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Heterocycles

Rhodium- and Platinum-Catalyzed [4+3] Cycloaddition with Concomitant Indole Annulation: Synthesis of Cyclohepta[*b*]indoles[**]

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Seven-membered rings fused with an indole, cyclohepta[*b*]-indoles, are present in many bioactive natural products such as silicine,[1] ervitsine,[2] and actinophyllic acid (Figure 1).[3]

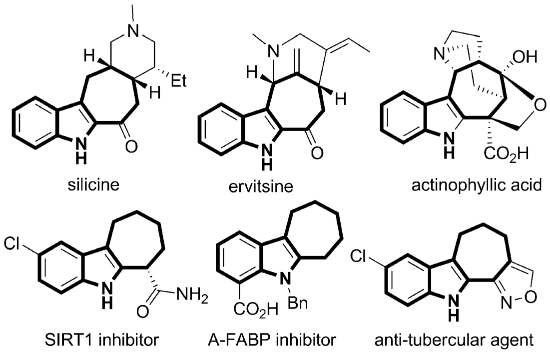
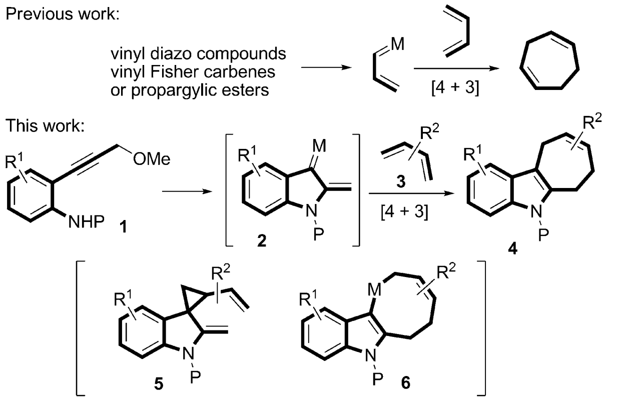


Figure 1. Representative cyclohepta[*b*]indoles.

They are also important structural motifs in numerous pharmaceuticals with various pharmacological properties such as inhibition of deacetylase SIRT1,[4] inhibition of adipocyte fatty-acid-binding protein (A-FABP),[5] and anti-tubercular activity.[6] Most previous efforts have focused on building the seven-membered ring and the indole separately by cyclization reactions.[4,5,7] Recently, an elegant three-component [4+3] cycloaddition was reported by Wu and co-workers for the synthesis of cyclohepta[*b*]indoles from indoles, aldehydes, and dienes.[8] It represents the first example of a [4+3] cycloaddition involving an indole as the 2π component. We herein report an efficient and versatile process that allows the simultaneous construction of both the indole and seven-membered ring through a [4+3] cycloaddition with concomitant indole annulation.[9]

Vinyl metal carbenes derived from vinyl diazo compounds can undergo formal [4+3] cycloadditions with dienes through a cyclopropanation/Cope rearrangement sequence (Scheme 1).[10,11] Similarly, vinyl Fisher carbenes[12] or vinyl gold carbenes derived from propargylic esters[13] can also react with dienes to form various seven-membered rings. It was recently reported that vinyl metal carbenes could be conveniently generated from propargylic ethers tethered with a nucleophile for a [3+2] cycloaddition[14] and a synthesis of furans.[15] We envisioned that the vinyl metal carbene **2**, derived from **1**, would undergo a formal [4+3] cycloaddition[16] with diene **3** to afford the cyclohepta[*b*]indole **4** by either a cyclopropanation/Cope rearrangement sequence involving the divinyl-cyclopropane **5**, or an unusual [4+4] cycloaddition to form the eight-membered metallacycle **6** with subsequent reductive elimination. Both indole and seven-membered rings may be constructed very efficiently in this tandem process from simple building blocks.



Scheme 1. [4+3] Cycloaddition of vinyl carbenes and dienes.

