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Synthesis of Sterically Hindered Ortho-Substituted Tetraphenylethenes. Electronic Effects in the McMurry Olefination Reaction

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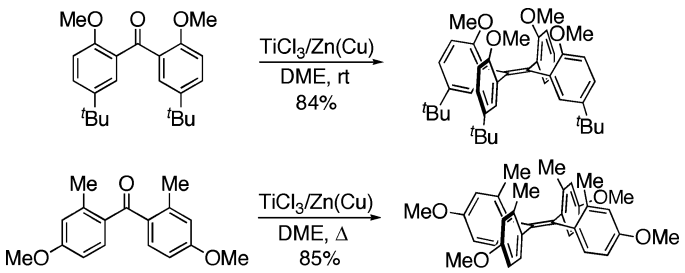
ABSTRACT



Contrary to literature consensus, the McMurry olefination reaction can be extended to the direct synthesis of sterically encumbered tetrakis-(2-substituted) tetraphenylethenes from the corresponding 2,2′-disubstituted benzophenones. The reaction exploits previously unrecognized substrate-based electronic effects that dominate over otherwise controlling steric considerations and provides highly efficient access to derivatives of tetrakis(2-hydroxyphenyl)ethene, a novel preorganized ligand system for polymetallic coordination chemistry and catalysis.

The reductive coupling of carbonyl compounds, a range of low-valent titanium reactions commonly referred to as the McMurry reaction, constitutes an important method for the synthesis of highly substituted alkenes.[1,2] McMurry reactions, however, are generally unsuitable for the preparation of sterically hindered tetraaryl olefins; the reaction leads instead to competitive reduction of the starting ketone and/or formation of coupled but overreduced 1,1,2,2,-tetrasubstituted ethanes. Ortho-substituted diaryl ketones in particular manifest this apparent steric limitation: neither bis(*ortho*-tolyl)-methanone nor bis(2-methoxyphenyl)methanone affords the corresponding olefin in acceptable yield under McMurry conditions.[3] The latter is converted exclusively to tetrakis-(2-methoxyphenyl)ethane (85% yield) upon reaction with $TiCl_4$/Zn/pyridine/THF.[4]

We recently introduced a novel preorganized tetradentate ligand system based on the tetrakis(2-hydroxyphenyl)ethene structural class **I**,[5] a differentially constrained analogue of the ubiquitous calix[4]arenes **II**. The rather inefficient three-step protocol developed for the olefination of bis(2-methoxyphenyl)methanone and the corresponding bis(5-*tert*-butyl) derivative[5a] prompted us to reinvestigate the McMurry reaction for the reductive coupling of ortho-substituted benzophenones. Here, we report that, contrary to literature consensus, the McMurry reaction of substituted benzophenones

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(3) Using $TiCl_3$/$LiAlH_4$, bis(*ortho*-tolyl)methanone gives a very low yield of tetrakis(2-methylphenyl)ethene (15%) along with tetrakis(2-methylphenyl)ethane (40%): (a) Willem, R.; Pepermans, H.; Hallenga, K.; Gielen, M.; Dams, R.; Giese, H. J. *J. Org. Chem.* **1983**, *48*, 1890−1898. (b) Bottine, F. A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 77−81.

(4) von Itter, F.-A.; Vögtle, F. *Chem. Ber.* **1985**, *118*, 2300−2313.

(5) (a) Verkerk, U. H.; Fujita, M.; Dzwiniel, T. L.; McDonald, R.; Stryker, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 9988−9989. (b) Fujita, M.; Qi, G.; Verkerk, U. H.; Dzwiniel, T. L.; McDonald, R.; Stryker, J. M. *Org. Lett.* **2004**, *6*, 2653−2656.

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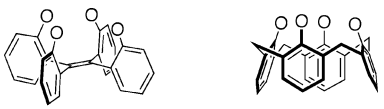
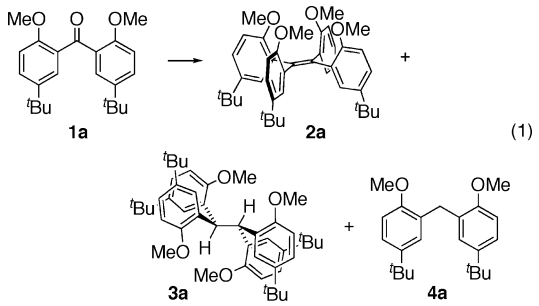
is dominated not by steric effects but by substrate-based electronic effects. On the basis of this newly recognized control element, the extension of the McMurry reaction to the preparation of a range of tetrakis(ortho-substituted) tetraphenylethylenes and related compounds has been realized.



