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Reactions of Zirconocene−1-Aza-1,3-diene Complexes with Acyl Cyanides: Substrate-Dependent Synthesis of Acyl- or Non-Acyl-Substituted Pyrroles

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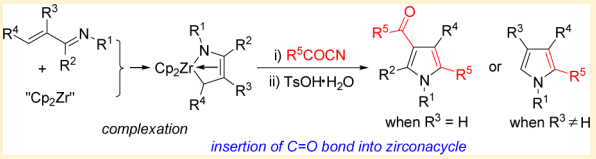
Supporting Information

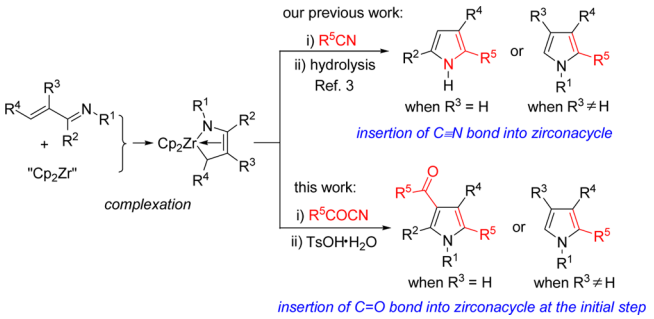
ABSTRACT: Insertion of acyl cyanides into azazirconacyclopentenes derived from 1,3-azadienes has been described, which affords acyl- or non-acyl-substituted pyrroles upon acidic quenching. These reactions are initialized through C═O insertion into the azazirconacycle to afford seven-membered oxaazazirconacycles. In the cases of 1,4- or 1,2,4-substituted azadienes, addition of a second molecule of acyl cyanide followed by cyclization upon acidic quenching leads to acyl-substituted pyrroles. In the cases of 1,3,4-substituted azadienes, the addition of a second molecule of acyl cyanide cannot proceed due to the steric hindrance caused by the R^3 group on the zirconium intermediate. Acidic quenching of the resulting zirconium intermediate affords non-acyl-substituted pyrroles.



INTRODUCTION

Zirconocene−1-aza-1,3-diene complexes, which can be described as σ^2,π-2-azazirconacyclo-3-pentenes, are attractive intermediates for further transformation reactions, since they can undergo various insertion reactions formally through their highly polarized Zr−C bonds with unsaturated compounds.[1,2] They are known to react with *tert*-butyl isocyanide,[1a] ketones,[1b,d,i] special imines,[1f] and $PhBCl_2$;[1h] nevertheless, the synthetic utility of these azadiene complexes has far less been explored. Recently, we have reported a direct insertion of nitriles into zirconocene−1-aza-1,3-diene complexes, which provided an efficient, regioselective, and controllable synthesis of *N*-H and/or *N*-substituted pyrroles upon acidic aqueous workup.[3,4] The reaction outcome was dependent on the substitution patterns of the azadiene substrates (Scheme 1). On the other hand, acyl cyanides are one of the most important classes of functionalized nitriles, and the proximity of the C═O and C≡N moieties in acyl cyanides enhances the electrophilicity of both groups.[5] During our study on the reactions of zirconacycles with acyl cyanides, we found that their C═O and C≡N bonds could both react with zirconacycles selectively.[6] For example, the C═O moiety of acyl cyanides was found to insert preferentially into the Zr−C(sp^3) bond of zirconacyclopentenes or zirconacyclopentanes[6a] or react selectively with a seven-membered zirconacyclocumulene,[6b] and the C≡N moiety of acyl cyanides was found to react with zirconium−butadiyne complexes preferentially at the initial step.[6c] These results promoted us to explore the reactivity of zirconocene−1-aza-1,3-diene complexes toward acyl cyanides. In this paper, we report the direct reaction of zirconocene−1-aza-1,3-dienes with acyl cyanides, which provides an efficient route to either acyl- or non-acyl-substituted pyrroles upon acidic quenching, depending also on the substitution patterns of the azadienes (Scheme 1).