The transformation from the propargylic ether **1** to the product **4** requires a metal catalyst which has enough π acidity[17] to induce cyclization of **1**, thus forming a carbene intermediate, and the ability to promote cycloadditions. The catalyst [$\{Rh(CO)_2Cl\}_2$] can facilitate 1,3-acyloxy migration of propargylic esters, a process that is typically catalyzed by π-acidic metals,[17] and effects cycloadditions as well.[18,19] When a mixture of the propargylic ether **1a** and diene **3a** was treated with this catalyst at 80 °C, no reaction occurred (Table 1, entry 1). We have previously found that electron-deficient phosphine or phosphite ligands often increase the acidity of rhodium catalysts and promote 1,2-acyloxy[20] or 1,3-acyloxy[19] migration of propargylic esters. Indeed, a mixture of the [4+3] cycloaddition product **4a** and simple indole **7** was observed when **1a** was treated with [$\{Rh(CO)_2Cl\}_2$] in the presence of such ligands (entries 2–4). The amount of **7** could be minimized by employing a greater excess of **3a** (entry 4). A 67 % yield of the isolated tricyclic product **4a** could be obtained in the presence of a rhodium(I) metal complex and an electron-deficient phosphite ligand.

We also examined $PtCl_2$, $PtCl_2$/alkene, and $PtCl_2/PPh_3$, all of which have been used in the generation of vinyl platinum

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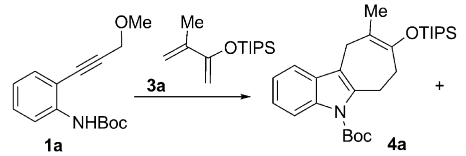
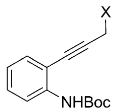
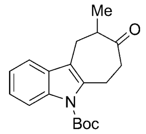
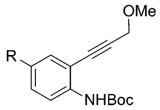
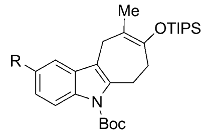
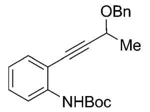
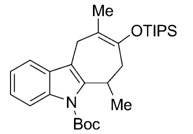
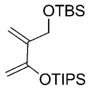
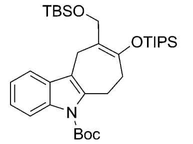
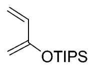
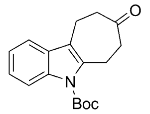
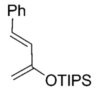
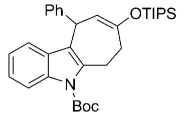
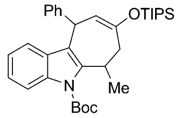
Table 1: Optimization for the reaction between **1a** and **3a**.[a]



Entry	Conditions	**4a** Yield [%][b]	**4a**/**7**
1[c]	$[\{\mathrm{Rh(CO)_2Cl}\}_2]$	no reaction	–
2[c]	$[\{\mathrm{Rh(CO)_2Cl}\}_2]$, $\mathrm{P[(CF_3)_2C_6H_3]_3}$	35	1:1
3[c]	$[\{\mathrm{Rh(CO)_2Cl}\}_2]$, $\mathrm{P(C_6F_5)_3}$	53	2:1
4	$[\{\mathrm{Rh(CO)_2Cl}\}_2]$, $\mathrm{P[OCH(CF_3)_2]_3}$	70 (67)[d]	4:1
5	$\mathrm{PtCl_2}$	28	1.6:1
6	$\mathrm{PtCl_2}$, octene	21	2:1
7	$[\mathrm{Pt(PPh_3)_2Cl_2}]$	no reaction	–
8	$\mathrm{PtCl_2}$, CO (1 atm)	18	4:1
9	$\mathrm{PtCl_2}$, $\mathrm{P[OCH(CF_3)_2]_3}$	66	8:1
10	$\mathrm{PtCl_2}$, $\mathrm{P[(CF_3)_2C_6H_3]_3}$	31	10:1
11	$\mathrm{PtCl_2}$, $\mathrm{P(C_6F_5)_3}$	85[d]	> 20:1
12	$[\mathrm{IrCl(CO)(PPh_3)_2}]$	no reaction	–
13	$\mathrm{PdCl_2}$	no reaction	–
14	$[\mathrm{AuClP}(p\text{-}\mathrm{CF_3C_6H_4})_3]$	no reaction	–

