Regioselective Synthesis of Highly Substituted Aromatic Sulfides via Carbonyl−Alkyne Exchange Reaction†

Daniel Obrecht,*,‡ Cornelia Zumbrunn,§ and Klaus Müller

F. Hoffmann-La Roche AG, Pharma Research, CH-4070 Basel, Switzerland

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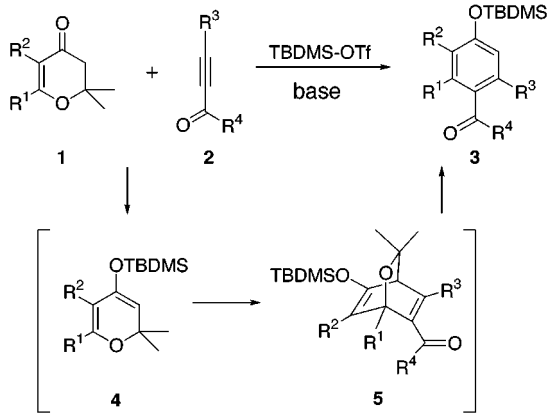
Carbonyl−alkyne exchange reaction of 2,2-dimethyldihydropyran-4-thione-derived dienes with acetylenic ketones leads to highly substituted aromatic sulfides. The reaction proceeds with a high degree of regioselectivity and in good yields. Addition of Et_2AlCl considerably increases the scope of usable acetylenic ketones. The starting materials, dihydropyran-4-one and α-alkynyl ketone derivatives, are readily available reactive building blocks. Additional diversity can be introduced through straightforward derivatization reactions at the sulfur atom. The use of solid-supported reagents and trapping agents allows the reaction to be carried out in a parallel format which might render such a concept attractive for the synthesis of compound libraries.

Introduction

Highly substituted aromatic compounds are constituents of many complex natural products, pharmaceutical drugs, agrochemicals, dyes, polymers, and additives. Although many transformations using mainly electrophilic and nucleophilic aromatic substitutions on the aromatic nucleus have been described in the past, more recent approaches resorted to the de novo construction of the aromatic moiety using mainly [4+2] cycloaddition strategies,[1−9] ensuring a higher predictability and fidelity of regiochemical control for the introduction of sterically and electronically demanding functional groups. Further approaches of successful de novo construction of highly substituted aromatic compounds include trimerization of acetylenes as described by Vollhardt[10] and reactions of cyclobutenones with acetylenes described by Danheiser,[11] Liebeskind,[12] and Moore.[13]

The carbonyl−alkyne exchange (CAE) reaction[14−19] of 2,2-dialkyl-2,3-dihydro-4*H*-pyran-4-ones **1** with electron-deficient acetylenes **2**, yielding protected phenols **3** (Scheme 1), which has been studied previously in our group,[20] constitutes a novel approach for the regioselective de novo construction of highly functionalized aromatic compounds. Thus, in situ transformation of dihydropyranones **1** into their corresponding silyl enol ethers **4** and [4+2] cycloaddition with acetylenes **2** yielded—via bicyclic intermediates **5** and electrocyclic extrusion of acetone—the protected phenols **3** in good to excellent yields (Scheme 1). The products were formed under very mild conditions, tolerating a wide range of functional groups. The high degree of regioselectivity observed in this reaction is in accordance with simple FMO considerations and earlier published work.[21,22] Since both dihydropyranone and α-alkynyl ketone derivatives are synthetically readily available building blocks,[20,23−27] this

Scheme 1



† Dedicated to Prof. Dr. Robert E. Ireland on the occasion of his 70th birthday.

‡ Present address: POLYPHOR Ltd., Winterthurerstr. 190, CH-8057 Zürich, Switzerland.

§ Part of Ph.D. thesis of C.Z., University of Zürich, 1998.

