

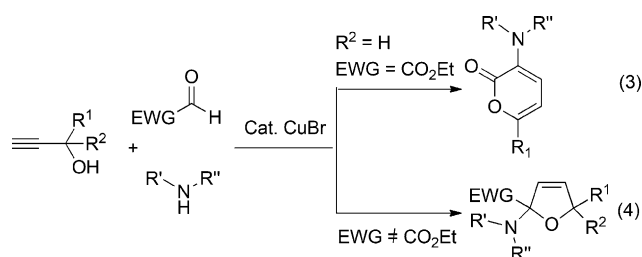
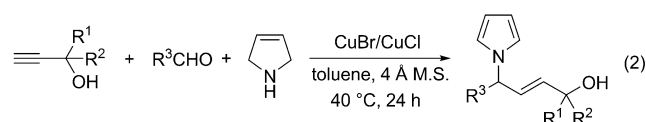
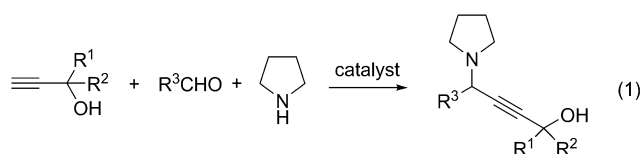
Copper(I)-Catalyzed Three-Component Reaction of Terminal Propargyl Alcohols, Aldehydes, and Amines: Synthesis of 3-Amino-2-pyrones and 2,5-Dihydrofurans**

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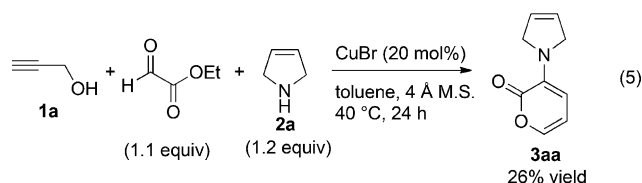
Dedicated to Professor Chengye Yuan on the occasion of his 90th birthday

Abstract: A novel copper(I)-catalyzed three-component reaction for the efficient synthesis of 3-amino-2-pyrones and 2,5-dihydrofurans from propargyl alcohols, aldehydes, and amines has been developed. The starting materials are easily available and the scope of this method is broad. Through mechanistic studies, it is believed that the three-component reaction consists of an A^3 -coupling to propargylic amine, alkyne–allene isomerization, and intramolecular cyclization of the allenol to form a furan. In case of using ethyl glyoxalate as the aldehyde, a ring-opening, lactonization, and isomerization process affords the 3-amino-2-pyrones.

The copper-catalyzed three-component coupling reactions of terminal alkynes, aldehydes, and amines for the formation of propargylic amines have been extensively developed [Eq. (1)].^[1,2] Our group has recently reported a copper-catalyzed semi-reductive A^3 -coupling of alkynes, aldehydes, and amines, and it afforded allylic amines with exclusive *E* stereoselectivity [Eq. (2); M.S. = molecular sieves].^[3] Herein, we report an unexpected formation of 3-amino-2-pyrones [Eq. (3); EWG = electron-withdrawing group] and 2,5-dihydrofurans [Eq. (4)] using electron-poor aldehydes.



During our studies on the scope and generality of this semi-reductive A^3 -coupling reaction,^[3] in the presence of copper(I) bromide in toluene at 40 °C for 24 hours, we unexpectedly observed that the reaction of prop-2-yn-1-ol (**1a**) and 3-pyrrolidine (**2a**) with ethyl glyoxalate as the aldehyde afforded an unexpected product, which was later identified as the 3-amino-2-pyrene (**3aa**) in 26% yield upon isolation [Eq. (5)].