[a] Reaction conditions: 10 mol% metal catalyst, 20 mol% ligand, diene **3a** (5 equiv), 80 °C, 1,4-dioxane, $\mathrm{Na_2CO_3}$, 12 h, unless noted otherwise. [b] Yields based on ^{1}H NMR spectroscopy. [c] Used 2 equiv of **3a**. [d] Yield of isolated product. Boc = *tert*-butoxycarbonyl, TIPS = triisopropylsilyl.

Table 2: Scope of propargylic ethers and acyclic dienes.[a]

Entry	**1**	**3**	Product	Yield [%]
				
1[b]	**1a** (X = OMe)	**3a**	**8a**	82
2[b]	**1b** (X = OBn)	**3a**	**8a**	80
				
3	**1c** ($\mathrm{R = CO_2Et}$)	**3a**	**4c**	83
4	**1d** (R = OMe)	**3a**	**4d**	86
5	**1e** ($\mathrm{R = CH_2OH}$)	**3a**	**4e**	52
6	**1f** (R = CHO)	**3a**	**4f**	83
				
7[c]	**1g**	**3a**	**4g**	56
				
8	**1a**	**3b**	**4ab**	90
				
9[b,d]	**1a**	**3c**	**8ac**	59
				
10[d]	**1a**	**3d**	**4ad**	66
				
11	**1g**	**3d**	**4gd**	50 (d.r. = 3:1)

[a] Reaction conditions: $\mathrm{PtCl_2}$ (10 mol%), $\mathrm{P(C_6F_5)_3}$ (20 mol%), diene **3** (5.0 equiv), 80 °C, 1,4-dioxane, $\mathrm{Na_2CO_3}$, 12 h. Yields are those of the isolated products. [b] The resulting product was treated with aqueous HCl (4 M). [c] Used 1.5 equiv of**3a**. [d] $[\{\mathrm{Rh(CO)_2Cl}\}_2]$ (5 mol%) and $\mathrm{P[OCH(CF_3)_2]_3}$ (20 mol%) were employed. TBS = *tert*-butyldimethylsilyl.

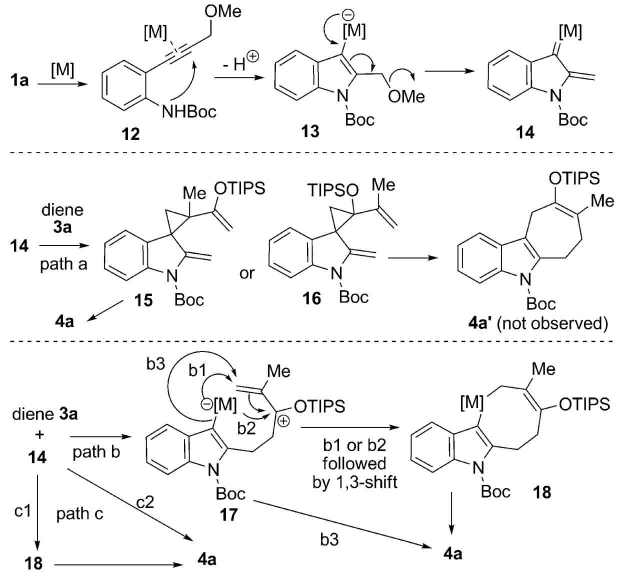
carbenes from propargylic ethers.[14,15] A low yield of **4a** or no product, however, was observed using these catalysts (Table 1, entries 5–8). We suspect that the coordination of the bidentate diene **3a** to $\mathrm{PtCl_2}$ may reduce the acidity of the metal. Electron-deficient phosphite or phosphine ligands were then added to further enhance the reactivity of the $\mathrm{PtCl_2}$ catalyst (entries 9–11). Indeed, the yield of **4a** was increased significantly. The tris(pentafluorophenyl)phosphine ligand provided the highest yield of the isolated product **4a** (entry 11). A lower catalyst loading led to lower conversion, and other metal catalysts did not afford the desired product (entries 12–14).

