and also in synthetic molecules,[1] and therefore, the catalytic asymmetric synthesis of these valuable building blocks has been explored as a worthwhile research area during the past decade.[2] In addition to asymmetric hydrogenation,[3] catalytic asymmetric C–C bond formation by nucleophilic addition to dihydroisoquinolines or isoquinolines has been given much attention in this regard.[4] Despite these efforts, there has been only one early report, by Shibasaki and co-workers in 2001, wherein dihydroisoquinolines having two different functionalities at the C1-position (tetrasubstituted carbon center) could be successfully generated in a catalytic asymmetric manner.[4b] Although a decade has passed since their pioneering discovery, no viable alternative to achieve this goal has emerged to date.[5]

During our studies on the use of C,N-cyclic azomethine imines (e.g. **1a**; Scheme 1) in the context of catalytic asymmetric 1,3-dipolar cycloadditions,[6] we became aware of their unique ability to act as prochiral electrophiles to dihydroisoquinolines. Namely, the copper-catalyzed reaction of **1a** with phenylacetylene furnished the alkynylation product and not the [3+2] cycloadduct, in contrast to the reaction of *N*,*N*′-cyclic azomethine imines, reported by Fu.[7] Although the asymmetric alkynylation of *N*-alkyl and *N*-aryl dihydroisoquinolinium salts has already been reported as a comparable method by Schreiber and Taylor, and Li and co-workers, respectively, these studies exhibited rather limited substrate scope or only modest selectivity.[8] What is even more important is the inability of this procedure to construct an asymmetric tetrasubstituted carbon center; Schreiber and Taylor only reported a racemic product, thus clearly leaving room for further development.

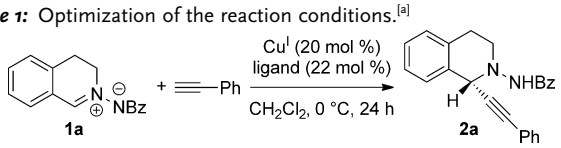


Scheme 1. 1,3-Dipolar cycloaddition versus alkynylation. Bz = benzoyl.

We report herein, the exploration of our alkynylation as a novel direct catalytic asymmetric method to provide a variety of chiral C1-alkynyl tetrahydroisoquinolines.[9] This investigation led to the discovery of a highly enantioselective alkynylation of azomethine imines catalyzed by a Cu^{I}/Ph-pybox complex (pybox = 2,6-bis(2-oxazolinyl)pyridine). This reaction has a remarkably broad substrate scope in terms of the aromatic substituents of the azomethine imines and the terminal alkynes. Although we faced the difficulty of attaining high enantioselectivity when using C1-substituted azomethine imines for the challenging formation of a tetrasubstituted carbon center, this issue could be successfully overcome by the addition of an axially chiral dicarboxylic acid, originally developed in this laboratory,[10] as a key co-catalyst.

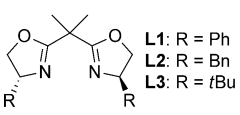
We commenced the study by screening the commercially available chiral ligands that are commonly used in copper-catalyzed asymmetric transformations, for the reaction of C,N-cyclic azomethine imine **1a** and phenylacetylene (Table 1).[11] Among the chiral bis(oxazoline) and pybox ligands that were examined at 20 mol% catalyst loading, (*R*,*R*)-Ph-pybox **L5** exhibited the best results, giving **2a** in 90% yield with 95% *ee* (Table 1, entries 2–6). The amount of the catalyst could then be decreased to 5 mol% without compromising the yield or selectivity (Table 1, entry 7). The choice of the copper source also had a significant impact on

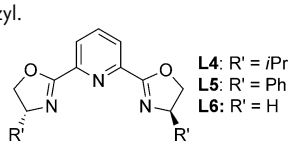
Table 1: Optimization of the reaction conditions.[a]



Entry	Metal	Ligand	Yield [%][b]	[*ee*] [%][c]
1	CuOAc	none	99	–
2	CuOAc	**L1**	>99	72
3	CuOAc	**L2**	43	45
4	CuOAc	**L3**	66	31
5	CuOAc	**L4**	74	52
6	CuOAc	**L5**	90	95
7[d]	CuOAc	**L5**	99	96
8	CuBr	**L5**	>99	27
9	CuI	**L5**	>99	4

[a] Performed with **1a** (0.10 mmol) and phenylacetylene (0.30 mmol) in the presence of the copper source (0.020 mmol) and the ligand (0.022 mmol). [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Performed with 5 mol% CuOAc and 5.5 mol% **L5**. Bn = benzyl.