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Inspired by this result and the potential of 3-amino-2-pyrones in organic synthesis for their biological activity such as selective cyclooxygenase-1 (COX-1) inhibitors,^[4] we started to explore the best reaction conditions for this three-component formation of the 3-amino-2-pyrene **3bb** using but-3-yn-2-ol (**1b**), ethyl glyoxalate, and pyrrolidine (**2b**) as the starting materials. The reaction at 40 °C yielded **3bb** in 61% yield (Table 1, entry 1). Other copper salts, such as CuCl, CuCl₂, and CuBr₂ also worked well for this reaction with similar yields (55–60%), while CuI delivered a poor yield (43%; entries 3–6). Notably, Cu(OAc)₂ and Cu(OTf)₂ showed low conversions (entries 7 and 8). Then various solvents were tested and 1,4-dioxane was found to be the most efficient (entry 9). Other solvents such as DME, THF, MTBE, CH₂Cl₂,

and CH_3CN are also suitable for this reaction (entries 10–14). Finally, we defined the reaction conditions used for entry 9 in Table 1 as the standard reaction conditions for further studies on this unique three-component reaction.

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

Entry	Catalyst	Solvent	Yield [%] ^[b]
1	CuBr	toluene	61
2 ^[c]	CuBr	toluene	57
3	CuCl	toluene	60
4	CuI	toluene	43
5	CuCl ₂	toluene	55
6	CuBr ₂	toluene	60
7	Cu(OAc) ₂	toluene	20
8	Cu(OTf) ₂	toluene	10
9	CuBr	1,4-dioxane	70
10	CuBr	DME	66
11	CuBr	THF	66
12	CuBr	MTBE	48
13	CuBr	CH_2Cl_2	61
14	CuBr	CH_3CN	54

[a] The reactions were carried on 1.0 mmol scale of **1b** in 3 mL of solvent with 4 Å M.S. (300 mg) for step 1; silica gel (500 mg) and toluene (5 mL) were used for step 2. [b] Determined by NMR spectroscopy. [c] The reaction was carried at 50 °C for step 1. DME = dimethyl ether, MTBE = methyl *tert*-butyl ether, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

We first explored the scope with respect to the propargyl alcohols reacting with ethyl glyoxalate and **2b** (Table 2). Besides the parent propargyl alcohol, a variety of different alkyl- and aryl-substituted propargyl alcohols are suitable for affording the corresponding products **3ab–hb** in moderate to good yields (entries 1–9). The reaction of heteroaryl-group-substituted propargyl alcohols, such as 1-(2-furyl)propargyl alcohol, also proceeded smoothly (entry 10). Even alkenyl-substituted propargyl alcohols gave the expected 3-amino-2-pyrone derivatives **3jb** and **3kb** in decent yields (entries 11 and 12). Furthermore, the reaction of **1b** with ethyl glyoxalate and **2b** was conducted on a gram scale, thus affording the desired product **3bb** in a yield similar to that obtained on small scale (entry 3).

Subsequently, the scope of amine substrates in this reaction was further investigated. The results are summarized in Table 3. The reaction of **1b** with **2a** resulted in **3ba** in 59 % yield (entry 2). When pyrrolidines having a 2-substituent, such as 2-methylpyrrolidine and 2-(methoxymethyl)pyrrolidine, were used, the reaction proceeded well (entries 3 and 4). Piperidine and dibutylamine are also compatible with this transformation, thus affording the expected products **3ae** and **3af** in moderate yields (entries 5 and 6).

When we used (*S*)-2-methylpyrrolidine (> 99 % *ee*) and (*S*)-2-(methoxymethyl)pyrrolidine (> 99 % *ee*) as the starting materials, the optically active 3-amino-2-pyrones (*S*)-**3bc**

Table 2: Reaction with various propargylic alcohols.^[a]

Entry	R	t [h]	3 Yield [%] ^[b]
1	H (1a)	0.3	55 (3ab)
2	Me (1b)	1	61 (3bb)
3 ^[c]	Me (1b)	5	61 (3bb)
4	<i>n</i> -C ₅ H ₁₁ (1c)	3.5	65 (3cb)
5 ^[d]	<i>i</i> Bu (1d)	9	50 (3db)
6 ^[d]	Cy (1e)	2	63 (3eb)
7 ^[d]	Bn (1f)	2	66 (3fb)
8	Ph (1g)	6	66 (3gb)
9 ^[d]	2-naphthyl (1h)	5	78 (3hb)
10 ^[d]	2-furyl (1i)	6	63 (3ib)
11 ^[d]	(<i>E</i>)-styryl (1j)	6	72 (3jb)
12 ^[d]	(<i>E</i>)-hex-1-en-1-yl (1k)	5	68 (3kb)