With the two catalysts in hand (Table 1, entries 4 and 11), we studied the scope of this tandem indole annulation/[4+3] cycloaddition with different propargylic ethers (Table 2, entries 1–7). The ketone **8a** was isolated in 82% yield after in situ hydrolysis of the silyl enol ether **4a** (entry 1). A benzyl ether could also be tolerated (entry 2), and other leaving groups (e.g. X = OH, OPiv, or Cl) led to a complex mixture. Electron-withdrawing or electron-donating groups on the benzene ring change the nucleophilicity of the aniline nitrogen atom, however the efficiency of the indole annulation/[4+3] cycloaddition did not change with either type of substituent (entries 3 and 4). A lower yield was observed for the substrate **1e** having a free alcohol (entry 5), and a formyl group did not interfere with the tandem reaction (entry 6). The secondary propargylic ether **1g** also participated in the tandem reaction and yielded **4g** (entry 7).

We next investigated the scope of acyclic dienes that could be used in this process (Table 2, entries 8–10). The more functionalized 2,3-disubstituted diene **3b** afforded **4ab** in high yield (entry 8, Table 2). The monosubstituted diene **3c** produced **8ac** in 59% yield in the presence of a rhodium catalyst (entry 9), and lower yields were obtained when various platinum catalysts were employed in this case. The same trend was also observed for **3d** (entry 10). When platinum catalysts were employed, the yield of **4ad** was 20–30% lower than that obtained from using the rhodium catalyst, and a diastereomeric mixture of **4gd** was isolated when **3d** was reacted with the propargylic ether **1g** (entry 11). A complex mixture was observed when substrate **1a** was treated with 2-methyl-1,3-butadiene in the presence of either the platinum or rhodium catalyst, thus suggesting that the siloxy substituent is critical for the reactivity of acyclic dienes.

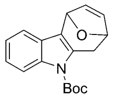
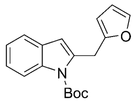
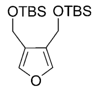
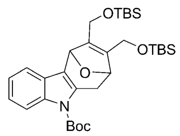
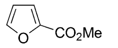
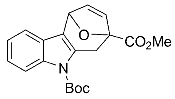
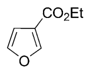
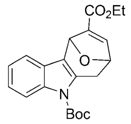
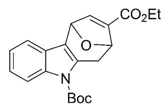
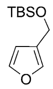
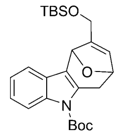
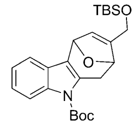
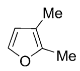
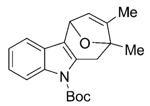
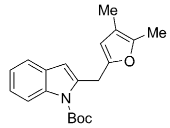
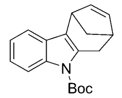
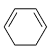
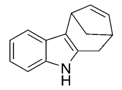
We were pleased to find that the furan **9a** participated in the tandem reaction and afforded the tetracyclic product **10a** in 71% yield (Table 3, entry 1). The arylation product **11a** was isolated in 14% yield. For the 3,4-disubstituted furan **9b**, a single product, **10b**, was observed (entry 2). The yields for the ester-substituted furans **9c** and **9d** were slightly lower (entries 3 and 4), and two tetracyclic isomers were obtained for the nonsymmetric furans **9d** and **9e** (entries 4 and 5). The 2,3-dimethylfuran **9f** only afforded one tetracyclic isomer (**10f**; entry 6), however, the arylation product **11f** was also obtained in this case. When pyrrole was employed, only the arylation product was observed.[21] To our surprise, the tetracyclic product **10g** could be prepared in 63% yield from the simple cyclopentadiene (**9g**; entry 7). Cyclohexadiene (**9h**) also participated in the tandem reaction and afforded the free indole **10h** after removing the Boc-protecting group (entry 8). It is worth mentioning that the substitution pattern of the products and the scope of dienes are complementary to that of the [4+3] cycloaddition for the synthesis of cyclohepta[*b*]indoles reported by Wu and coworkers[8]

