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Preparative and Mechanistic Studies on Copper-Mediated 1,6-Addition Reactions to a 2,4-Dienone

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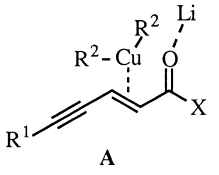
Abstract—The 2,4-dienone 4a-methyl-4,4a,5,6-tetrahydro-3*H*-naphthalen-2-one (**1**) was found to react with cyano-Gilman reagents $R_2CuLi{\cdot}LiCN$ (R=Me, *n*-Bu, Ph) or Grignard reagents in the presence of catalytic amounts of copper 2-(dimethylaminomethyl)thiophenolate with complete 1,6-regioselectivity and high *trans*-diastereoselectivity. NMR-spectroscopic investigations revealed that these Michael-additions proceed via π-complexes **5** which may be transformed into the 1,6-adducts **6** via short-lived copper(III) species.

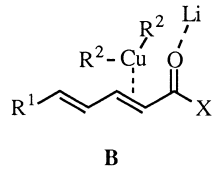
Introduction

The 1,4-addition reaction of organocopper reagents to olefinic and acetylenic Michael acceptors is one of the classical methods for the regio- and stereoselective formation of carbon–carbon bonds.[1] The major advantage of organocopper compounds over other organometallic reagents used in Michael additions is that their reactivity and selectivity can be controlled by 'tuning' of the reagent, making them highly useful for the total synthesis of complex target molecules like natural products, pharmaceuticals and chiral auxiliaries. Recent developments involve new protocols for copper-catalyzed 1,4-additions,[2] the use of functionalized cuprates[3] and, most notably, the discovery of a new class of chiral ligands for highly enantioselective copper-catalyzed 1,4-addition reactions of organozinc compounds to selected enones.[4] These investigations have led to highly sophisticated organocopper reagents and new ways for conducting their reactions.

In terms of the substrates, however, little has changed until recently. Only in the last 10 years or so, copper-mediated addition reactions to Michael acceptors with extended multiple bond systems (in other words, with two or more reactive positions) were examined intensively and found to take place with high regio- and stereoselectivities,[1b,5] in particular when the substrate contains at least one triple bond besides one or more conjugated double bonds. These unusual reaction types not only open up novel entries to interesting target molecules but also provide deeper insight into the mechanisms of copper-mediated bond formation. For example, 1,6-cuprate additions to acceptor-substituted enynes were used in the synthesis of functionalized allenes which were utilized, inter alia, in stereoselective inter- and intramolecular Diels–Alder cycloadditions, aldol reactions and Ireland–Claisen rearrangements.[1b,5,6] Mechanistic investigations by NMR spectroscopy have revealed that these transformations proceed via π-complexes **A** with an interaction between the π-system of the C=C double bond and the nucleophilic copper atom (a soft–soft interaction in terms of the HSAB principle), as well as a second interaction between the hard lithium ion of the cuprate and the hard carbonyl oxygen atom.[1b,5,7] Kinetic measurements have revealed that an intramolecular rearrangement of the π-complex occurs in the rate-determining step of the reaction; these experimental findings were explained in a mechanistic model involving two short-lived σ-copper(III) species.[7c]



A



B

In contrast, the mechanism of copper-mediated 1,6-addition reactions to acceptor-substituted dienes[5,8] is less well understood although these reactions have been utilized frequently in target-oriented synthesis.[9,14] The favorite substrates are

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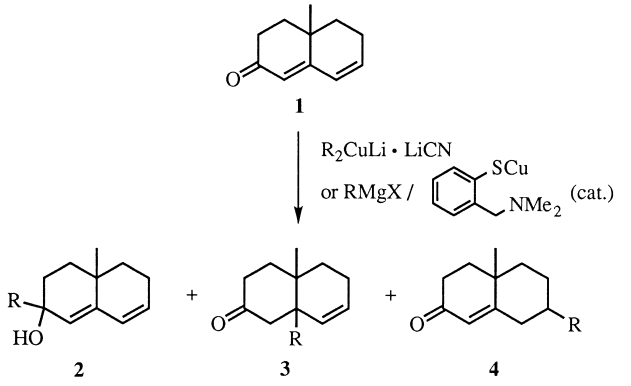
Table 1. Copper-mediated addition reactions to dienone **1**