Scheme 1. Zirconium-Mediated Synthesis of Substituted Pyrroles from 1-Aza-1,3-dienes



RESULTS AND DISCUSSION

At the beginning, the zirconium-mediated reaction of 1,4-diphenyl-substituted azadiene **1a** with benzoyl cyanide **3a** was examined (Table 1, entry 1). Treatment of azazirconacyclopentene **2a**[1a,i,3] (R^1, R^4 = Ph, R^2 = H), prepared by the reaction of **1a** with 1.3 equiv of Negishi reagent,[7] with 3 equiv of benzoyl cyanide (**3a**) in THF at 50 °C for 3 h resulted in the formation of several products according to TLC analysis after the resulting mixture was quenched with 3 N HCl solution. A major product could be isolated in 57% yield, which was assigned to be tetrasubstituted 3-acylpyrrole **4a**. The results

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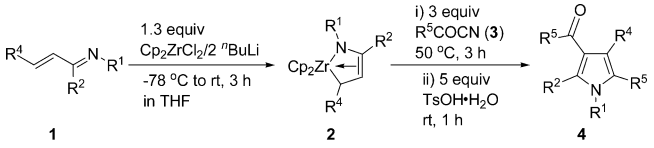
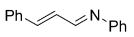
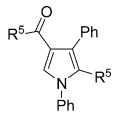
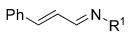
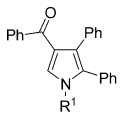
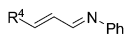
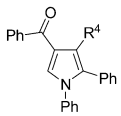
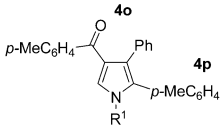
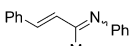
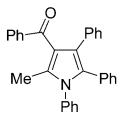
Table 1. Zirconium-Mediated Synthesis of 3-Acylpyrroles from 1,4- or 1,2,4-Substituted Azadienes



1 2 4

entry	azadiene	R^5COCN	product	yield (%)[a]
1	 **1a**	R^5COCN **3a**, R^5 = Ph	 **4a**	68
2	**1a**	**3b**, R^5 = *p*-MeC_6H_4	**4b**	56
3	**1a**	**3c**, R^5 = *p*-ClC_6H_4	**4c**	52
4	**1a**	**3d**, R^5 = *p*-FC_6H_4	**4d**	53
5	**1a**	**3e**, R^5 = *p*-$CF_3C_6H_4$	**4e**	42
6	**1a**	**3f**, R^5 = 2-furyl	**4f**	40
7	**1a**	**3g**, R^5 = 2-thienyl	**4g**	48
8	 **1b**, R^1 = *p*-$MeOC_6H_4$	**3a**	 **4h**	69
9	**1c**, R^1 = 3,4,5-$(MeO)_3C_6H_2$	**3a**	**4i**	67
10[b]	**1d**, R^1 = *p*-ClC_6H_4	**3a**	**4j**	49
11	**1e**, R^1 = 1-naphthyl	**3a**	**4k**	65
12	 **1f**, R^4 = *p*-MeC_6H_4	**3a**	 **4l**	50
13	**1g**, R^4 = *p*-$MeOC_6H_4$	**3a**	**4m**	54
14	**1h**, R^4 = *p*-BrC_6H_4	**3a**	**4n**	47
15	**1i**, R^4 = *p*-FC_6H_4	**3a**	**4o**	67
16	**1c**, R^1 = 3,4,5-$(MeO)_3C_6H_2$	**3b**	 **4p**	44
17	 **1j**	**3a**	 **4q**	46

[a]Isolated yields. [b]The reaction was carried out at 80 °C for 3 h after **3a** was added.

indicated that two molecules of benzoyl cyanide reacted with zirconacycle **2** during the process. We envisioned that the choice of an appropriate quenching reagent might be crucial for achieving a clean transformation. After many trials, we found that the desired pyrrole **4a** could be obtained in a satisfactory yield of 68% after the reaction mixture was quenched by 5.0 equiv of TsOH·H_2O and stirred at room temperature for 1 h (Table 1, entry 1). Decreasing the amount of PhCOCN to 2 equiv afforded **4a** in a lower yield of 53%. Reducing the amount of the quenching reagent of TsOH·H_2O to 2.5 equiv also gave a lower yield of **4a** (14%).