Possible mechanisms for the tandem indole annulation/[4+3] cycloaddition are shown in Scheme 2. The metal carbene **14** can be generated by 5-*endo*-cyclization and elimination of methanol.[14,15] Several potential pathways can be proposed for the cycloaddition. In path a, cyclopropanation of diene **3a** may afford the divinylcyclopropanes **15** or **16**, which undergo Cope rearrangement to produce the products **4a** or **4a′**, respectively. In path b, nucleophilic attack of the silyl enol ether onto the vinyl carbene may produce the ionic intermediate **17**. The metallacycle **18** can be formed through path b1 directly or from a six-membered metallacycle by path b2 followed by a 1,3-shift. Reductive elimination of



Scheme 2. Proposed mechanisms for the [4+3] cycloaddition accompanied by an indole annulation.

Table 3: Scope of cyclic dienes for the tandem reaction with the propargylic ether **1a**.[a]

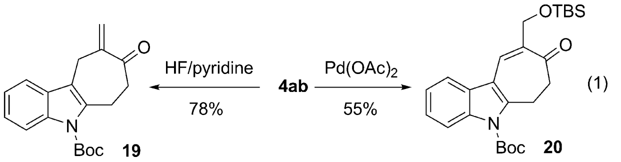
Entry	9	Products[b]	
1[c]	 **9a**	 **10a** (71 %)	 **11a** (14 %)
2	 **9b**	 **10b** (79 %)	
3	 **9c**	 **10c** (52 %)	
4	 **9d**	 **10d** (44 %)	 **10d′** (23 %)
5	 **9e**	 **10e** (83 %)[d] **10e** /**10e′** = 1:1.5	 **10e′**
6	 **9f**	 **10f** (58 %)	 **11f** (30 %)
7	 **9g**	 **10g** (63 %)	
8	 **9h**	 **10h** (61 %)[e]	

[a] Reaction conditions: $PtCl_2$ (10 mol%), $P(C_6F_5)_3$ (20 mol%), diene **5** (1.5–5.0 equiv), 80°C, 1,4-dioxane, Na_2CO_3, 12 h. [b] Yield for isolated product given within parentheses. [c] $PtCl_2$ (5 mol%), $P(C_6F_5)_3$ (10 mol%) [d] Yield for **10e** and **10e′** combined. [e] The Boc protecting group was removed by the treatment with trifluoroacetic acid. The yield is the overall yield for two steps.

18 can then afford the product **4a**. Alternatively, cyclization through path b3 may produce product **4a** directly. In path c1, a concerted [4+4] cycloaddition between the carbene **14** and diene **3a** may also lead to metallacycle **18**. A [4+3] cycloaddition with a concomitant elimination of the metal through path c2 is also possible and may yield product **4a** directly.

Based on the regioselectivity reported previously,[10,11] cyclopropanation of diene **3a** should occur on the electron-rich silyl enol ether selectively and afford the cyclopropane **16**, which would produce the isomeric product **4a′**. Since only isomer **4a** was observed, [4+3] cycloadditions through paths b or c are more likely for the dienes **3** and **9**. This reactivity represents a new class of [4+3] cycloadditions in which the 2π component is an indole derivative.[8]

Treatment of the product **4ab** with HF/pyridine provided **19**, which could be easily functionalized [Eq. (1)]. Saegusa oxidation[22] of the same silyl enol ether yielded enone **20**.