Method[a]	R	Regioselectivity **2: 3**: **4**	Yield	*trans*-**4**:*cis*-**4**
A	Me	<1: <1: >99	79	98:2
A	*n*-Bu	<1: <1: >99	54	97:3
A	Ph	<1: <1: >99	81[b]	96:4
B	Me	<1: <1: >99	78	95:5
B	*n*-Bu	<1: <1: >99	78	96:4
B	Ph	<1: <1: >99	68	98:2

[a] Method A: $R_2CuLi{\cdot}LiCN$ (2 equiv.); method B: RMgX (1.5–2.3 equiv.)/copper 2-(dimethylaminomethyl)thiophenolate (5 mol%).
[b] 31% consumption of the starting material.

steroids with a dienone structure,[10] as well as tetrahydro-3*H*-naphthalen-2-ones, which can be considered as model substrates for doubly unsaturated steroids.[11] The interest in these transformations was prompted by the desire to prepare new, unnatural corticosteroids with possible interesting pharmacological activities. Particularly intriguing are estradiol derivatives bearing an alkyl chain in the 7α-position since these steroids were found to bind with high affinity and specificity to estrogen receptors; i.e. they are effective antiestrogenic agents[12] and may therefore be useful for the treatment of mammary tumors (breast cancer).[13] The obvious way to introduce a carbon group in the 7-position of a steroid backbone is a copper-mediated 1,6-addition to an activated doubly unsaturated $\Delta^{4,6}$-derivative; indeed, the desired regioselectivity is observed in many cases.[10,11,13,14] Here, the major challenge is control of the diastereoselectivity of the Michael addition since the 7β-isomers are less effective enzyme inhibitors.[13] In general, a high preference for the addition of methyl nucleophiles from the α-side was observed;[10] by contrast, introduction of longer alkyl chains via copper-promoted 1,6-addition reactions to $\Delta^{4,6}$-steroids normally gives unsatisfactory α:β ratios.[13,14]

In this work, we present the results of a combined preparative and spectroscopic study of copper-mediated 1,6-addition reactions to 4a-methyl-4,4a,5,6-tetrahyrdro-3*H*-naphthalen-2-one (**1**). This study was carried out in order to improve the unsatisfactory regioselectivities reported earlier[11a] and to gather information on the mechanism of these Michael additions. In particular, we wanted to establish whether cuprate π-complexes of type **B** or different intermediates are involved in the reactions; the former might indicate similarities in the mechanistic pathways of 1,6-cuprate additions to acceptor-substituted dienes and enynes, respectively.

Preparative Studies

In a series of papers, Marshall and coworkers[11] have reported copper-assisted addition reactions of Grignard reagents to various tetrahydro-3*H*-naphthalen-2-ones. In the case of dienone **1**, treatment with several alkylmagnesium halides in the presence of catalytic amounts of $Cu(OAc)_2$ provided mixtures of the 1,2- and 1,6-addition products **2** and **4**, respectively, the latter mainly as *trans*-isomer.[11a] The 1,4-adduct **3** was not formed under these conditions, although 1,4-addition was frequently observed as side reaction with other tetrahydro-3*H*-naphthalen-2-ones.[11b–d] In order to improve the unsatisfactory regioselectivity, we examined Michael additions to **1**[15] under alternative stoichiometric and catalytic conditions, i.e. by using the cyano-Gilman reagents $R_2CuLi{\cdot}LiCN$ (method A) or Grignard reagents in the presence of 5 mol% of van Koten's catalyst copper 2-(dimethylaminomethyl)thiophenolate (method B; see Table 1). This particular copper arenethiolate has already proven to be highly useful in catalytic 1,6-addition reactions to acceptor-substituted enynes.[6f]

