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An Efficient Gold-Catalyzed Domino Process for the Construction of Tetracyclic Ketoethers

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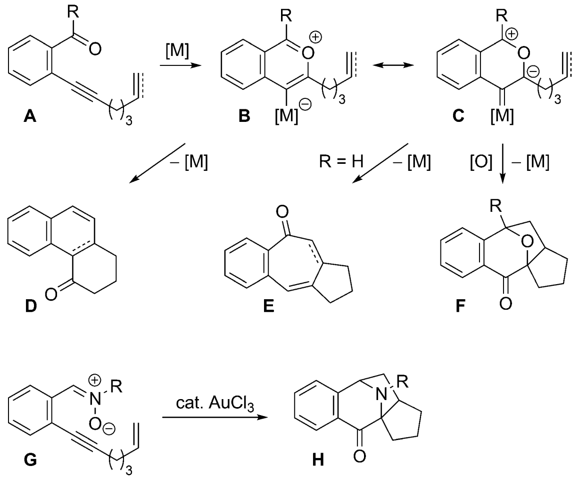
In the last decade gold has emerged as a transition metal that can catalyze a variety of synthetically useful transformations with high efficacy,[1] in particular cyclizations and cycloadditions.[2] Pioneering work[3,4] on metal-catalyzed benzannulations with diyne or enyne carbonyl compounds **A** showed that naphthalenes **D** are obtained from the diynes with Au^{III}-catalysts and the corresponding dihydronaphthalenes **D** from the enynes with $Cu(OTf)_2$ (Scheme 1).



Scheme 1. Metal-catalyzed domino reactions of diyne and enyne carbonyl compounds **A** and the corresponding nitrones **G**. [M] = metal catalyst, [O] = oxidant.

The isobenzopyrylium intermediate **B** reacts here with net [4+2] cycloaddition,[3–6] which can also result from 1,3-dipolar cycloaddition (cf. **C**) and subsequent 1,2-shift.[7] In contrast, dienones or enones **E** were formed by Au^{III}-catalysis with diyne and enyne benzaldehydes **A** bearing a geminal diester group between the C,C multiple bonds.[8] Previously, polycycles of type **F** were accessible only from α-diazocarbonyl compounds under Rh^{II} catalysis[9] or through photolysis of α,β-epoxyketones.[10] In more recent work on transition-metal catalysis, the transformation of enyne benzaldehydes **A** to polyoxacycles **F** by Rh^{I} catalysis at high temperature[11] as well as Pt^{II} catalysis was reported, whereby the latter provides the tetracycle only as a byproduct.[12] An Au^{III}-catalyzed reaction of a benzaldehyde substrate of type **A** with a terminal allene to give a tetracycle of type **F** was described as well.[13] In all these cases, water apparently acts as external oxidant. Alternatively, an iodine-mediated transformation to **F** under alkaline conditions can be performed for enyne benzaldehydes **A**, which might be problematic with ketones **A** (R = alkyl) bearing α-C–H bonds.[14] N-Bridged polycyclic ketones **H** corresponding to **F** were prepared from nitrones **G** by means of gold catalysis[15] via an intramolecular redox process to generate the ketone function.[16]

Herein we report an efficient gold-catalyzed domino reaction of enyne aldehydes and ketones **A** as well as related substrates to afford tetracyclic ketoethers **F** and heteroaromatic analogues by using pyridine *N*-oxides[17] as external oxidants.[18] In addition, we show that an alternative tethering[3] of the reactive units in **A** (cf. **4**) also allows a domino reaction to constitutionally isomeric tetracycles under these conditions.[10]