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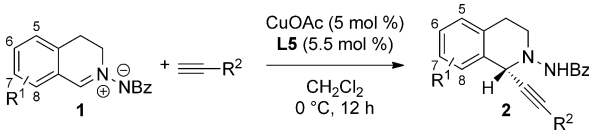
the enantioselectivity as observed in the use of copper bromide and iodide (Table 1, entries 8 and 9).

We then examined the substrate scope of this asymmetric alkynylation, as shown in Table 2. Initially, the reaction tolerance to the substituent on the aromatic ring of the azomethine imines was investigated because most of the previous reports on the catalytic asymmetric synthesis of di- or tetra-hydroisoquinolines failed to clarify this point. C,N-Cyclic azomethine imines bearing a methyl group at the 5-, 6-, 7-, or 8-positions could be converted into the corresponding products with *ee* values ranging from 85 to 94%, thus proving the high reaction tolerance to the position of the substituent (Table 2, entries 1–4). In addition, this catalytic system could also be applied to azomethine imines having either electron-donating or electron-withdrawing functionalities on the aromatic ring (Table 2, entries 5–8). In almost all cases, the products could be obtained in nearly quantitative yields by using two equivalents of the terminal alkyne. With regard to the variation of terminal alkynes, aryl, alkenyl, alkyl, and silyl acetylenes could be utilized to give the products in high yields and enantioselectivities (Table 2, entries 10–18), with 2-tolylacetylene and 1-heptyne being the only two exceptions (Table 2, entries 9 and 17).

Prompted by this success, we looked at the more challenging task of asymmetric alkynylation of C1-substituted azomethine imine **3a**, with the aim of constructing a chiral tetrasubstituted carbon center (Table 3). Gratifyingly, the reaction proceeded smoothly to give the alkynylated compound **4a** in good yield, although the enantioselectivity remained at a moderate level (Table 3, entry 1). A re-

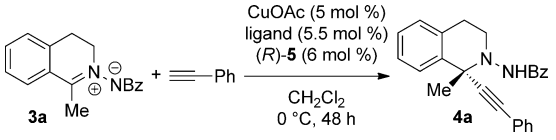
Table 2: Catalytic asymmetric alkynylation of C,N-cyclic azomethine imines.[a]



Entry	R^1	R^2	Yield [%][b]	[*ee*] [%][c]
1	5-Me (**1b**)	Ph	>99 (**2b**)	91
2	6-Me (**1c**)	Ph	>99 (**2c**)	94
3	7-Me (**1d**)	Ph	>99 (**2d**)	85
4	8-Me (**1e**)	Ph	>99 (**2e**)	90
5	6-Br (**1f**)	Ph	>99 (**2f**)	93
6	7-Br (**1g**)	Ph	96 (**2g**)	94
7	6-MeO (**1h**)	Ph	>99 (**2h**)	89
8	7-MeO_2C (**1i**)	Ph	93 (**2i**)	89
9	H (**1a**)	2-tolyl	>99 (**2j**)	43
10	H	3-tolyl	>99 (**2k**)	94
11	H	4-tolyl	>99 (**2l**)	95
12	H	4-BrC_6H_4	>99 (**2m**)	90
13	H	4-$MeOC_6H_4$	>99 (**2n**)	94
14	H	cyclohexenyl	88 (**2o**)	91
15	H	cyclohexyl	82 (**2p**)	89
16	H	cyclopropyl	>99 (**2q**)	90
17	H	C_5H_{11}	94 (**2r**)	75
18	H	TMS	89 (**2s**)	96

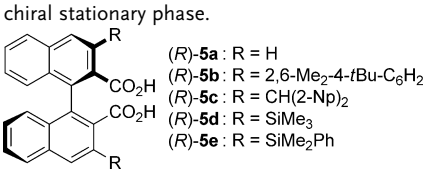
[a] Reaction conditions: **1** (0.30 mmol), terminal alkyne (0.60 mmol), CuOAc (0.015 mmol) and **L5** (0.0165 mmol). [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

Table 3: Optimization of the reaction conditions for the formation of the tetrasubstituted carbon center.[a]