(1)

In summary, a novel indole annulation/[4+3] cycloaddition sequence was developed for the synthesis of various substituted cyclohepta[*b*]indoles. Both acyclic and cyclic dienes participated in this tandem reaction, and high regioselectivity was observed for the [4+3] cycloaddition in most cases. Application of this method to the synthesis of natural products and pharmaceutical agents is underway and will be reported in due course.

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[1] A. Shafiee, A. Ahond, A. M. Bui, Y. Langlois, C. Riche, P. Potier, *Tetrahedron Lett.* **1976**, *17*, 921.

[2] M. Andriantsiferana, R. Besselievre, C. Riche, H. P. Husson, *Tetrahedron Lett.* **1977**, *18*, 2587.

[3] a) A. R. Carroll, E. Hyde, J. Smith, R. J. Quinn, G. Guymer, P. I. Forster, *J. Org. Chem.* **2005**, *70*, 1096; b) T. Taniguchi, C. L. Martin, K. Monde, K. Nakanishi, N. Berova, L. E. Overman, *J. Nat. Prod.* **2009**, *72*, 430.

[4] A. D. Napper, J. Hixon, T. McDonagh, K. Keavey, J. F. Pons, J. Barker, W. T. Yau, P. Amouzegh, A. Flegg, E. Hamelin, R. J. Thomas, M. Kates, S. Jones, M. A. Navia, J. Saunders, P. S. DiStefano, R. Curtis, *J. Med. Chem.* **2005**, *48*, 8045.

[5] T. Barf, F. Lehmann, K. Hammer, S. Haile, E. Axen, C. Medina, J. Uppenberg, S. Svensson, L. Rondahl, T. Lundbaeck, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1745.

[6] E. Yamuna, R. A. Kumar, M. Zeller, K. J. R. Prasad, *Eur. J. Med. Chem.* **2012**, *47*, 228.

[7] a) M. L. Bennasar, B. Vidal, J. Bosch, *J. Am. Chem. Soc.* **1993**, *115*, 5340; b) M. L. Bennasar, B. Vidal, J. Bosch, *J. Org. Chem.* **1997**, *62*, 3597; c) C. L. Martin, L. E. Overman, J. M. Rohde, *J. Am. Chem. Soc.* **2008**, *130*, 7568; d) R. G. Vaswani, J. J. Day, J. L. Wood, *Org. Lett.* **2009**, *11*, 4532; e) M. Amat, N. Llor, B. Checa, E. Molins, J. Bosch, *J. Org. Chem.* **2010**, *75*, 178; f) C. L. Martin, L. E. Overman, J. M. Rohde, *J. Am. Chem. Soc.* **2010**, *132*, 4894; g) H. Zaimoku, T. Taniguchi, H. Ishibashi, *Org. Lett.* **2012**, *14*, 1656.

[8] X. Han, H. Li, R. P. Hughes, J. Wu, *Angew. Chem.* **2012**, *124*, 10536; *Angew. Chem. Int. Ed.* **2012**, *51*, 10390.

[9] For recent reviews on indole synthesis, see: a) J. Barluenga, F. Rodriguez, F. J. Fananas, *Chem. Asian J.* **2009**, *4*, 1036; b) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195; c) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469.

[10] For reviews on sequential cyclopropanation and Cope rearrangement, see: a) H. M. L. Davies, *Tetrahedron* **1993**, *49*, 5203; b) H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev.* **2009**, *38*, 3061.

[11] For selected examples of sequential cyclopropanation and Cope rearrangement, see: a) H. M. L. Davies, H. D. Smith, O. Korkor, *Tetrahedron Lett.* **1987**, *28*, 1853; b) H. M. L. Davies, M. J. McAfee, C. E. M. Oldenburg, *J. Org. Chem.* **1989**, *54*, 930; c) R. P. Reddy, H. M. L. Davies, *J. Am. Chem. Soc.* **2007**, *129*, 10312; d) J. P. Olson, H. M. L. Davies, *Org. Lett.* **2008**, *10*, 573.