Alkyne **1a** easily available through Sonogashira coupling of 2-iodoacetophenone and 4,4-dimethyl-6-hepten-1-yne[19] was selected to determine suitable reaction conditions (Table 1). Catalyst screening started with $IPrAuCl/AgNTf_2$ and $PPh_3AuCl/AgNTf_2$ with pyridine *N*-oxide **3a** as an oxidant in dichloroethane (entries 1 and 2). These combinations already produced the desired tetracycle **2a**, albeit with moderate yields. The relative configuration of **2a** was unambiguously determined by X-ray diffraction analysis.[20] Even $AgNTf_2$ alone showed a corresponding reactivity, although to a lesser extent and accompanied by the formation of decomposition products (entry 3). The $gold^{I}$ species $Me_4tBuXPhosAuNTf_2$[21] provided **2a** in very high yield (entry 4). Fortunately, AuCl already caused a similarly efficient transformation in only a fraction of the time (entry 5), and its higher oxidized counterpart $AuCl_3$ led to a further increase in yield in just 10 min (entry 6). Even with a catalyst loading of only 0.1 mol% $AuCl_3$, **2a** was isolated in almost quantitative yield, but only after a significantly prolonged reaction time (entry 7).[22] Dichloromethane and nitromethane proved to be suitable solvents as well (entries 8 and

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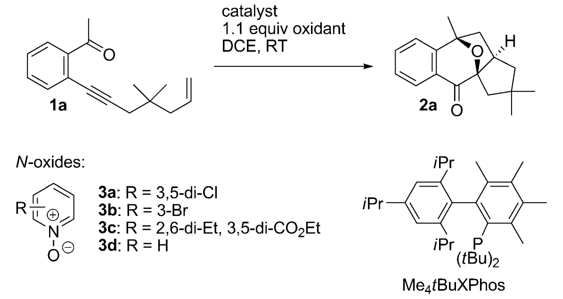
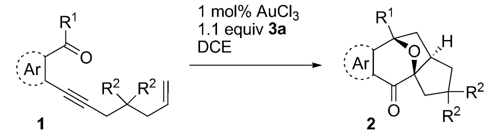
Table 1. Reaction optimization.

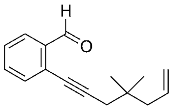
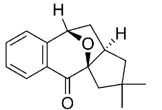
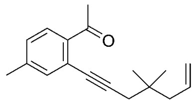
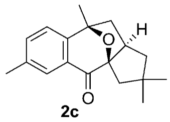
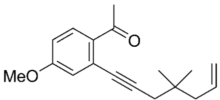
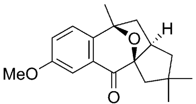
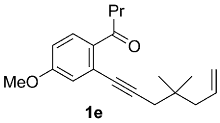
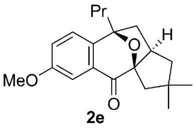
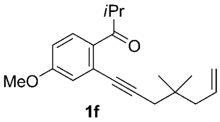
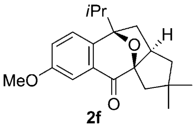
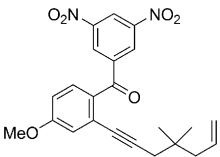
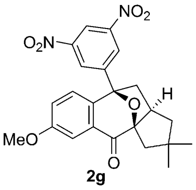
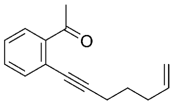
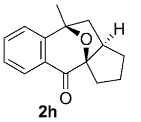
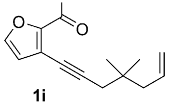
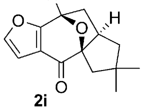
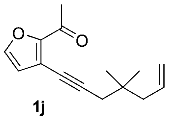
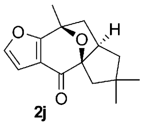
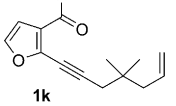
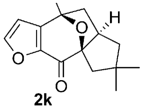
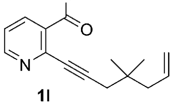
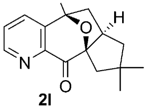