I II

Using bis(5-*tert*-butyl-2-methoxyphenyl)methanone **1a** as the test substrate, we initially undertook an empirical optimization of the relevant reaction parameters (Table 1).[6]



1a **2a** **3a** **4a** (1)

Table 1. Reagents, Conditions,[a] and Product Distribution in the McMurry Olefination Reaction of Benzophenone **1a**[6]

entry	Ti source	reductant (equiv)	activation time (h)[b]	T_{react} (°C)[c]	yield (%)[d] 2a	3a	4a
1	$TiCl_3$	$LiAlH_4$ (0.5)	14	rt	14	9	61
2	$TiCl_3$	$LiAlH_4$ (0.25)	14	rt	38	27	16
3[e]	$TiCl_3$	$LiAlH_4$ (0.25)	14	rt	30	9	30
4	$TiCl_3$	Zn(Cu) (0.5)	14	rt	74	20	5
5	$TiCl_3$	Zn(Cu) (0.5)	0	rt	60	21	1
6	$TiCl_3$	Zn(Cu) (0.5)	2	rt	51	24	4
7	$TiCl_3$	Zn(Cu) (0.5)	6	rt	48	26	2
8	$TiCl_3$	Zn(Cu) (4.0)	14	rt	63	13	22
9	$TiCl_3$	Zn(Cu) (1.0)	14	rt	74	13	14
10	$TiCl_3$	Zn(Cu) (0.5)	14	reflux	65	19	0
11	$TiCl_3$	Zn(Cu) (0.5)	14	37	68	20	3
12[f]	$TiCl_3$·1.5DME	Zn(Cu) (0.5)	0	rt	79	4[i]	7[i]
13[g]	$TiCl_3$·1.5DME	Zn(Cu) (0.5)	14	rt	78	7[i]	4[i]
14[h]	$TiCl_3$	Zn(Cu) (0.5)	14	rt	84	5[i]	7[i]

[a] In DME solvent, unless otherwise noted. [b] Reaction time to generate the low-valent titanium reagent ($LiAlH_4$, rt; Zn(Cu), 89 °C). [c] Temperature of the reductive coupling reaction. [d] Isolated yields after careful purification by flash column chromatography. [e] THF used as solvent. [f] Large-scale experiment using 6.0 g of **1a**. [g] Large-scale experiment using 13.7 g of **1a**. [h] Large-scale experiment using 9.6 g of **1a**. [i] For these experiments, the yields of the minor products were obtained by ^{1}H NMR integration of the crude product mixture, normalized to the isolated yield of **2a**.

In nearly all cases, the McMurry reaction proceeds to give three principal reduction products, accompanied by traces of other, unidentified, byproducts (eq 1). The low-valent titanium species generated from titanium trichloride and $LiAlH_4$ is a generally inferior reagent, with the highest percentage of undesired reduction products **3a** and **4a** obtained from using the literature-optimized[3a] 1:0.5 molar ratio of $TiCl_3$/$LiAlH_4$ (entry 1). Lowering the ratio of $TiCl_3$/$LiAlH_4$ to 1:0.25 dramatically improves the isolated yield of olefination product **2a** (entry 2), but the reaction remains dominated by reduction products. Replacement of DME with THF as solvent promotes simple reduction over coupling (entry 3), a predictable consequence of the increased propensity for hydrogen atom donation from tetrahydrofuran over an acyclic ether.

To suppress the formation of reactive surface hydrides,[7] $LiAlH_4$ was replaced by Zn(Cu), another standard McMurry reductant.[2] The use of Zn(Cu) proved transforming, dramatically shifting the product distribution to provide, for the first time, reasonable selectivity for the formation of the desired tetraarylethylene product (entry 4).