It was found that under both conditions examined here, i.e. by treatment with stoichiometric amounts of cyano-Gilman reagents $R_2CuLi{\cdot}LiCN$ or with Grignard reagents under catalysis with copper 2-(dimethylaminomethyl)thiophenolate, dienone **1** reacted with complete 1,6-regioselectivity to provide enones **4** with R=Me, *n*-Bu and Ph. Thus, these conditions are clearly superior to those reported previously.[11a] THF or mixtures of diethyl ether with THF were used as solvent; in the NMR-spectroscopic investigations described below, an interesting dependence of the reactivity on the solvent was observed. When the 1,6-addition was carried out with cyano-Gilman reagents, mixtures of **4** and the corresponding 3-enone were obtained initially; brief treatment with sodium methanolate served to isomerize the latter to **4** which was then isolated with high purity. In contrast to this, deconjugated 3-enones were not formed under the catalytic conditions, making the subsequent basic isomerization unnecessary. As observed before,[11] the stoichiometric and catalytic 1,6-additions to **1** examined here proceeded with high *trans*-diastereoselectivity (95–98% ds).

NMR-Spectroscopic Investigations

It was already stated in the Introduction that low-temperature NMR spectroscopy is the method of choice for mechanistic investigations of copper-promoted reactions. In order to establish whether π-complexes analogous to **B** or different intermediates are involved in 1,6-cuprate additions to 2,4-dienones, we examined reaction mixtures obtained from **1** and $R_2CuLi{\cdot}LiCN$ (R=Me, *n*-Bu) by this method. In the case of lithium dimethylcyanocuprate, only starting material was detected spectroscopically when pure THF-d_8 was used as solvent; warming up of the sample did not induce the 1,6-addition but lead only to decomposition of the cuprate. Thus, diethyl ether has to present in order to induce the conjugate addition; in preparative runs, this solvent is usually introduced with the commercially available ethereal solutions of MeLi. When an NMR-sample of **1** and $Me_2CuLi{\cdot}LiCN$ was prepared under these conditions,

Table 2. ^{13}C NMR chemical shifts of dienone **1**, π-complexes **5** and enolates **6**

Compound	R	Solvent	C-1	C-2	C-7	C-8	C-8a
1	–	$CDCl_3$	123.4	199.9	137.9	127.6	162.1
5	Me	THF-d_8/Et_2O (~1:1)	83.0	[a]	133.5	118.5	84.4
5	*n*-Bu	THF-d_8	[a]	[a]	141.2	129.4	113.9
6	Me	THF-d_8/Et_2O (~1:1)	100.6	163.4	30.5	116.5	144.4
6	*n*-Bu	THF-d_8	99.9	163.1	[a]	114.2	144.2

[a] Not detected.

i.e. in a 1:1 mixture of diethyl ether and THF-d_8, we were indeed able to detect π-complex **5** (R=Me) besides starting material **1** by ^{13}C NMR spectroscopy at −80°C (Table 2). After warming up of the sample to −60°C, this was converted completely into the addition product **6**. The analogous intermediates with R=*n*-Bu were observed by using *n*-Bu_2CuLi·LiCN; due to the higher reactivity of this cuprate, the reaction proceeded rapidly in pure THF-d_8 even at low temperature, so that a mixture of π-complex **5** and enolate **6** was already observed at −80°C (Table 2; Fig. 1). Again, warming of the sample resulted in the complete conversion of the π-complex into the 1,6-adduct (Scheme 1).