No.	Catalyst [mol %]	Oxidant	Time	Yield [%][a]
1	IPrAuCl/AgNTf$_2$ (1)	**3a**	3 h	50
2	PPh$_3$AuCl/AgNTf$_2$ (2)	**3a**	2 h	54
3	AgNTf$_2$ (1)	**3a**	19 h	20
4	Me$_4$*t*BuXPhosAuNTf$_2$ (1)	**3a**	6.5 h	95
5	AuCl (1)	**3a**	15 min	85
6	**AuCl$_3$ (1)**	**3a**	**10 min**	**96**
7	AuCl$_3$ (0.1)	**3a**	22 h	98
8[b]	AuCl$_3$ (1)	**3a**	30 min	94
9[c]	AuCl$_3$ (1)	**3a**	1.5 h	93
10	PtCl$_2$ (12)	**3a**[d]	1 d	–[e]
11	Rh$_2$(oct)$_4$ (5)	**3a**[d]	1 d	–[f]
12	AuCl$_3$ (2)	**3b**[g]	2 h	70
13	AuCl$_3$ (1)	**3c**	20 min	64
14	AuCl$_3$ (1)	**3d**	55 min	47
15	AuCl$_3$ (1)	UHP[d]	30 min	40
16	AuCl$_3$ (1)	–	2.4 h	–[h]

[a] Yield of isolated product. [b] Dichloromethane as solvent. [c] Nitromethane as solvent. [d] 1.2 equivalents. [e] Traces of **2a** according to GCMS analysis. [f] No conversion according to GC/MS analysis. [g] 1.6 equivalents. [h] Unselective formation of many products. DCE: 1,2-dichloroethane, IPr 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Tf = trifluoromethanesulfonyl, oct = octanoate, UHP = urea hydrogen peroxide complex.

Table 2. Scope of the gold-catalyzed domino reaction.



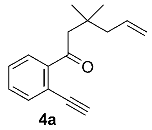
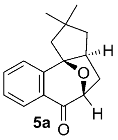
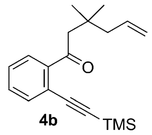
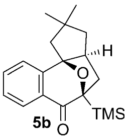
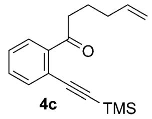
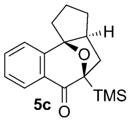
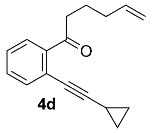
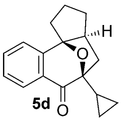
No.	Substrate	Product	Conditions	Yield [%][a]
1	 **1b**	 **2b**	RT 30 min	85
2	 **1c**	 **2c**	RT 1 h	62
3	 **1d**	 **2d**	50 °C 2 h	71
4	 **1e**	 **2e**	50 °C 16 h	75
5	 **1f**	 **2f**	65 °C 18 h	71
6	 **1g**	 **2g**	50 °C 15 min	88
7	 **1h**	 **2h**	RT 2 h	80
8	 **1i**	 **2i**	50 °C 28 h	64 (83)[b]
9	 **1j**	 **2j**	50 °C 22 h	67
10	 **1k**	 **2k**	50 °C 5.5 h	79
11	 **1l**	 **2l**	50 °C 2 h	70 (90)[b]

[a] Yield of isolated product. [b] Based on recovered starting material.

9). Platinum(II)chloride and rhodium(II)octanoate turned out to be unreactive (entries 10 and 11). Variation of the oxidant showed that in addition to the hygroscopic *N*-oxide **3b** also the oxidized Hantzsch ester **3c**,[21] unsubstituted pyridine-*N*-oxide (**3d**), and even the urea hydrogen peroxide complex can be used with less efficiency (entries 12–15), whereas an unselective product formation was observed in the absence of any oxidant (entry 16).