Among the operational parameters, the impact of reagent preparation time is highly significant, despite previous reports that no reduction of $TiCl_3$ by Zn(Cu) occurs in the absence of substrate.[8] Omitting the reagent preparation step entirely produces several unidentified minor compounds at the expense of the desired alkene (entry 5), but intermediate reagent preparation times inexplicably produce less selective reactions (entries 6 and 7). Neither the reductant stoichiometry (entries 8 and 9) nor the reaction temperature (entries 10 and 11) exerts more than an incremental effect on yields and product distributions.[9]

The reaction is reasonably tolerant of the titanium source; both bulk unsolvated $TiCl_3$ and first quality $TiCl_3$·1.5DME function very similarly.[10] The latter reagent, however, is relatively insensitive to the reagent preparation time, providing nearly identical results under both standard conditions and the operationally advantageous "instant" method[8b] (entries 12 and 13). Finally, the reaction provides greater selectivity at larger scale (entry 14): this substrate, clearly, suffers no inhibitory steric effect.

The dramatic shift in product distribution observed by using the $TiCl_3$/Zn(Cu) reagent rather than $TiCl_3$/$LiAlH_4$ suggests the incorporation of strongly Lewis acidic [Zn(II)?] coordination sites into the reagent, promoting substrate binding and reduction *on the reagent surface*, strongly favoring the bimolecular olefination. Substrate binding may arise via chelation of the proximal ether and carbonyl functionality or via unidentate coordination of the electron-rich carbonyl. To address this question and distinguish steric from electronic effects, a series of differentially substituted benzophenones have been investigated (Table 2).

(6) Complete experimental procedures and characterization data are provided as Supporting Information.

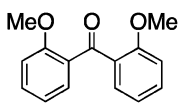
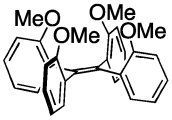
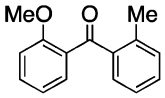
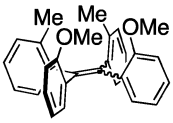
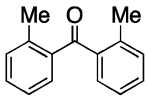
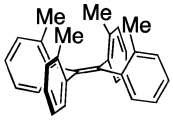
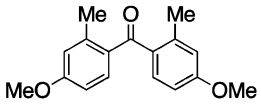
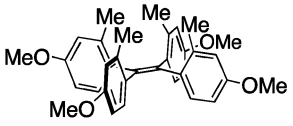
(7) The $TiCl_3$/$LiAlH_4$/THF reagent consists principally of the hydride-rich cluster $[HTiCl(thf)_{0.5}]_x$, a potential source of H•, H_2, and reactive hydride: Aleandri, L. E.; Becke, S.; Bogdanivic, B.; Jones, D. J.; Rozière, J. *J. Organomet. Chem.* **1994**, *472*, 97−112.

(8) (a) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991−6010. (b) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215−5229. (c) Bogdanivic, B.; Bolte, A. *J. Organomet. Chem.* **1995**, *501*, 109−121. (d) Stahl, M.; Pidun, U.; Frenking, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2234−2237.

(9) Control experiments conducted by adding tetrakis(5-*tert*-butyl-2-methoxyphenyl)ethene **2a** to an active McMurry reduction of 2,2′-dimethoxybenzophenone **1b** clearly indicate that overreduction product **3a** *does not arise from direct reduction of* ***2a***.

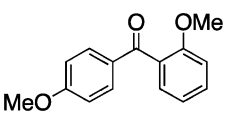
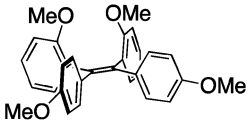
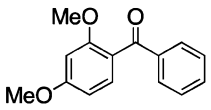
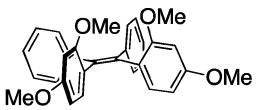
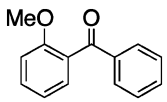
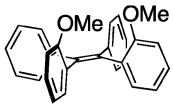
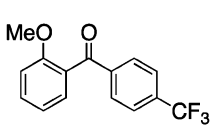
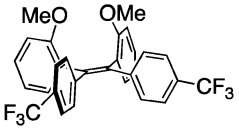
(10) The unsolvated $TiCl_3$ powder has recently become difficult to obtain commerically. $TiCl_3$·1.5DME is conveniently prepared from $TiCl_4$ and Ti powder in DME: Sullivan, J. M. U.S. Patent 6307063, 2001.