After the synthetic protocol was established, the reaction scope was next investigated. The representative results are shown Table 1. First, the scope of acyl cyanides **3** was explored by using azadiene **1a** as a reaction partner. It was found that the desired 3-acylpyrroles **4b−e** were formed in moderate yields through the reactions with the corresponding acyl cyanides **3b−e** bearing electron-donating (*p*-Me) or electron-withdrawing (*p*-Cl, *p*-F or *p*-CF_3) groups at the para position of aryl substituents (entries 2−5). Heteroaryl-substituted acyl cyanides such as **3f,g** with 2-furyl and 2-thienyl functionalities were also compatible with this reaction, furnishing the corresponding pyrroles **4f,g** in 40% and 48% yields, respectively (entries 6 and 7). Next, the substituent effect of the R^1 group on the nitrogen of the azadienes **1** was examined. When the reactions of *N*-(*p*-methoxyphenyl)-, *N*-(3,4,5-trimethoxyphenyl)-, and *N*-(*p*-chlorophenyl)-substituted azadienes **1b−d** were employed, the corresponding pyrroles **4h−j** were obtained in 49−69% yields (entries 8−10). It was also found that the reaction of **1e** bearing a bulky *N*-(1-naphthyl) group proceeded well to give **4k** in 65% yield (entry 11). Regarding the R^4 substituents on alkene terminus of azadienes **1**, both electron-donating (*p*-Me, *p*-MeO) and electron-withdrawing (*p*-Br, *p*-F) groups on aryl rings were tolerated well to afford **4l−o** in 47−67% yields (entries 12−15), indicating that the electronic nature of R^4 had little influence on the product yields. Pyrrole **4p**, with three different substituents on the pyrrole ring, could be easily constructed by this method (entry 16). It was noted that the methods for the regioselective synthesis of multisubstituted pyrroles with different substituents from the easily accessible starting materials under mild reaction conditions are limited.[8] In addition, azadiene **1j** bearing one more substituent (Me group) at the C-2 position could also smoothly react with benzoyl cyanide to give the fully substituted pyrrole **4q** in 46% yield (entry 17). The structures of 3-acylpyrroles were unambiguously confirmed by X-ray crystallographic analysis of product **4p**.[9]

Interestingly, when 1,3,4-trisubstituted azadiene **1k** was employed as the substrate, tetrasubstituted pyrrole **5a** without acyl substitution was formed in 73% yield (Table 2, entry 1). The results indicated that only one molecule of acyl cyanide was incorporated into the product. In this case, the use of 2.0 equiv of acyl cyanide was enough to achieve the best product yields. We also briefly investigated the substrate scope of this type of reaction. When *p*-Me- and *p*-Cl-substituted aroyl cyanides and 2-thienyl acyl cyanide were used as the coupling partners to react with **1k**, the corresponding pyrroles **5b−5d** were obtained in 62−72% yields (entries 2−4). For *N*-aryl substituents of azadienes, the *p*-OMe or *p*-Cl groups on aryl rings were well accommodated, leading to **5e,f** in 47% and 55% yields, respectively (entries 5 and 6). *C*-3-Hexyl-substituted azadiene **1n** afforded **5g** in a lower yield of 30% (entry 7). Azadiene **1o** bearing a phenyl group at the C-3 position was also well suited for this reaction, furnishing **5h** in 70% yield (entry 8). It was noted that the pyrrole products **5** are the same as those obtained through the zirconium-mediated reactions of 1,3,4-trisubstituted azadienes with nitriles.[3] Pyrroles constitute important classes of natural products,[10] synthetic pharmaceuticals,[11] and functional materials.[12] Especially, multiply substituted pyrroles have been shown to display important biological activities such as antibacterial,[13a] antiviral,[13b] and antiinflammatory[13c] activity. Our method provides a mild and efficient route to these compounds.