Table 2 illustrates the scope of the gold-catalyzed domino reaction under optimized conditions. Similarly to ketone **1a**, aldehyde **1b** was converted rapidly and with high yield into tetracyclic ketoether **2b**, the relative configuration of which was also confirmed by X-ray diffraction analysis (entry 1).[20] The methyl-substituted aromatic ketone **1c** already reacted at room temperature as well (entry 2). When a methoxy group that can additionally interact with the Lewis acid AuCl$_3$ is present at the aromatic nucleus, the reaction temperature should be slightly increased to achieve a marked turnover (entries 3–6). However, then even α-branching (**1f**) and an electron-deficient aromatic moiety (**1g**) are well-tolerated in the ketones. Interestingly, substrate **1h** lacking a geminal dimethyl substitution between alkyne and olefin reacted almost as efficiently as ketone **1a** (entry 7). Thus, a Thorpe–Ingold or *gem*-disubstituent effect[23] is not imperative for a smooth formation of tetracycles **2**, which considerably extends the synthetic applicability of the domino process reported here. Also electron-rich (**1i**–**k**) as well as electron-deficient heteroaromatic substrates (**1l**) reacted at 50 °C to give the desired tetracyclic products in good yields (entries 8–11).

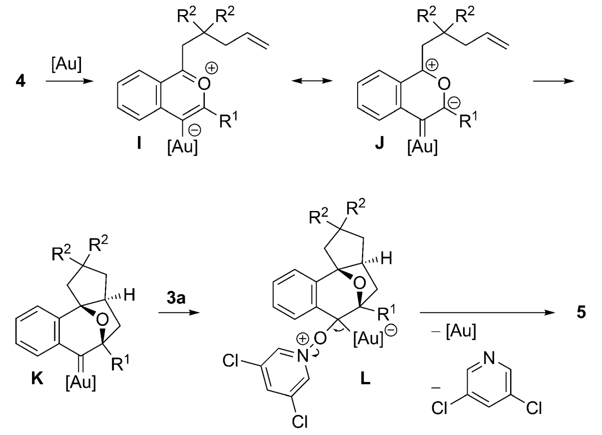
Table 3. Alternative tethering of the reactive units.

No.	Substrate	Product	Conditions	Yield [%][a]
1	 **4a**	 **5a**	RT 1 h	–[b], 90[c]
	⇓	↑ [d]		
2	 **4b**	 **5b**	RT 2 h	73
3	 **4c**	 **5c**	RT 5 h	71
4	 **4d**	 **5d**	50 °C 5 h	57 (84)[e]

[a] Yield of isolated product. [b] Unselective formation of many products. [c] From **5b**. [d] K_2CO_3, MeOH, RT, 18 h. [e] Based on recovered starting material.

Since ketones with α-C–H bonds can be used without problems under the conditions found here, an alternative tethering[3] of the reactive units was investigated too (Table 3). Initially, ketone **4a** was subjected to the conditions optimized for **1a**, but a variety of other products was formed instead of tetracycle **5a** (Table 3, entry 1). As the terminal alkyne **4a** was prepared by desilylation of the trimethylsilyl derivative **4b**, we also studied **4b** as a substrate for the gold-catalyzed domino reaction (entry 2). Indeed, TMS substitution of the alkyne allowed a rapid and efficient transformation already at room temperature into the α-silylketone **5b**, the relative configuration of which was secured by X-ray diffraction analysis.[20] With potassium carbonate in methanol a mild desilylation of **5b** succeeded to give **5a** in high yield. As the reactions of substrates **4c**[24] and **4d** indicate, again no geminal disubstitution in the alkyl bridge to the olefin is necessary (entries 3 and 4). Although the cyclopropyl substrate **4d** was heated to 50 °C to increase conversion, its transformation to **5d** proceeded smoothly and without competing ring expansion.[25] Thus, the hydrobenzoazulene ring systems of the dolastane and neodolastane diterpenes (**2a**–**h**)[26a] as well as of the daphnane, tigliane, and rhamnofolane diterpenes (**5a**–**d**)[26b] can be obtained by the domino process reported here.

Mechanistically, formation of the tetracyclic ketoethers **2** and **5** can be rationalized as illustrated in Scheme 2 for **5**. An intramolecular 6-*endo*-dig attack of the carbonyl oxygen atom on the gold-activated alkyne to give the isobenzopyrylium intermediate **I** and a subsequent intramolecular 1,3-dipolar cycloaddition (c.f. **J**) afford gold carbenoid **K**. Intermolecular oxidation of **K** with the *N*-oxide **3a** leads eventually via adduct **L** to the isolated product **5** with regeneration of the gold catalyst. Regardless of the nature of the substrates[27a] and the gold catalyst,[27b,c] no products resulting from an initiating 5-*exo*-dig cyclization were observed in our studies. Moreover, even in the absence of a *gem* disubstitution in the tether, a [3+2] cycloaddition was involved for all substrates, making its participation[7] also likely for the formation of products **D** from **A** (c.f. Scheme 1).