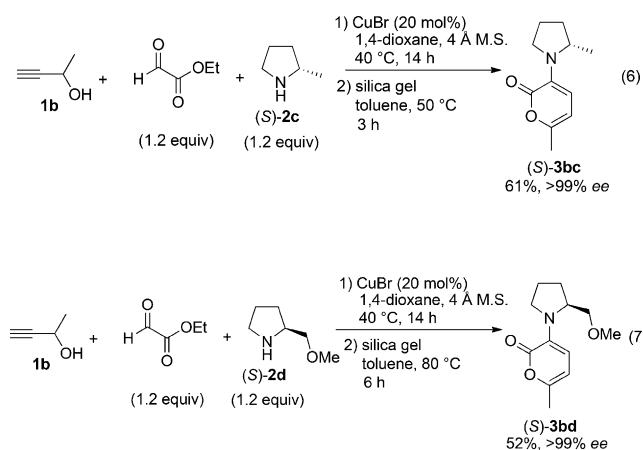
[a] The reactions were carried on 1.0 mmol scale of **1** in 3 mL of 1,4-dioxane with 4 Å M.S. (300 mg) for step 1; silica gel (500 mg) and toluene (5 mL) were used for step 2. [b] Yield of isolated product. [c] The reaction was carried on 15 mmol scale of **1b** in 40 mL of THF with 4 Å M.S. (1.5 g) and CuBr (10 mol %) for step 1; silica gel (8 g) and toluene (30 mL) were used for step 2. [d] Silica gel (700 mg) was used for step 2.

Table 3: Reaction with various amines.^[a]

R 1 H (1.2 equiv) $\text{R}'\text{-N-H-N}''$ 2 (1.2 equiv) 1) CuBr (20 mol%) 1,4-dioxane, 4 Å M.S. 40 °C, 14 h 2) silica gel toluene, 50 °C, <i>t</i> 3				
Entry	1 (R)	2	<i>t</i> [h]	3 Yield [%] ^[b]
1	1 a (H)	 2a	1.5	43 (3aa)
2 ^[c]	1 b (Me)	 2a	2.5	59 (3ba)
3	1 b (Me)	 2c	3	65 (3bc)
4 ^[c,d]	1 b (Me)	 2d	3.5	53 (3bd)
5 ^[c,d]	1 a (H)	 2e	6	44 (3ae)
6 ^[c,d]	1 a (H)	 2f	3	44 (3af)

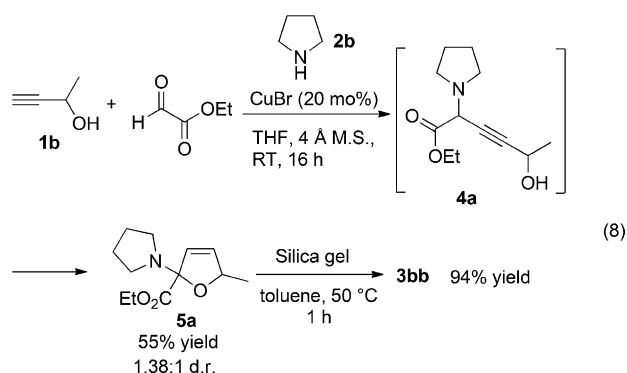
[a] The reactions were carried on 1.0 mmol scale of **1** in 3 mL of 1,4-dioxane with 4 Å M.S. (300 mg) for step 1; silica gel (500 mg) and toluene (5 mL) were used for step 2. [b] Yield of isolated product. [c] Silica gel (700 mg) was used for step 2. [d] The reactions were carried at 80 °C for the step 2.

(61 %) and (*S*)-**3bd** (52 %), respectively, were also afforded without obvious racemization, as determined by chiral-column HPLC analysis [Eqs. (6) and (7)].