It was noteworthy that when the reaction mixture of zirconacycle **2** derived from 1,4-substituted azadienes was quenched with saturated aqueous $NaHCO_3$ solution, a different product was formed. For example, enaminone **6c** was isolated in 61% yield upon quenching the reaction mixture of zirconacycle **2c** and benzoyl cyanide with saturated aqueous $NaHCO_3$ solution (Scheme 2). The results indicated that the

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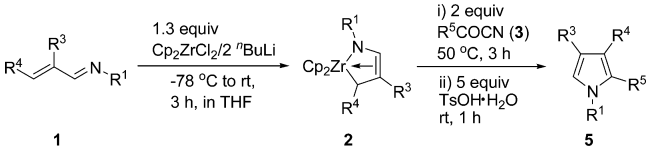
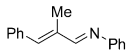
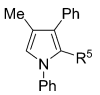
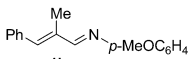
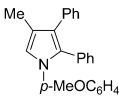
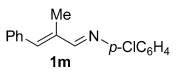
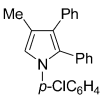
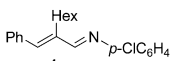
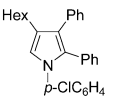
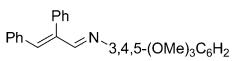
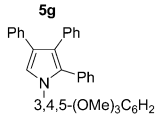
Table 2. Zirconium-Mediated Synthesis of Non-Acyl-Substituted Pyrroles from 1,3,4-Trisubstituted Azadienes

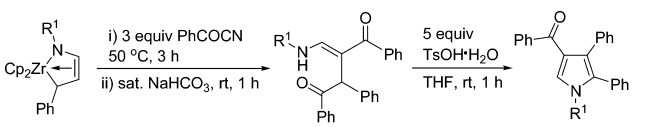


1 2 5

entry	azadiene	R^5COCN	product	yield (%)[a]
1	 **1k**	R^5COCN **3a**, R^5 = Ph	 **5a**	73
2	**1k**	**3b**, R^5 = *p*-MeC_6H_4	**5b**	72
3	**1k**	**3c**, R^5 = *p*-ClC_6H_4	**5c**	71
4	**1k**	**3g**, R^5 = 2-thienyl	**5d**	62
5	 **1l**	**3a**	 **5e**	47
6	 **1m**	**3a**	 **5f**	55
7	 **1n**	**3a**	 **5g**	30
8	 **1o**	**3a**	 **5h**	70

[a]Isolated yields.

Scheme 2. Quenching the Reaction Mixture by Saturated $NaHCO_3$ Solution and Formation of 3-Acylpyrrole 4i



2c R^1 = 3,4,5-$(MeO)_3C_6H_2$ — **6c**, 61% (containing ca. 10% byproduct) — **4i**, 97% (estimated)

product distribution was strongly affected by quenching reagents. **6c** was contaminated with ca. 10% of a byproduct and trace amounts of other species, which could not be separated from each other by column chromatography. The byproduct was suggested to be an imine (see intermediate **11** in Scheme 3). To our delight, **6c** could be obtained in pure form by recrystallization. The X-ray crystallographic analysis of **6c** verified its structure.[9] Compound **6c** (with 10% of the byproduct) could be converted into 3-acylpyrrole **4i** in excellent yield by treating with $TsOH·H_2O$ (Scheme 2). The high yield of **4i** also indicated that the byproduct contained in **6c** was also transformed into the pyrrole product under the reaction conditions. The results suggested that enaminone **6c** was the key reaction intermediate, and cyclization of **6c** to pyrroles occurred during the acidic quenching. The addition of both of the acyl cyanides to azazirconacycles possibly occurs before quenching, since acyl cyanides decompose rapidly in saturated aqueous $NaHCO_3$ solution.