Comparison of the ^{13}C NMR chemical shifts of π-complex **5** (R=Me) and starting material **1** reveals large upfield shifts of the resonances of C-1 ($\Delta\delta$=−40 ppm) and C-8a ($\Delta\delta$=−78 ppm) which is typical for the interaction of the electron-rich cuprate with this double bond[1d,7] (the assignment was made with the DEPT method). In contrast, the resonances of the other olefinic double bond show only slight upfield shifts ($\Delta\delta$<10 ppm). The analogous behavior was found for the π-complex **5** with R=*n*-Bu; although the resonance of C-1 could not be detected in this case, the upfield shift for C-8a ($\Delta\delta$=−48 ppm) again indicates coordination of the cuprate at this double bond. Similar chemical shifts were reported by Bertz and Smith[16] for a π-complex formed from 4a-methyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one and lithium dimethylcuprate. Unfortunately, we were not able to detect the carbonyl resonance of both π-complexes; one would expect small shifts caused by interaction with the lithium ion of the cuprate.[1b,7,16] The enolates **6** formed by warming up of the NMR samples of the π-complexes **5** were found to show

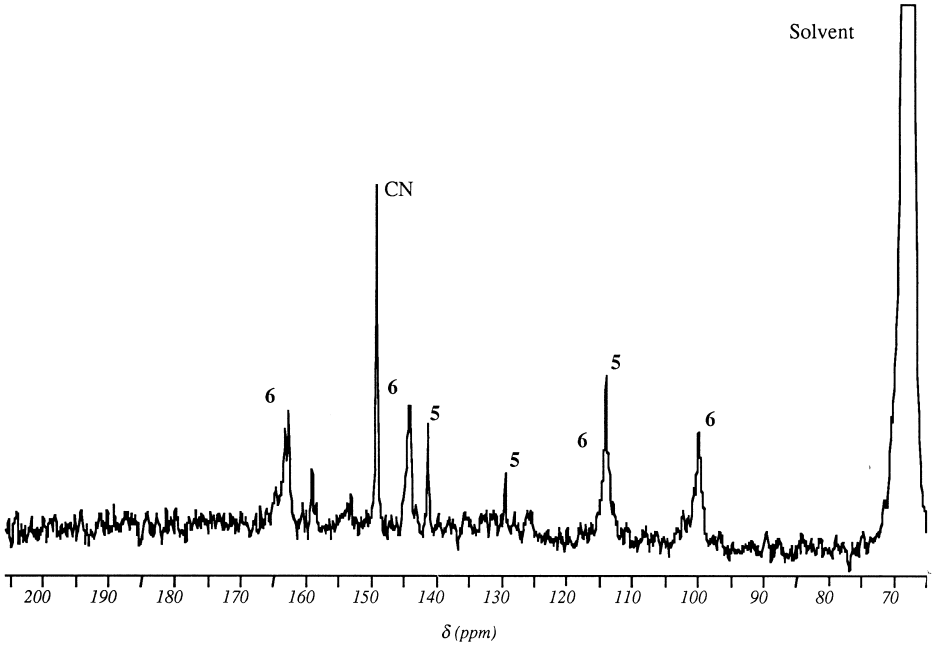
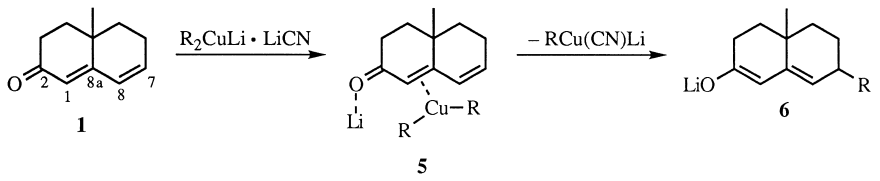
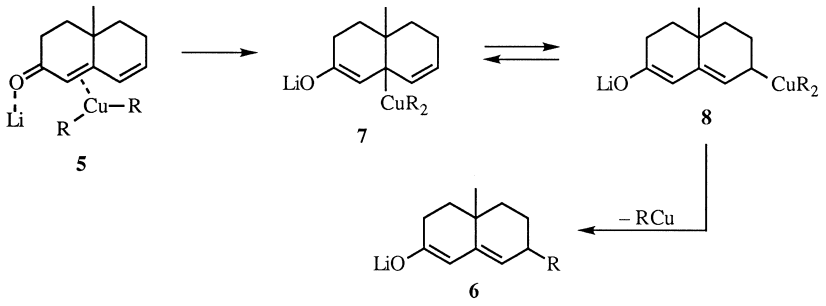


Figure 1. Part of the ^{13}C NMR spectrum of a mixture of π-complex **5** and enolate **6** (R=*n*-Bu; THF-d_8, −80°C).