Scheme 2. Mechanism for the formation of the tetracyclic ketoethers exemplified by products **5**. [Au] = gold catalyst.

In summary, a mild and efficient oxidative domino cyclization/cycloaddition of enyne aldehydes and ketones **1** and **4** to give the polyfunctional tetracycles **2** or **5**, respectively, succeeded using gold(III)chloride as the catalyst already with low loading in the presence of pyridine *N*-oxide **3a**. A geminal disubstitution in the tether between alkyne and alkene was not required, and instead of a terminal alkyne not tolerated in **4**, the corresponding trimethylsilyl derivative could be used without any problems.

Acknowledgements

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Keywords: catalysis · cycloaddition · domino reactions · gold · oxidation

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[1] *Modern Gold Catalyzed Synthesis* (Eds.: A. S. K. Hashmi, F. D. Toste), WILEY-VCH, Weinheim, **2012**.

[2] Selected recent reviews: a) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; b) P. Belmont, E. Parker, *Eur. J. Org. Chem.* **2009**, 6075–6089; c) A. Das, S. M. Abu Sohel, R.-S. Liu, *Org. Biomol. Chem.* **2010**, *8*, 960–979; d) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675–691; e) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692–706; f) S. Sengupta, X. Shi, *ChemCatChem* **2010**, *2*, 609–619; g) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360–5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; h) S. P. Nolan, *Acc. Chem. Res.* **2011**, *44*, 91–100; i) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994–2009; j) M. Bandini, *Chem. Soc. Rev.* **2011**, *40*, 1358–1367; k) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657–1712; l) M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2011**, *47*, 6536–6544; m) A. Pradal, P. Y. Toullec, V. Michelet, *Synthesis* **2011**, 1501–1514; n) H. Huang, Y. Zhou, H. Liu, *Beilstein J. Org. Chem.* **2011**, *7*, 897–936; o) F. López, J. L. Mascareñas, *Beilstein J. Org. Chem.* **2011**, *7*, 1075–1094; p) B. Alcaide, P. Almendros, J. M. Alonso, *Molecules* **2011**, *16*, 7815–7843; q) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448–2462; r) D. Garayalde, C. Nevado, *ACS Catal.* **2012**, *2*, 1462–1479; s) N. Huguet, A. M. Echavarren, *Top. Organomet. Chem.* **2011**, *43*, 291–324.

[3] N. Asao, K. Sato, Menggenbateer, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 3682–3685.

[4] For intermolecular cycloadditions with alkynes and alkenes, see: a) N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 12650–12651; b) N. Asao, T. Kasahara, Y. Yamamoto, *Angew. Chem.* **2003**, *115*, 3628–3630; *Angew. Chem. Int. Ed.* **2003**, *42*, 3504–3506.

[5] a) G. Dyker, D. Hildebrandt, J. Liu, K. Merz, *Angew. Chem.* **2003**, *115*, 4536–4538; *Angew. Chem. Int. Ed.* **2003**, *42*, 4399–4402; b) G. Dyker, D. Hildebrandt, *J. Org. Chem.* **2005**, *70*, 6093–6096.

[6] a) N. Asao, *Synlett* **2006**, 1645–1656; b) N. T. Patil, Y. Yamamoto, *Arkivoc* **2007**, 6–19.

[7] B. F. Straub, *Chem. Commun.* **2004**, 1726–1728.

[8] N. Kim, Y. Kim, W. Park, D. Sung, A. K. Gupta, C. H. Oh, *Org. Lett.* **2005**, *7*, 5289–5291.