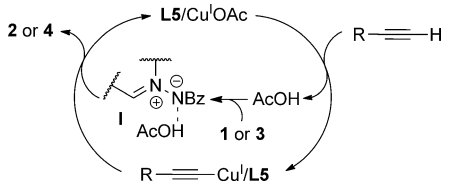
entry	ligand	(*R*)-**5**	Yield [%][b]	[*ee*] [%][c]
1	**L5**	none	>99	68
2	**L1**	none	trace	–
3	**L5**	(*R*)-**5a**	96	76
4	**L5**	(*R*)-**5b**	97	54
5	**L5**	(*R*)-**5c**	94	88
6	**L5**	(*R*)-**5d**	94	94
7	**L5**	(*R*)-**5e**	99	94
8	ent-**L5**	(*R*)-**5e**	67	−44
9	**L6**	(*R*)-**5e**	68	12

[a] Reaction conditions: **3a** (0.30 mmol), phenylacetylene (0.60 mmol), CuOAc (0.015 mmol), ligand (0.0165 mmol) and (*R*)-**5** (0.018 mmol). [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.



(*R*)-**5a**: R = H
(*R*)-**5b**: R = 2,6-Me_2-4-*t*Bu-C_6H_2
(*R*)-**5c**: R = CH(2-Np)$_2$
(*R*)-**5d**: R = $SiMe_3$
(*R*)-**5e**: R = $SiMe_2$Ph

examination of the chiral ligands was unfruitful, as demonstrated by the sluggish reaction when using bis(oxazoline) **L1** (Table 3, entry 2). Accordingly, we then focused on the development of an alternative strategy to improve the enantioselectivity; this strategy took into consideration the catalytic cycle, which likely involves an acid-base concerted process.[12] As shown in Scheme 2, the formation of the copper



Scheme 2. Tentative catalytic cycle.

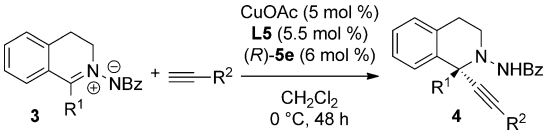
acetylide from the terminal alkyne and copper acetate would liberate acetic acid and this free acetic acid would protonate azomethine imine. Thus, electrophilically activated azomethine imine **I** would then react with nucleophilic copper acetylide. Based on the assumption of this tentative catalytic cycle, it can be envisaged that the replacement of the role of acetic acid by a chiral Brønsted acid would open an attractive way to enhance the selectivity. On the assumption that a more acidic chiral Brønsted acid, which is simply added to the reaction flask, would exchange with acetic acid in situ without the need for the preformation of a new copper/chiral Brønsted acid complex, we initiated the addition of some representative axially chiral dicarboxylic acids (*R*)-**5** as co-catalysts.[10,13,14] As anticipated, this investigation revealed the high dependence of the enantioselectivity on the 3,3′-sub-

stituents of the chiral dicarboxylic acids; the highest catalytic activity could be attained by using either (*R*)-**5d** or (*R*)-**5e** (Table 3, entries 3–7).[15] The enantioselectivity of the process could be drastically improved from 68% *ee* to 94% *ee*, just by adding 6 mol% of the catalyst. Owing to the greater generality of (*R*)-**5e**, which became apparent in the later study, we chose the combination of **L5** and (*R*)-**5e** as the optimized reaction conditions. Using the diastereomeric pair composed of *ent*-**L5** and (*R*)-**5e** as the chiral catalyst had an adverse effect on the reactivity, and the opposite enantiomer (**4a**) was obtained in diminished yield and modest *ee* value (Table 3, entry 8). The role of the dicarboxylic acid was evaluated to be supplementary, given the fact that the use of achiral pybox ligand **L6** (see, Table 1) in conjunction with (*R*)-**5e** resulted in poor stereoinduction (Table 3, entry 9).

With the optimized reaction conditions for the formation of the tetrasubstituted carbon center established, the substrate scope of the asymmetric alkynylation of C1-substituted C,N-cyclic azomethine imines was investigated (Table 4). A variety of terminal alkynes could be incorporated to generate a tetrasubstituted carbon center at the C1-position with high enantioselectivity (Table 4, entries 1–6). Notably, the chain length of the C1 substituent had only minimal impact on the reactivity and selectivity (Table 4, entries 7–10). These established reaction conditions were then applied in the alkynylation of C1-unsubstituted azomethine imine **1a** and 1-heptyne, to give an improvement in the enantioselectivity (Table 4, entry 11, for comparison, see Table 2, entry 17).