Table 2. McMurry Reaction of bis(ortho-Substituted) Diarylmethanones **1b**−**e**[a]

entry	substrate	products:[6]		
	structure (ν_{co} in DME)[b]	tetraarylethene **2**[c]		-ethane **3**[c]
		structure/conditions/yield		yield
				**3b**
1	**1b** (1648)	**2b**	A: 76	15
				**3c**[d]
2	**1c** (1665)	**2c**	A: 26[e,f]	10[e]
3			B: 23[e,f]	13[e]
				**3d**
4	**1d** (1667)	**2d**	A[g]: 18	7
5			B: 70	15
				**3e**
6	**1e** (1655)	**2e**	A: 52[h]	27
7			B: 85	14

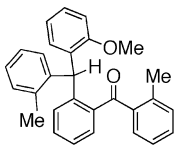
[a] Conditions: $TiCl_3$, 0.5 equiv of Zn(Cu), DME. Reagent preparation: 14 h at reflux. **A**, reaction at room temperature; **B**, reaction at reflux. [b] Carbonyl infrared absorption (cm^{-1}) in anhydrous DME. [c] Complete characterization provided as Supporting Information. [d] Tetraphenylethane product obtained as a ~1:1 diastereomeric mixture. [e] Yields derived from NMR integration of the purified but inseparable product mixture. [f] Two additional byproducts **5** (rt, 26%; reflux, 0%) and **6** (rt, 17%; reflux, 16%) are also isolated. [g] Recovered benzophenone **1d** (39%) and bis(*ortho*-tolyl)methanol (28%) were also obtained. [h] Benzophenone **1e** (15%) was also recovered.

Table 3. McMurry Reaction of Unsymmetrically Substituted Diarylmethanones **1f**−**i**[a]

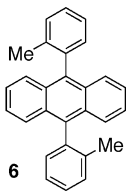
entry	substrate	products:[6]		
	structure (ν_{co} in DME)[b]	tetraarylethene **2**[c]		-ethane **3**[c]
		structure/conditions/yield		yield
				**3f**[d]
1	**1f** (1662)	**2f**	A: 76[e] (*Z*/*E*: 8)	10
				**3g**[d]
2	**1g** (1659)	**2g**	A: 76[e] (*Z*/*E*: 8)	7
				**3h**[d]
3	**1h** (1669)	**2h**	A: 36[f] (*Z*/*E*: 17)	19
4			B: 67[f] (*Z*/*E*: 13)	17
				**3i**[d]
5	**1i** (1671)	**2i**	A: 31[e] (*Z*/*E*: 9)	–[g]
6			B: 67[e] (*Z*/*E*: 6)	–[g]

[a] Conditions: $TiCl_3$, 0.5 equiv of Zn(Cu), DME, 14 h reagent preparation time (reflux). **A**, reaction at room temperature; **B**, reaction at reflux. [b] C=O stretching absorption frequency (cm^{-1}) of substrates in anhydrous DME. [c] Product identification provided as Supporting Information. [d] Ethane obtained as a ~1:1 diastereomeric mixture. [e] Stereochemistry assignment tentative, based on spectroscopic comparisons to the rigorously assigned isomers *Z*-**2h** and *E*-**2h**. [f] Major product is the *Z*-isomer, as determined by X-ray crystallography.[6] [g] Yield not determined; the ethane(s) could not be isolated free from minor byproducts.

The reaction of bis(2-methoxyphenyl)methanone **1b** proceeds in comparable yield and selectivity to the closely analogous **1a** (entry 1). Replacement of one methoxy substituent with the less-electron-donating but roughly isosteric methyl group (**1c**, entries 2 and 3) substantially undermines the McMurry process. Two additional compounds are isolated from this reaction, ipso-substitution product **5** and anthracene **6**, with the latter presumably being derived from the former by a second ipso-substitution reaction.