Scheme 1.



Scheme 2.

rather broad signals in the ^{13}C NMR spectra (Fig. 1), indicating the presence of different aggregates (e.g. monomeric and dimeric enolates). The chemical shifts observed for **6** are in the typical range, in particular those of C-1 ($\delta \approx 100$) and C-2 ($\delta \approx 163$).[1b,7,16]

Discussion and Conclusions

In this work, we have shown that the 2,4-dienone 4a-methyl-4,4a,5,6-tetrahydro-3*H*-naphthalen-2-one (**1**) reacts with cyano-Gilman reagents $R_2CuLi \cdot LiCN$ (R=Me, *n*-Bu, Ph) or Grignard reagents in the presence of catalytic amounts of copper 2-(dimethylaminomethyl)thiophenolate with complete 1,6-regioselectivity and high *trans*-diastereoselectivity. These conditions are clearly superior to those reported earlier[11a] inasmuch as no 1,2- and 1,4-addition products are formed. Additionally, we were able to show by low-temperature NMR-spectroscopic investigations that these Michael-additions proceed via π-complexes **5** which are converted into the 1,6-adducts **6** upon warming up. Thus, cuprate additions to **1** proceed via analogous intermediates as 1,6-addition reactions to acceptor-substituted enynes.[1b,5,7] These experimental findings make it reasonable to assume similar mechanistic models (Scheme 2).

Thus, the π-complex **5** may transform into the σ-copper(III) species **7** which may be in equilibrium with another copper(III) compound **8**. In principle, both intermediates can undergo reductive eliminations to produce the 1,4-addition product from **7** and the 1,6-adduct from **8**. The experimentally observed exclusive formation of the 1,6-addition product **6** may indicate that the hypothetical equilibrium lies on the side of intermediate **8**, or that the reductive elimination of **8** occurs much faster than from **7**.

Further work is in progress in order to corroborate this mechanistic proposal. In particular, we intend to carry out kinetic studies in order to gather information about the rate-determining step of 1,6-cuprate additions to 2,4-dienones.[7c]

Experimental

General methods

Analytical thin-layer chromatography (TLC) was performed with precoated silica gel $60F_{254}$ plates (E. Merck). THF was distilled from Na/benzophenone and diethyl ether from $LiAlH_4$ under argon immediately prior to use. CuCN was obtained from E. Merck; MeLi, PhLi and *n*-BuLi were used from Acros, and Grignard reagents from Aldrich. Column chromatography was carried out with E. Merck silica gel 60 (70–230 mesh). GC analyses were performed with a Carlo Erba GC 8000 model equipped with a CP-Sil DB 5 or DB 1701 column. Infrared spectra were recorded on a Perkin–Elmer model 1600 FT-IR. Mass spectra were obtained with a A.E.I. or Varian AMT 311 spectrometer using electron impact (EI) ionization at 70 eV. NMR spectra were recorded with Bruker WM 250, WM 400, DRX 400 or DRX 500 spectrometers.