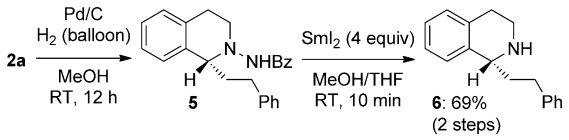
To remove the benzamide group of the products to access chiral tetrahydroisoquinolines we performed two synthetic applications. As shown in Scheme 3, after the hydrogenation of the alkyne moiety of **2a**, the N–N bond could be easily cleaved by SmI_2 to give the tetrahydroisoquinoline **6** in 69% (2 steps).

Table 4: Catalytic asymmetric alkynylation of C1-substituted C,N-cyclic azomethine imines.[a]



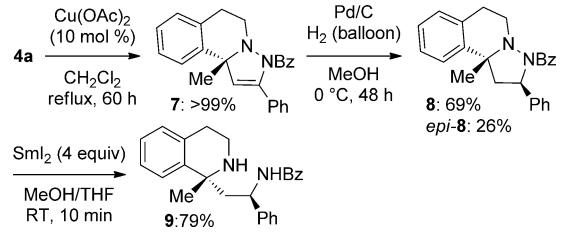
Entry	R^1	R^2	Yield [%][b]	[*ee*] [%][c]
1	Me (**3a**)	4-tolyl	97 (**4b**)	93
2	Me	4-BrC_6H_4	>99 (**4c**)	94
3	Me	4-$MeOC_6H_4$	>99 (**4d**)	95
4	Me	cyclohexenyl	90 (**4e**)	92
5	Me	cyclopropyl	98 (**4f**)	89
6	Me	C_5H_{11}	89 (**4g**)	88
7	Et (**3b**)	Ph	86 (**4h**)	94
8	Et	C_5H_{11}	84 (**4i**)	90
9	Bu (**3c**)	Ph	93 (**4j**)	88
10[d]	Bu	C_5H_{11}	85 (**4k**)	79
11[e]	H (**1a**)	C_5H_{11}	94 (**2r**)	88

[a] Reaction conditions: **3** (0.30 mmol), terminal alkyne (0.60 mmol), CuOAc (0.015 mmol), **L5** (0.0165 mmol) and (*R*)-**5e** (0.018 mmol). [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Performed for 60 h.[e] Performed for 12 h.



Scheme 3. N–N Bond cleavage of the product.

A synthetic procedure exploiting the alkyne and the benzamide moiety to give a tetrahydroisquinoline with an additional stereocenter was developed using **4a** as the starting material (Scheme 4). A copper-catalyzed cyclization of **4a** proceeded to give dihydropyrazole **7**, which upon hydrogenation furnished pyrazoline **8** with modest diastereoselectivity. Subsequent cleavage of the N–N bond led to **9**, thus incorporating the amide nitrogen in the product.[16]



Scheme 4. Incorporation of the benzamide in the alkyne moiety.

In conclusion, we succeeded in developing a direct catalytic asymmetric alkynylation using C,N-cyclic azomethine imines as a novel prochiral electrophile to give chiral tetrahydroisoquinoline derivatives. The procedure established herein offered two distinct advantages, which have not been realized by precedents. One advantage is the broad substrate scope with regard to both the prochiral electrophiles and the alkynes. The other, more important advantage is the capability to construct a tetrasubstituted carbon center at the C1-position by applying a catalyst system composed of copper^{I}/pybox and an axially chiral dicarboxylic acid. To the best of our knowledge, this is the first catalytic asymmetric reaction wherein terminal alkynes directly add to the C=N double bond to give a chiral tetrasubstituted carbon center with high enantioselectivity.[17,18]

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[1] a) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669; b) K. W. Bentley, *Nat. Prod. Rep.* **2004**, *21*, 395; c) K. W. Bentley, *Nat. Prod. Rep.* **2005**, *22*, 249; d) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444.

[2] a) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341; b) M. Ahamed, M. H. Todd, *Eur. J. Org. Chem.* **2010**, 5935.

[3] a) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916; b) S.-M. Lu, Y.-Q. Wang, X.-W. Han, Y.-G. Zhou, *Angew. Chem.* **2006**, *118*, 2318; *Angew. Chem.*

Int. Ed. **2006**, *45*, 2260; c) C. Li, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208.