[12] a) W. D. Wulff, D. C. Yang, C. K. Murray, *J. Am. Chem. Soc.* **1988**, *110*, 2653; b) J. Barluenga, F. Aznar, A. Martin, S. Garciagranda, M. A. Salvado, P. Pertierra, *J. Chem. Soc. Chem. Commun.* **1993**, 319; c) J. Barluenga, F. Aznar, A. Martin, J. T. Vazquez, *J. Am. Chem. Soc.* **1995**, *117*, 9419; d) J. Barluenga, F. Aznar, M. Fernandez, *Chem. Eur. J.* **1997**, *3*, 1629; e) M. Hoffmann, M. Buchert, H. U. Reissig, *Chem. Eur. J.* **1999**, *5*, 876; f) J. Barluenga, J. Alonso, F. Rodriguez, F. J. Fananas, *Angew. Chem.* **2000**, *112*, 2555; *Angew. Chem. Int. Ed.* **2000**, *39*, 2459; g) J. Barluenga, J. Alonso, F. J. Fananas, *Chem. Eur. J.* **2005**, *11*, 4995; h) F. Aznar, M. Fananas-Mastral, J. Alonso, F. J. Fananas, *Chem. Eur. J.* **2008**, *14*, 325.

[13] a) K. Miki, K. Ohe, S. Uemura, *J. Org. Chem.* **2003**, *68*, 8505; b) B. W. Gung, L. N. Bailey, J. Wonser, *Tetrahedron Lett.* **2010**, *51*, 2251; c) D. Garayalde, K. Kruger, C. Nevado, *Angew. Chem.* **2011**, *123*, 941; *Angew. Chem. Int. Ed.* **2011**, *50*, 911.

[14] K. Saito, H. Sogou, T. Suga, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2011**, *133*, 689.

[15] P. A. Allegretti, E. M. Ferreira, *Org. Lett.* **2011**, *13*, 5924.

[16] For recent reviews on [4+3] cycloadditions, see: a) M. Harmata, *Adv. Synth. Catal.* **2006**, *348*, 2297; b) M. Harmata, *Chem. Commun.* **2010**, *46*, 8886; c) M. Harmata, *Chem. Commun.* **2010**, *46*, 8904; d) A. G. Lohse, R. P. Hsung, *Chem. Eur. J.* **2011**, *17*, 3812.

[17] For selected reviews on π-acidic metal catalysis, see: a) N. Marion, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 2806; *Angew. Chem. Int. Ed.* **2007**, *46*, 2750; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; c) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; d) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395; e) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692; f) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232; g) X.-Z. Shu, D. Shu, C. M. Schienebeck, W. Tang, *Chem. Soc. Rev.* **2012**, *41*, 7698.

[18] a) D. Shu, X. Li, M. Zhang, P. J. Robichaux, W. Tang, *Angew. Chem.* **2011**, *123*, 1382; *Angew. Chem. Int. Ed.* **2011**, *50*, 1346; b) X. Li, S. Huang, C. M. Schienebeck, D. Shu, W. Tang, *Org. Lett.* **2012**, *14*, 1584.

[19] S. Huang, X. Li, C. L. Lin, I. A. Guzei, W. Tang, *Chem. Commun.* **2012**, *48*, 2204.

[20] a) X.-z. Shu, S. Huang, D. Shu, I. A. Guzei, W. Tang, *Angew. Chem.* **2011**, *123*, 8303; *Angew. Chem. Int. Ed.* **2011**, *50*, 8153; b) X.-z. Shu, X. Li, D. Shu, S. Huang, C. M. Schienebeck, X. Zhou, P. J. Robichaux, W. Tang, *J. Am. Chem. Soc.* **2012**, *134*, 5211.

[21] C. J. Cramer, S. E. Barrows, *J. Org. Chem.* **1998**, *63*, 5523.

[22] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011.