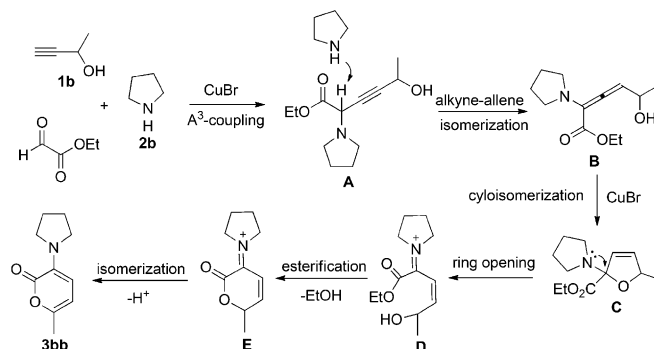
As a comparison, simple alkyl- and aryl-substituted terminal alkynes as well as but-3-yn-1-ol failed to afford even the corresponding propargylic amines.^[5] Instead, the reaction resulted in an unidentified mixture. When the hydroxy group was protected as the methyl ether (with 3-methoxyprop-1-yne), no expected product or the corresponding propargylic amine was obtained (for details see Scheme S1 in the Supporting Information). Thus, the alcohol unit on the propargylic position is helping even in the first step.

To provide further insight into the reaction mechanism, we monitored the reaction carefully. Although attempts to isolate the propargylic amine **4a** failed, we did isolate an intermediate, which was identified as the five-membered furan derivative **5a** in 55% yield and 1.38:1 d.r. [Eq. (8)], before the silica gel treatment. Upon treatment with silica gel in toluene at 50 °C for 1 hour the final six-membered product **3bb** was afforded.



Based on the above results, we proposed a plausible mechanism for the formation of 3-amino-2-pyrones as depicted in Scheme 1. Firstly, copper-catalyzed A^3 -coupling of **1b**, ethyl glyoxalate, and **2b** afforded the propargylamine intermediate **A**,^[5] which may isomerize to give the allenol intermediate **B** under the mediation of pyrrolidine as a base.^[6] Then copper-catalyzed intramolecular cyclization of **B** led to the furan derivative **C**,^[7] which gave the ring-opening product

D after the cleavage of the cyclic C–O bond because of the presence of the amine functionality. Finally, **3bb** is formed by intramolecular transesterification/C=C isomerization sequence.



Scheme 1. The proposed mechanism.

Based on this, we further reasoned that the reaction with aldehydes containing an electron-withdrawing group may afford the furan derivatives of type **C**, which are common structural building blocks in many bioactive natural and unnatural products.^[8,9] Thus, we first examined the reaction of phenylglyoxal (with the benzoyl group replacing the ester group in glyoxalate) with **1b** and piperidine (**2e**) under the present catalytic system. Indeed, the five-membered furan derivative **5b** was obtained in 70% yield and 1.56:1 d.r. (Table 4, entry 1). Using phenylglyoxal, we carried out the reaction with different tertiary propargylic alcohols and secondary amines. In all cases, the reactions proceeded smoothly yielding the corresponding 2,5-dihydrofuran derivatives **5c–i** in good yields (entries 2–8). In addition, the reaction may also be extended to different aldehydes: pyruvic aldehyde was found to be equally efficient (entry 9), and a heterocyclic aldehyde such as 2-pyridylaldehyde also gave the desired product **5k** in 51% yield (entry 10). Even **5l** was obtained from *p*-nitrobenzaldehyde in a moderate yield when the reaction was conducted at 80 °C, most probably because of the strong electron-withdrawing effect of the nitro group (entry 11). These results further support the mechanism presented in Scheme 1.

In conclusion, we have developed a novel copper-catalyzed three-component tandem process for the synthesis of 3-amino-2-pyrones and 2,5-dihydrofurans from easily available propargyl alcohols, amines, and aldehydes. The mild reaction conditions and simple operation of this domino reaction reported here and the potential of the products make it of high interest to scientific community. Further investigation of the scope and synthetic application of this copper-catalyzed cascade reaction are still being pursued in our laboratory.