5



6

Replacement of the remaining methoxy substituent with a methyl group leads to poor conversion at room temperature and substantial formation of the simple diarylmethanol product (entry 4). Surprisingly, however, conducting the reaction at reflux temperature leads to the isolation of tetrakis(1-methylphenyl)ethene **2d** in very good yield (entry 5), providing *for the first time*[3] reaction conditions for successful olefination of this sterically challenging and electronically unactivated substrate.

The electronic influence of conjugating methoxy substituents can be isolated from interacting steric effects by appending *para*-methoxy substituents to bis(2-methylphenyl)-methanone **1d** (entries 6 and 7). At room temperature, bis-(4-methoxy-2-methylphenyl)methanone **1e** undergoes markedly higher conversion (viz., nearly 3-fold), albeit with little change in product distribution. At reflux, however, this substrate undergoes the McMurry olefination with remarkably high selectivity and yield. Although multidentate substrate coordination to the heterogeneous surface might well be invoked to rationalize the reaction of bis(ortho-

substituted) **1b**, such a chelation effect is not possible in the para-substituted benzophenone **1e**.

To complement this assessment of substrate-based electronic perturbations in the McMurry reaction, a series of substrates incorporating a substantial reduction in steric demands at the carbonyl functionality were also investigated (Table 3). Relocation of one *ortho*-methoxy substituent to the para-position in either ring maintains the high efficiency of the McMurry reaction (**1f**/**1g**, entries 1 and 2), delivering a yield and product distribution almost identical to that obtained from bis(2-methoxyphenyl)methanone **1b**. Contrary to expectations, however, *deletion* of one *ortho*-methoxy substituent leads to a dramatic decrease in both selectivity and yield (**1h**, entry 3), despite mitigating the steric effect: *this McMurry reaction is dominated by electronic rather than steric effects*. Increasing the reaction temperature at least partially compensates for the electronic deactivation, restoring both yield and selectivity (entry 4).

As inferred from the results obtained from bis(ortho-substituted) benzophenones **1d** and **1e**, the relative reactivities of substrates **1f**−**h** are inconsistent with a substrate chelation effect. The results, instead, track the basicity of the carbonyl functionality, as measured by the carbonyl absorption frequencies in the infrared spectra (Table 3).

The impact of the electrophilic *para*-trifluoromethyl substituent in substrate **1i** (entries 5 and 6) is considerably more ambiguous, returning yields and product distributions nearly identical to those of 2-methoxybenzophenone **1h**, both at room temperature and at reflux. The near fidelity in infrared absorption frequencies for the carbonyl functionality in the two substrates (see Table 3) suggests that conjugation to the carbonyl functionality[11] is dominated by the arene bearing the electron-donating methoxy substituent, with the trifluoromethyl group exerting surprisingly little influence on the electron density at the carbonyl.

With the exception of 2-methoxy-2′-methylbenzophenone **1c**, which is diverted into a unique reactivity manifold, the qualitative correlation of carbonyl infrared absorption energy with observed reactivity in the McMurry reaction extends to both series of benzophenone subtrates. The general preference for the formation of the *Z*-olefin from the unsymmetrically substituted series of substrates (Table 3) is a significant bonus, albeit very difficult to rationalize.

The development of a McMurry protocol for the direct synthesis of tetrakis(2-methoxyphenyl)ethene derivatives (e.g., **2a** and **2b**) from the corresponding 2,2′-dimethoxybenzophenone renders obsolete our prior synthetic route[5a] to these potentially important ligand systems.

Further extensions in scope and continued investigation and exploitation of electronic effects in the McMurry olefination of sterically hindered bis(ortho-substituted) diaryl ketones remain under investigation.

Acknowledgment. We thank NSERC-CRO for financial support and R. McDonald and M. Ferguson for X-ray structures. M.-K.C. thanks Alberta Ingenuity/Killam Trusts for a postdoctoral fellowship. We also thank Paul D. Fancy for preparing substrate **1g**.

Supporting Information Available: Experimental procedures and complete characterization data for all new compounds; details of the X-ray crystallography for compounds *Z*-**2h**, **3e**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The two benzophenone arene rings cannot simultaneously maintain planarity with the carbonyl functionality, a consequence of ortho-substituent peri-interactions and, presumably, four-electron repulsion of methoxy and carbonyl lone electron pairs.