On the basis of the above observation, we tentatively propose the following reaction mechanism for the formation of pyrroles (Scheme 3). In comparison with our previous work concerning zirconium-promoted reactions of azadienes with nitriles, in this reaction, insertion of the C═O bond[14] rather than the C≡N bond of acyl cyanide into the Zr−C(sp^3) bond of azazirconacyclopentene **2** occurs to provide the seven-membered oxaazazirconacycle **7**. **7** might also be formed through the reaction of alkenyl zirconaaziridine **8** with acyl cyanide via a *syn*-S_E2' process.[15] *β*-Cyanide elimination[6a] of **7** affords the ring-opened zirconium species **10**. In the case of R^3 = H, the enamine moiety in **10** attacks the second molecule of acyl cyanide to give the imine intermediate **11**, which tautomerizes to enamine **6** in the presence of acid or base. Cyclization of **6** under acidic conditions leads to 3-acylpyrrole **4**. However, other possible reaction pathways for the formation of **11** cannot yet be excluded. For example, nucleophilic attack of **7** through its enamine moiety to acyl cyanide followed by *β*-cyanide elimination might also give intermediate **11**. In the case of $R^3 \neq$ H, the zirconium intermediate **10** cannot react with the second molecule of acyl cyanide due to the steric hindrance caused by the R^3 group. Thus, upon quenching and cyclization of the resulting intermediate **13** under the acidic conditions, the non-acyl-substituted pyrrole **5** is formed.

CONCLUSION

In summary, insertion of acyl cyanides into azazirconacyclopentenes derived from 1,3-azadienes has been described, which affords acyl- or non-acyl-substituted pyrroles upon acidic quenching. These reactions are initialized through C═O insertion into the azazirconacycle to afford seven-membered oxaazazirconacycles. In the cases of 1,4- or 1,2,4-substituted azadienes, addition of a second molecule of acyl cyanide followed by cyclization upon acidic quenching leads to acyl-substituted pyrroles. In the cases of 1,3,4-substituted azadienes, the addition of a second molecule of acyl cyanide cannot proceed due to the steric hindrance caused by the R^3 group on the zirconium intermediate. Acidic quenching of the resulting zirconium intermediate affords non-acyl-substituted pyrroles. Further studies on the reaction mechanism and the new reactivity of zirconocene-1-aza-1,3-diene complexes toward other electrophiles are in progress in our laboratory.

EXPERIMENTAL SECTION

Typical Procedure for the Synthesis of 3-Acylpyrrole 4a. To a solution of Cp_2ZrCl_2 (0.19 g, 0.65 mmol) in THF (5 mL) was added dropwise *n*-BuLi (0.81 mL, 1.3 mmol, 1.6 M solution in hexane) at −78 °C. After this mixture was stirred for 1 h at the same temperature, (*E*)-*N*-((*E*)-3-phenylallylidene)aniline (**1a**; 103.6 mg, 0.5 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 3 h. Benzoyl cyanide (196.7 mg, 1.5 mmol) was added, and the reaction mixture was stirred at 50 °C for 3 h. Then 5.0 equiv of $TsOH·H_2O$ (475.6 mg, 2.5 mmol) was added, and the resulting mixture was stirred at room temperature for 1 h. Water was then added, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution. The aqueous layer was neutralized by adding saturated $NaHCO_3$ solution and then extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 20/1) to afford the product **4a** in 68% yield (135.8