1,6-addition reactions of cyano-Gilman reagents (Method A)

To a suspension of 179 mg (2.0 mmol) of CuCN in 20 mL of diethyl ether or THF was added dropwise at −30°C 4.0 mmol of MeLi (1.6 M solution in diethyl ether), *n*-BuLi (2.4 M in hexane) or PhLi (2.0 M in cyclohexane/diethyl ether). The mixture was stirred for 15 min at −30°C, cooled to −80°C, and then treated with 162 mg (1.0 mmol) of 4a-methyl-4,4a,5,6-tetrahydro-3*H*-naphthalen-2-one (**1**) in 4 mL of solvent. The mixture was allowed to warm to 0°C, and 5 mL of 2 N H_2SO_4 was added. The copper salts were removed by filtration through Celite, and the filtrate was treated with 5 mL of a 1 M solution of NaOMe in methanol. After 15 min, 10 mL of water was added, the organic layer was separated, and the aqueous layer was washed with diethyl ether. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2; diethyl ether/cyclohexane, 1:3).

Copper-catalyzed 1,6-addition reactions (Method B)

To a suspension of 23 mg (0.1 mmol) of copper 2-(dimethylaminomethyl)thiophenolate in 30 mL of THF was added at −30°C 0.1 mmol of MeMgI (1.4 M solution in diethyl ether), *n*-BuMgCl (2.0 M in THF) or PhMgBr (1.4 M in diethyl ether/toluene/THF). After stirring for 15 min the mixture was warmed to 0°C. During 1 h 324 mg (2.0 mmol) of 4a-methyl-4,4a,5,6-tetrahydro-3*H*-naphthalen-2-one (**1**) in 4 mL of THF and 4.5 mmol of the Grignard reagent in 2 mL of THF were added dropwise and simultaneously to the catalyst suspension using a syringe pump. Then 5 mL of 2N H_2SO_4 was added, and the copper salts were removed by filtration through Celite. The filtrate was dried with $MgSO_4$ and concentrated in vacuo. The crude

product was purified by column chromatography (SiO_2; diethyl ether/cyclohexane, 1:3).

***trans*-4a,7-Dimethyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (4, R=Me).**[11a] *Method A:* From 162 mg (1.0 mmol) of **1** in 4 mL of THF, 179 mg (2.0 mmol) of CuCN in 20 mL of diethyl ether, and 2.5 mL (4.0 mmol) of MeLi; yield: 141 mg (79%) of **4** (R=Me) as a yellow viscous liquid. *Method B:* From 162 mg (1.0 mmol) of **1** in 2 mL of THF, 12 mg (0.05 mmol) of copper 2-(dimethylaminomethyl)thiophenolate in 20 mL of THF, and 1.1 mL (1.5 mmol) of MeMgI; yield: 136 mg (78%) of **4** (R=Me) as a yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.67 (s, 1H, 1-H), 2.55–1.17 (m, 11H), 1.16 (s, 3H, 4a-CH_3), 0.81 (d, J=7.1 Hz, 3H, 7-CH_3).

***trans*-7-Butyl-4a-methyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (4, R=*n*-Bu).** *Method A:* From 162 mg (1.0 mmol) of **1** in 4 mL of THF, 179 mg (2.0 mmol) of CuCN in 15 mL of THF and 5 mL of diethyl ether, and 1.7 mL (4.0 mmol) of *n*-BuLi; yield: 118 mg (54%) of **4** (R=*n*-Bu) as a yellow viscous liquid. *Method B:* From 324 mg (2.0 mmol) of **1** in 4 mL of THF, 23 mg (0.1 mmol) of copper 2-(dimethylaminomethyl)thiophenolate in 30 mL of THF, and 2.3 mL (4.6 mmol) of *n*-BuMgCl; yield: 341 mg (78%) of **4** (R=*n*-Bu) as a yellow viscous liquid. IR (neat): ν=2924 cm^{-1} (CH), 1669 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.72 (s, 1H, 1-H), 2.55 (m, 1H, 8-H), 2.45 (m, 1H, 3-H), 2.33 (m, 1H, 3-H), 2.11 (m, 1H, 8-H), 1.91-1.82 (m, 4H), 1.78–1.73 (m, 3H), 1.53 (m, 1H, 6-H), 1.43 (m, 1H, 7-H), 1.30–1.21 (m, 4H), 1.25 (s, 3H, 4a-CH_3), 0.88 (t, J=7.1 Hz, 4′-H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=199.4 (×, C-2), 169.6 (×, C-8a), 125.9 (+, C-1), 37.9 (−, C-5), 37.2 (−, C-8), 35.9 (+, C-7), 35.8 (×, C-4a), 34.6 (−, C-4), 34.1 (−, C-3), 30.9 (−, C-1′), 29.5 (−, C-2′), 25.4 (−, C-6), 22.7 (−, C-3′), 22.3 (+, 4a-CH_3), 14.0 (+, C-4′). MS (EI, 70 eV): m/z (%)=220 (73, M^+), 192 (74, M−CO), 163 (72, M−C_3H_5O), 135 (58, M−C_5H_9O), 121 (100, M−$C_6H_{11}O$). $C_{15}H_{24}O$ (220.18): calcd: C 81.76, H 10.98; found: C 81.47, H 10.84.