[4] a) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327; b) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784; c) S.-i. Murahashi, Y. Imada, T. Kawakami, K. Harada, Y. Yonemushi, N. Tomita, *J. Am. Chem. Soc.* **2002**, *124*, 2888; d) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 6858; *Angew. Chem. Int. Ed.* **2005**, *44*, 6700; e) K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 6212; *Angew. Chem. Int. Ed.* **2005**, *44*, 6058; f) N. Sasamoto, C. Dubs, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2006**, *128*, 14010; g) C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume, M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859; h) M. Miyazaki, N. Ando, K. Sugai, Y. Seito, H. Fukuoka, T. Kanemitsu, K. Nagata, Y. Odanaka, K. T. Nakamura, T. Itoh, *J. Org. Chem.* **2010**, *76*, 534.

[5] a) D. Brózda, K. Hoffman, M. D. Rozwadowska, *Heterocycles* **2006**, *69*, 119; b) K. Frisch, K. A. Jørgensen, *Org. Biomol. Chem.* **2007**, *5*, 2966.

[6] a) T. Hashimoto, Y. Maeda, M. Omote, H. Nakatsu, K. Maruoka, *J. Am. Chem. Soc.* **2010**, *132*, 4076; b) T. Hashimoto, M. Omote, K. Maruoka, *Angew. Chem.* **2011**, *123*, 3551; *Angew. Chem. Int. Ed.* **2011**, *50*, 3489.

[7] a) R. Shintani, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 10778; b) A. Suárez, C. W. Downey, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11244.

[8] a) A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006**, *8*, 143; b) Z. Li, P. D. MacLeod, C.-J. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590.

[9] For pioneering work on catalytic asymmetric alkynylations, see: a) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **1999**, *121*, 11245; b) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806; c) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373; d) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687; e) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638; f) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 2651; *Angew. Chem. Int. Ed.* **2002**, *41*, 2535; g) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; h) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760.

[10] a) T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054; b) T. Hashimoto, K. Maruoka, *Synthesis* **2008**, 3703; c) T. Hashimoto, M. Hirose, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 7556; d) T. Hashimoto, N. Uchiyama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 14380; e) T. Hashimoto, H. Kimura, K. Maruoka, *Tetrahedron: Asymmetry* **2010**, *21*, 1187; f) T. Hashimoto, H. Kimura, K. Maruoka, *Angew. Chem.* **2010**, *122*, 6996; *Angew. Chem. Int. Ed.* **2010**, *49*, 6844.

[11] a) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119; b) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561.

[12] The inspiring work by Arndtsen and co-workers on copper/amino acid co-catalyzed asymmetric alkynylation of aldimines revealed that Boc-proline acts as a hydrogen-bond donor for imines independently to copper acetylide: Y. Lu, T. C. Johnstone, B. A. Arndtsen, *J. Am. Chem. Soc.* **2009**, *131*, 11284.

[13] For the catalytic asymmetric conjugate addition of alkynes using chiral monophosphoric acid as a counteranion, see: R. Yazaki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 10275.

[14] For a review on asymmetric catalysis with two chiral units, see: S. Piovesana, D. M. Scarpino Schietroma, M. Bella, *Angew. Chem.* **2011**, *123*, 6340; *Angew. Chem. Int. Ed.* **2011**, *50*, 6216.

[15] T. Hashimoto, T. Takagaki, H. Kimura, K. Maruoka, *Chem. Asian J.* **2011**, *6*, 1936.

[16] The absolute configuration of the alkynylated product **4a** was determined by the derivatization of **9**, see the Supporting Information for details.

[17] Catalytic asymmetric alkynylation of an α-CF_3 ketimino ester using a stoichiometric amount of dimethylzinc was reported recently: G. Huang, J. Yang, X. Zhang, *Chem. Commun.* **2011**, *47*, 5587.

[18] For recent examples for the catalytic asymmetric alkynylation of ketones, see: a) T. Ohshima, T. Kawabata, Y. Takeuchi, T. Kakinuma, T. Iwasaki, T. Yonezawa, H. Murakami, H. Nishiyama, K. Mashima, *Angew. Chem.* **2011**, *123*, 6420; *Angew. Chem. Int. Ed.* **2011**, *50*, 6296; b) N. Chinkov, A. Warm, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 3014; *Angew. Chem.* **2011**, *123*, 3014; *Angew. Chem. Int. Ed.* **2011**, *50*, 2957; c) G.-W. Zhang, W. Meng, H. Ma, J. Nie, W.-Q. Zhang, J.-A. Ma, *Angew. Chem.* **2011**, *123*, 3600; *Angew. Chem.* **2011**, *123*, 2669; *Angew. Chem. Int. Ed.* **2011**, *50*, 2621.