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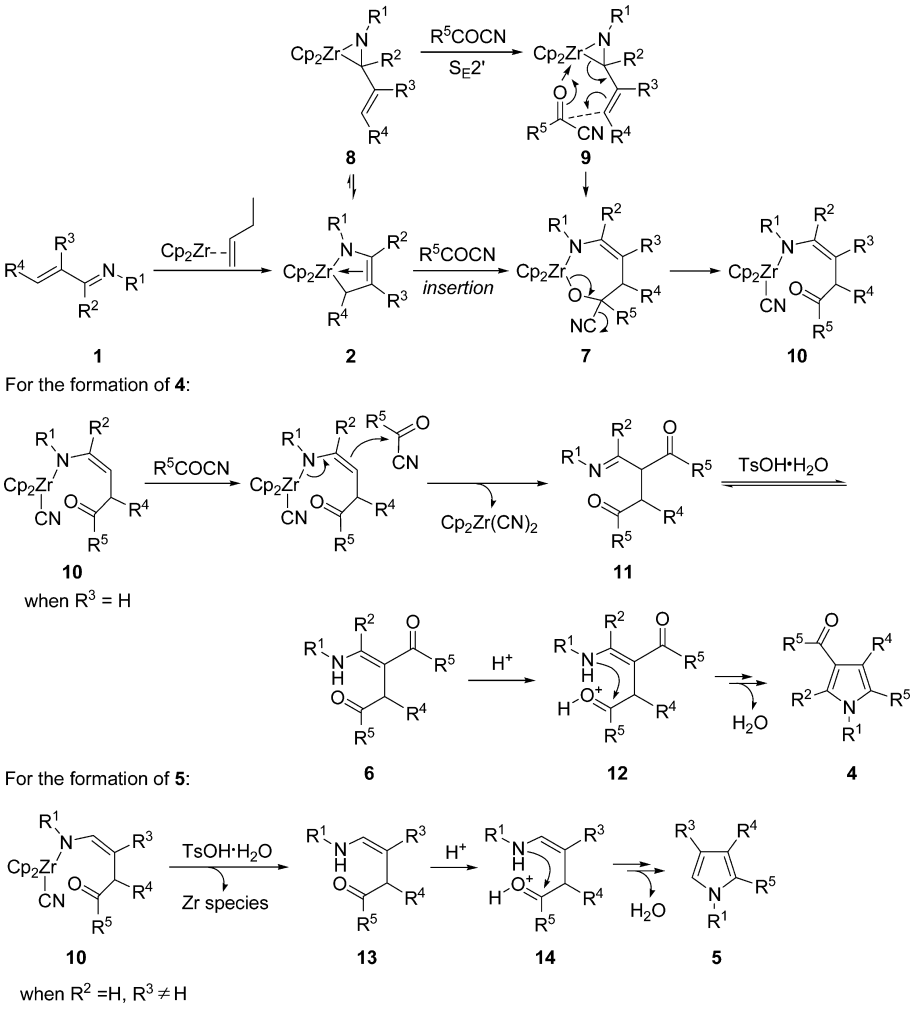
Scheme 3. Possible Reaction Mechanism



mg) as a light yellow solid. Mp: 169−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ 6.93−6.95 (m, 2H), 7.05−7.43 (m, 17H), 7.87 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ 122.96, 125.37, 125.78, 126.02, 127.13, 127.36, 127.43, 127.77, 127.88, 128.91, 129.29, 129.99, 130.54, 130.65, 130.88, 131.51, 132.81, 134.31, 139.06, 139.67, 190.85. IR (film): 3053, 1643, 1597, 1498, 1476, 1444, 1388, 1327, 1306, 1216, 1068, 1024, 1012, 897, 780, 764, 693, 672 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{22}NO$ $[M + H]^+$ 400.1696, found 400.1690.

Typical Procedure for the Synthesis of Non-Acyl-Substituted Pyrrole 5a. To a solution of Cp_2ZrCl_2 (0.19 g, 0.65 mmol) in THF (5 mL) was added dropwise *n*-BuLi (0.81 mL, 1.3 mmol, 1.6 M solution in hexane) at −78 °C. After this mixture was stirred for 1 h at the same temperature, (*E*)-*N*-((*E*)-2-methyl-3-phenylallylidene)aniline (**1k**; 110.7 mg, 0.5 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 3 h. Benzoyl cyanide **3a** (131.1 mg, 1.0 mmol) was added, and the reaction mixture was stirred at 50 °C for 3 h. Then 5.0 equiv of TsOH·H_2O (475.6 mg, 2.5 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. Water was then added, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution. The aqueous layer was neutralized by adding saturated $NaHCO_3$ solution and then extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (petroleum ether/dichloromethane 10/1) to afford the product **5a** in 73% yield (113.4 mg) as a white solid. Mp: 161−163 °C. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ 2.16 (s, 3H), 6.82 (s, 1H), 6.91−6.93 (m, 2H), 7.03−7.07 (m, 5H), 7.12−7.24 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ 11.00, 118.67, 121.38, 124.82, 125.58, 125.62, 126.04, 126.30, 127.72, 127.84, 128.72, 130.30, 130.39, 130.74, 132.19, 135.91, 140.29. IR (film): 3040, 2919, 1598, 1529, 1503, 1389, 1371, 807, 762, 748, 737, 697 cm^{-1}. HRMS (ESI): calcd for $C_{23}H_{20}N$ $[M + H]^+$ 310.1590, found 310.1587. The spectroscopic data are in agreement with those previously reported.[3]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00801.