***trans*-4a-Methyl-7-phenyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (4, R=Ph).** *Method A:* From 80 mg (0.45 mmol) of **1** in 2 mL of THF, 90 mg (1.0 mmol) of CuCN in 5 mL of THF and 5 mL of diethyl ether, and 1.0 mL (2.0 mmol) of PhLi; yield: 27 mg (81%, due to 31% consumption of **1**) of **4** (R=Ph) as a yellow viscous liquid. *Method B:* From 324 mg (2.0 mmol) of **1** in 4 mL of THF, 23 mg (0.1 mmol) of copper 2(dimethylaminomethyl)thiophenolate in 30 mL of THF, and 3.3 mL (4.6 mmol) of PhMgBr; yield: 327 mg (68%) of **4** (R=Ph) as a yellow viscous liquid. IR (neat): ν=2931 cm^{-1} (CH), 1670 (C=O), 1613 (C=C). ^{1}H NMR: (400 MHz, $CDCl_3$): δ=7.28–7.16 (m, 5H, Ph-H), 5.93 (s, 1H, 1-H), 3.34–3.32 (m, 1H, 7-H), 2.89–2.51 (m, 2H, 8-H), 2.68–2.35 (m, 2H, 3-H), 1.85–1.70 (m, 4H, 5-H, 6-H), 1.40–1.35 (m, 2H, 4-H), 1.31 (s, 3H, 4a-CH_3). ^{13}C NMR (100.6 MHz, $CDC1_3$): δ=199.5 (×, C-2), 170.9 (×, C-8a), 144.6 (×, C-1′), 127.9, 127.4 (+, C-2′, C-3′, C-5′, C-6′), 125.7 (+, C-4′), 125.6 (+, C-1), 38.7 (+, C-7), 37.4 (−, C-5), 35.6 (×, C4a), 35.5 (−, C-8), 34.6 (−, C-4), 33.8 (−, C-3), 27.8 (−, C-6), 22.2 (+, 4a-CH_3). MS (EI, 70 eV): m/z (%)=240 (100, M^+), 183 (35, M−C_3H_5O), 144 (37, C_6H_8O), 91 (47, M−$C_{10}H_{13}O$).

Preparation of the NMR samples of π-complexes 5

The preparation was carried out in a round-bottom flask with attached NMR tube. To a suspension of 45 mg (0.5 mmol) of CuCN in 0.3 mL of THF-d_8 was added at −30°C 0.63 mL (1.0 mmol) of MeLi (1.6 M solution in diethyl ether) or 0.5 mL (1.0 mmol) of *n*-BuLi (2.0 M solution in THF-d_8). The mixture was stirred for 15 min at −30°C, cooled to −100°C, and a solution of 81 mg (0.5 mmol) of **1** in 0.2 mL of THF-d_8 (precooled to −100°C) was added. The mixture was transfered into the NMR tube (precooled to −100°C) and degassed by three freeze-pump-thaw cycles. The NMR tube was sealed under vacuum and stored in liquid nitrogen prior to the NMR experiments.

Acknowledgements

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