Experimental Section

CuBr (98% purity, 215.3 mg, 1.5 mmol), 4 Å M.S. (1.5000 g), **1b** (1.0512 g, 15 mmol)/THF (15 mL), **2b** (1.2801 g, 18 mmol)/THF (15 mL), and ethyl glyoxalate (50% in toluene, 3.6801 g, 18 mmol)/THF (10 mL) were sequentially added to a 50 mL flame-dried

Table 4: The reactions with other electron-poor aldehydes.^[a]

$ \begin{array}{c} \text{R}^1 \\ \\ \text{C} \equiv \text{C} - \text{C}(\text{R}^2) - \text{OH} \\ \text{1} \end{array} + \text{R}^3\text{CHO} + \begin{array}{c} \text{R}^1 \\ \\ \text{N} - \text{R}^2 \\ \text{2} \end{array} \xrightarrow[\text{40 } ^\circ\text{C, } t]{\text{CuBr (20 mol\%), 1,4-dioxane, 4 \AA M.S.}} \begin{array}{c} \text{R}^3 \quad \text{R}^1 \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \quad \\ \text{N} - \text{R}^2 \quad \text{O} \\ \text{5} \end{array} $					
Entry	1 (R ¹ , R ²)	R ³	2	t [h]	5 Yield [%] ^[b]
1 ^[c]	1b (H, Me)	Bz		16.5	70 (5b)
2 ^[c]	1l (Me, Me)	Bz		14	75 (5c)
3 ^[c]	1m (Et, Et)	Bz		14	69 (5d)
4 ^[c]	1n [-(CH ₂) ₃]	Bz		14	68 (5e)
5 ^[c]	1o [-(CH ₂) ₄]	Bz		14	69 (5f)
6 ^[c]	1l (Me, Me)	Bz		14.5	65 (5g)
7 ^[c]	1l (Me, Me)	Bz		14.5	74 (5h)
8 ^[c]	1l (Me, Me)	Bz		14.5	78 (5i)
9	1l (Me, Me)	Ac		16.5	66 (5j)
10	1l (Me, Me)	2-pyridyl		16.5	51 (5k)
11 ^[d,e]	1l (Me, Me)	4-NO ₂ C ₆ H ₄		19	50 (5l)

[a] The reactions were carried on 1.0 mmol scale of **1** in 3 mL of 1,4-dioxane with 4 Å M.S. (300 mg). [b] Yield of isolated product. [c] Phenylglyoxal monohydrate was used. [d] The reaction was carried at 80 °C. [e] The ratio of **1**/aldehyde/**2** was 1.5:1:1.5. Bz = benzoyl.

Schlenk tube under an Ar atmosphere. The reaction mixture was then stirred at 40 °C until completion of the reaction as monitored by TLC (14 h). The crude reaction mixture was filtered through a short pad of silica gel using ether (40 mL). After evaporation, the residue was dissolved in toluene (30 mL) and treated with silica gel (8 g) at 50 °C until completion of the reaction as monitored by TLC (5 h). The crude reaction mixture was filtrated through a short pad of silica gel using diethyl ether (140 mL). After evaporation, the residue was purified by chromatography on silica gel to afford **3bb** (1.6324 g, 61 %; eluent petroleum ether/ethyl acetate = 20:1 to 10:1) as a solid: m.p. 70–71 °C (ethyl acetate); ¹H NMR (300 MHz, CDCl₃): δ = 5.94 (d, J = 7.2 Hz, 1H, C=CH), 5.83 (d, J = 7.2 Hz, 1H, C=CH), 3.44–3.30 (m, 4H, 2 × NCH₂), 2.15 (s, 3H, CH₃), 1.98–1.85 ppm (m, 4H, 2 × CH₂); ¹³C NMR (75 MHz, CDCl₃): δ = 160.6, 149.6, 133.7, 112.5, 103.9, 49.5, 24.9, 18.7 ppm; MS (ESI) m/z = 180 [M+H⁺]; IR (neat): ν̄ = 2970, 2939, 2916, 2893, 2824, 1703, 1638, 1559, 1487, 1473, 1458,

1396, 1382, 1369, 1346, 1320, 1248, 1213, 1183, 1160, 1110, 1087, 1051, 1039, 1015 cm⁻¹; elemental analysis calcd (%) for C₁₀H₁₃NO₂: C 67.02, H 7.31, N 7.82; found: C 67.15, H 7.19, N 7.93.