Experimental details and NMR spectra of all new products (PDF)

Crystallographic data of compounds **4p** and **6c** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For zirconocene-1-aza-1,3-diene complexes, see: (a) Davis, J. M.; Whitby, R. J.; Jaxa-Chamiec, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1743−1745. (b) Scholz, J.; Nolte, M.; Krüger, C. *Chem. Ber.* **1993**, *126*, 803−809. (c) Barluenga, J.; Sanz, R.; González, R.; Fañanás, F. J. *J. Chem. Soc., Chem. Commun.* **1994**, 989−990. (d) Enders, D.; Kroll, M.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1673−1675. (e) Thomas, D.; Baumann, W.; Spannenberg, A.; Kempe, R.; Rosenthal, U. *Organometallics* **1998**, *17*, 2096−2102. (f) Scholz, J.; Kahlert, S.; Görls, H. *Organometallics* **2004**, *23*, 1594−1603. (g) Guan, H. *Curr. Org. Chem.* **2008**, *12*, 1406−1430. (h) Fang, X.; Assoud, J. *Organometallics* **2008**, *27*, 2408−2410. (i) Zhang, J.; Krause, J. A.; Huang, K.-W.; Guan, H. *Organometallics* **2009**, *28*, 2938−2946.

(2) For titanium−1-aza-1,3-diene complexes, see: (a) Cohen, S. A.; Bercaw, J. E. *Organometallics* **1985**, *4*, 1006−1014. (b) Kahlert, S.; Görls, H.; Scholz, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1857−1861. (c) Scholz, J.; Görls, H. *Organometallics* **2004**, *23*, 320−322. (d) Mitsui, K.; Sato, T.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 490−492.

(3) Yu, S.; Xiong, M.; Xie, X.; Liu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11596−11599.

(4) For reactions of nitriles with zirconacycles or zirconocene complexes, see: (a) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137−7141. (b) Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802−6806. (c) Zhou, S.; Liu, D.; Liu, Y. *Organometallics* **2004**, *23*, 5900−5902. (d) Sun, X.; Wang, C.; Li, Z.; Zhang, S.; Xi, Z. *J. Am. Chem. Soc.* **2004**, *126*, 7172−7173. (e) Zhang, W.-X.; Zhang, S.; Sun, X.; Nishiura, M.; Hou, Z.; Xi, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 7227−7231. (f) Zhang, S.; Sun, X.; Zhang, W.-X.; Xi, Z. *Chem. - Eur. J.* **2009**, *15*, 12608−12617. (g) Zhang, S.; Zhang, W.-X.; Xi, Z. *Chem. - Eur. J.* **2010**, *16*, 8419−8426. (h) Zhang, S.; Zhang, W.-X.; Zhao, J.; Xi, Z. *J. Am. Chem. Soc.* **2010**, *132*, 14042−14045. (i) Zhang, S.; Zhang, W.-X.; Zhao, J.; Xi, Z. *Chem. - Eur. J.* **2011**, *17*, 2442−2449. (j) Zhao, J.; Zhang, S.; Zhang, W.-X.; Xi, Z. *Organometallics* **2011**, *30*, 3464−3467. (k) Zhao, J.; Zhang, S.; Zhang, W.-X.; Xi, Z. *Organometallics* **2012**, *31*, 8370−8374. (l) You, X.; Yu, S.; Liu, Y. *Organometallics* **2013**, *32*, 5273−5276.

(5) Hünig, S.; Schaller, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 36−49.

(6) (a) Zhou, S.; Yan, B.; Liu, Y. *J. Org. Chem.* **2005**, *70*, 4006−4012. (b) Fu, X.; Chen, J.; Li, G.; Liu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5500−5504. (c) Yu, S.; You, X.; Liu, Y. *Chem. - Eur. J.* **2012**, *18*, 13936−13940.

(7) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336−3346.