[9] a) A. Padwa, L. Precedo, M. A. Semones, *J. Org. Chem.* **1999**, *64*, 4079–4088; b) Review: A. Padwa, *Tetrahedron* **2011**, *67*, 8057–8072.

[10] K. S. Feldman, *Tetrahedron Lett.* **1983**, *24*, 5585–5586.

[11] S. Shin, A. K. Gupta, C. Y. Rhim, C. H. Oh, *Chem. Commun.* **2005**, 4429–4431.

[12] C. H. Oh, S. M. Lee, C. S. Hong, *Org. Lett.* **2010**, *12*, 1308–1311.

[13] A. K. Gupta, C. Y. Rhim, C. H. Oh, R. S. Mane, S.-H. Han, *Green Chem.* **2006**, *8*, 25–28.

[14] Y.-X. Xie, Z.-Y. Yan, B. Qian, W.-Y. Deng, D.-Z. Wang, L.-Y. Wu, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* **2009**, 5451–5453.

[15] a) H.-S. Yeom, J.-E. Lee, S. Shin, *Angew. Chem.* **2008**, *120*, 7148–7151; *Angew. Chem. Int. Ed.* **2008**, *47*, 7040–7043; b) J. Jeong, H.-S. Yeom, O. Kwon, S. Shin, *Chem. Asian J.* **2011**, *6*, 1977–1981.

[16] For an intramolecular redox process in a gold-catalyzed reaction of nitro alkynes, see: A. M. Jadhav, S. Bhunia, H.-Y. Liao, R.-S. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1769–1771.

[17] a) L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259; b) Review: J. Xiao, X. Li, *Angew. Chem.* **2011**, *123*, 7364–7375; *Angew. Chem. Int. Ed.* **2011**, *50*, 7226–7236.

[18] Recently, one example of a corresponding Ag^I-catalyzed transformation of an enyne benzaldehyde **A** in the presence of pyridine-*N*-oxide with moderate yield was published: S. Zhu, R. Liang, H. Jiang, W. Wu, *Angew. Chem.* **2012**, *124*, 11019–11023; *Angew. Chem. Int. Ed.* **2012**, *51*, 10861–10865.

[19] D. H. Hua, *J. Am. Chem. Soc.* **1986**, *108*, 3835–3837.

[20] CCDC-939890 (**2a**), 939891 (**2b**), and 939889 (**5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] Y. Wang, K. Ji, S. Lan, L. Zhang, *Angew. Chem.* **2012**, *124*, 1951–1954; *Angew. Chem. Int. Ed.* **2012**, *51*, 1915–1918.

[22] At a reaction temperature of 50 °C and a loading of 0.1 mol% $AuCl_3$, **2a** was isolated already after 2 h in 75% yield.

[23] a) R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc. Trans.* **1915**, *107*, 1080–1106; b) Review: M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735–1766.

[24] A. Padwa, K. E. Krumpe, M. D. Weingarten, *J. Org. Chem.* **1995**, *60*, 5595–5603.

[25] C.-W. Li, K. Pati, G.-Y. Lin, S. M. A. Sohel, H.-H. Hung, R.-S. Liu, *Angew. Chem.* **2010**, *122*, 10087–10090; *Angew. Chem. Int. Ed.* **2010**, *49*, 9891–9894.

[26] a) M. Hiersemann, H. Helmboldt, *Top. Curr. Chem.* **2005**, *243*, 73–136; b) R. K. Devappa, H. P. S. Makkar, K. Becker, *J. Am. Oil Chem. Soc.* **2011**, *88*, 301–322.

[27] a) J. Jeong, D. Ray, C. H. Oh, *Synlett* **2012**, *23*, 897–902; b) A. S. K. Hashmi, A. M. Schuster, S. Gaillard, L. Cavallo, A. Poater, S. P. Nolan, *Organometallics* **2011**, *30*, 6328–6337; c) G. Ung, M. Soleilhavoup, G. Bertrand, *Angew. Chem.* **2013**, *125*, 787–790; *Angew. Chem. Int. Ed.* **2013**, *52*, 758–761.

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