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- [1] For selected reviews, see: a) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472–1483; b) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263–4275; c) V. V. Kouznetsov, L. Y. Vargas Méndez, *Synthesis* **2008**, 491–506; d) C.-J. Li, *Acc. Chem. Res.* **2010**, *43*, 581–590; e) W.-J. Yoo, L. Zhao, C.-J. Li, *Aldrichimica Acta* **2011**, *44*, 43–51; f) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790–3807.
- [2] For selected examples on copper-catalyzed synthesis of propargylamines by A³-coupling, see: a) M. K. Patil, M. Keller, B. M. Reddy, P. Pale, J. Sommer, *Eur. J. Org. Chem.* **2008**, 4440–4445; b) M. Lakshmi Kantam, S. Laha, J. Yadav, S. Bhargava, *Tetrahedron Lett.* **2008**, *49*, 3083–3086; for the enantioselective version, see: c) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639; d) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.* **2003**, *42*, 5763–5766; *Angew. Chem.* **2003**, *115*, 5941–5944; e) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem. Int. Ed.* **2004**, *43*, 5971–5973; *Angew. Chem.* **2004**, *116*, 6097–6099; f) A. Bisai, V. K. Singh, *Org. Lett.* **2006**, *8*, 2405–2408; g) Z. Shao, X. Pu, X. Li, B. Fan, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, *20*, 225–229; h) S. Nakamura, M. Ohara, Y. Nakamura, N. Shibata, T. Toru, *Chem. Eur. J.* **2010**, *16*, 2360–2362; i) W. Fan, S. Ma, *Chem. Commun.* **2013**, *49*, 10175–10177.
- [3] W. Fan, W. Yuan, S. Ma, *Nat. Commun.* **2014**, *5*, 3884.
- [4] a) Q. F. Zhou, Y. Zhu, W. F. Tang, T. Lu, *Synthesis* **2010**, 211–216; b) X. P. Chu, Q. F. Zhou, S. Zhao, F. F. Ge, M. Fu, J. P. Chen, T. Lu, *Chin. Chem. Lett.* **2013**, *24*, 120–122.
- [5] Y. Yamamoto, H. Hayashi, T. Saigoku, H. Nishiyama, *J. Am. Chem. Soc.* **2005**, *127*, 10804–10805.
- [6] a) S. Shi, T. Wang, V. Weingand, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2014**, *53*, 1148–1151; *Angew. Chem.* **2014**, *126*, 1166–1170; b) S. Chen, X. Li, H. Zhao, B. Li, *J. Org. Chem.* **2014**, *79*, 4137–4141.
- [7] For selected examples on the metal-catalyzed cyclization of allenols to 2,5-dihydrofurans, see: a) L.-I. Olsson, A. Claesson, *Synthesis* **1979**, 743–745; b) S. S. Nikam, K. H. Chu, K. K. Wang, *J. Org. Chem.* **1986**, *51*, 745–747; c) J. A. Marshall, C. A. Schon, *J. Org. Chem.* **1995**, *60*, 5966–5968; d) J. A. Marshall, R. H. Yu, J. F. Perkins, *J. Org. Chem.* **1995**, *60*, 5550–5555; e) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537–2538; for a copper-catalyzed cycloisomerization reaction of allene, see: f) S. Ma, Z. Yu, S. Wu, *Tetrahedron* **2001**, *57*, 1585–1588.
- [8] For reviews, see: a) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795–819; b) F. Perron, K. F. Albizzati, *Chem. Rev.* **1989**, *89*, 1617–1661; c) M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407–2473.
- [9] a) J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180–7184; b) S. J. Shieh, J. S. Fan, M. Chandrasekharam, F.-L. Liao, S.-L. Wang, R.-S. Liu, *Organometallics* **1997**, *16*, 3987–3992; c) M. P. Doyle, D. C. Forbes, M. N. Protopopova, S. A. Stanley, M. M. Vasbinder, K. R. Xavier, *J. Org. Chem.* **1997**, *62*, 7210–7215.