(8) For reviews, see: (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402−4421. (b) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084−3213. For recent papers, see: (c) Li, X.; Chen, M.; Xie, X.; Sun, N.; Li, S.; Liu, Y. *Org. Lett.* **2015**, *17*, 2984−2987. (d) Magar, D. R.; Ke, Y.-J.; Chen, K. *Asian J. Org. Chem.* **2013**, *2*, 330−335. (e) Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674−1683. (f) Tan, B.; Shi, Z.; Chua, P. J.; Li, Y.; Zhong, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 758−761. (g) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem. - Eur. J.* **2007**, *13*, 9973−9981. (h) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465−2468. (i) Mataka, S.; Kitagawa, H.; Misumi, O.; Tashiro, M.; Kamata, K. *J. Chem. Soc., Chem. Commun.* **1993**, 670−671.

(9) See the Supporting Information.

(10) For reviews, see: Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801−1839.

(11) (a) Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446−4456. (b) Zhou, H.; Chen, J.; Meagher, J. L.; Yang, C.-Y.; Aguilar, A.; Liu, L.; Bai, L.; Cong, X.; Cai, Q.; Fang, X.; Stuckey, J. A.; Wang, S. *J. Med. Chem.* **2012**, *55*, 4664−4682.

(12) (a) *Electronic Materials: The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: Weinheim, Germany, 1997. (b) Facchetti, A.; Abbotto, A.; Beverina, L.; van der Boom, M. E.; Dutta, P.; Evmenenko, G.; Pagani, G. A.; Marks, T. J. *Chem. Mater.* **2003**, *15*, 1064−1072. (c) Danil de Namor, A. F.; Khalife, R. *J. Phys. Chem. B* **2008**, *112*, 15766−15774.

(13) (a) Bürli, R. W.; McMinn, D.; Kaizerman, J. A.; Hu, W.; Ge, Y.; Pack, Q.; Jiang, V.; Gross, M.; Garcia, M.; Tanaka, R.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1253−1257. (b) Almerico, A. M.; Diana, P.; Barraja, P.; Dattolo, G.; Mingoia, F.; Loi, A. G.; Scintu, F.; Milia, C.; Puddu, I.; La Colla, P. *Il Farmaco* **1998**, *53*, 33−40. (c) Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, C.; Alfonso, S.; Rovini, M.; Valenti, S.; Giorgi, G.; Calderone, V.; Martelli, A.; Testai, L.; Sautebin, L.; Rossi, A.; Papa, G.; Ghelardini, C.; Mannelli, L. D. C.; Giordani, A.; Anzellotti, P.; Bruno, A.; Patrignani, P.; Anzini, M. *J. Med. Chem.* **2011**, *54*, 7759−7771.

(14) For insertion of a C═O bond into Zr−C bonds, see: (a) Copéret, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695−698. (b) Zhao, C.; Yu, T.; Xi, Z. *Chem. Commun.* **2002**, 142−143. (c) Zhao, C.; Yan, J.; Xi, Z. *J. Org. Chem.* **2003**, *68*, 4355−4360. (d) Zhao, C.; Lu, J.; Yan, J.; Xi, Z. *Tetrahedron Lett.* **2003**, *44*, 6895−6898. (e) Yu, T.; Sun, X.; Wang, C.; Deng, L.; Xi, Z. *Chem. - Eur. J.* **2005**, *11*, 1895−1902. (f) Lu, J.; Mao, G.; Zhang, W.; Xi, Z. *Chem. Commun.* **2005**, 4848−4850. (g) Suzuki, N.; Shimura, T.; Sakaguchi, Y.; Masuyama, Y. *Pure Appl. Chem.* **2011**, *83*, 1781−1788. (h) Bender, G.; Kehr, G.; Fröhlich, R.; Petersen, J. L.; Erker, G. *Chem. Sci.* **2012**, *3*, 3534−3540. (i) Fu, X.; Yu, S.; Fan, G.; Liu, Y.; Li, Y. *Organometallics* **2012**, *31*, 531−534.

(15) Zhou, Y.; Chen, J.; Zhao, C.; Wang, E.; Liu, Y.; Li, Y. *J. Org. Chem.* **2009**, *74*, 5326−5330.

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