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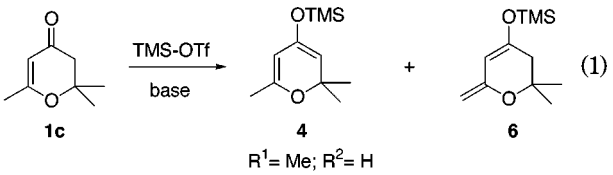
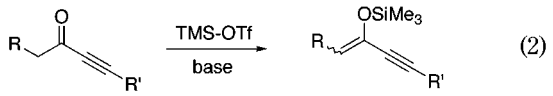
reaction allows the synthesis of a wide range of aromatic compounds. Nevertheless, this method showed some limitations. Low yields were obtained in CAE reactions when dihydropyranones bearing a slightly acidic hydrogen on the R^1 substituent were used, which is probably due to partial exocyclic enolization and thus formation of dienes of type **6** (eq 1). Such s-trans-configurated dienes are unable to undergo 1,4-cycloaddition reactions.



(1)

Similarly, the synthesis was restricted to the use of nonenolizable acetylenic ketones due to conversion of the α-alkynyl ketone into a conjugated enyne system via trans-silylation, thus inactivating the dienophile (eq 2).

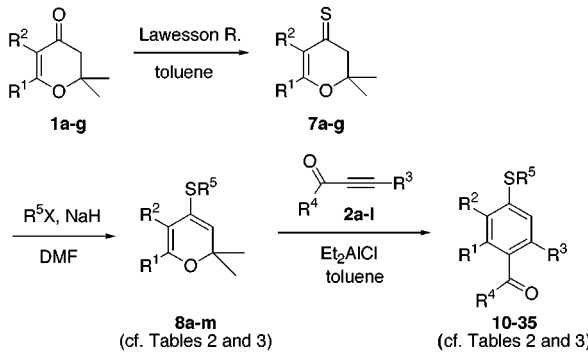


(2)

The isolation of the intermediate dienes would therefore be preferable in order to avoid the addition of silylating agent and base during the cycloaddition step. Unfortunately, isolation of **4** proved difficult due to the sensitivity of the silyl enol ether toward hydrolysis.

In this paper, we describe the synthesis of dihydropyranthiones **7** (Scheme 2) as the sulfur analogues of the parent dihydropyranones **1** and their use in CAE reactions. The increased stability toward hydrolysis of cyclic dienes **8** as compared to the silyl enol ethers **4** allowed the isolation of intermediates **8** and thus the stepwise performance of CAE reactions. In addition, we could demonstrate that Et_2AlCl efficiently catalyzes the CAE reaction between dienes of type **8** and dienophiles **2**, thus significantly broadening the scope of accessible substituents and functional groups. The wide applicability of this reaction prompted us to investigate its use in parallel synthesis of aromatic compound libraries.

Scheme 2



1a: R^1 = Ph, R^2 = H
1b: R^1 = t-Bu, R^2 = H
1c: R^1 = CH_3, R^2 = H
1d: R^1 = H, R^2 = H
1e: R^1 = CH_3, R^2 = CH_3
1f: R^1 = CO_2Bu, R^2 = H
1g: R^1 = CH_3, R^2 = CO_2t-Bu

2a: R^3 = CO_2CH_3, R^4 = OCH_3
2b: R^3 = H, R^4 = OCH_3
2c: R^3 = CO_2CH_3, R^4 = Ph
2d: R^3 = $CH(OEt)_2$, R^4 = Ph
2e: R^3 = $CH(OEt)_2$, R^4 = CF_3
2f: R^3 = CH_2OTHP, R^4 = CF_3
2g: R^3 = CO_2CH_3, R^4 = CH_3
2h: R^3 = $SiMe_3$, R^4 = Ph
2i: R^3 = Br, R^4 = 3,4,5-$(OCH_3)_3C_6H_2$
2k: R^3 = Br, R^4 = OCH_3
2l: R^3 = Br, R^4 = CH_3

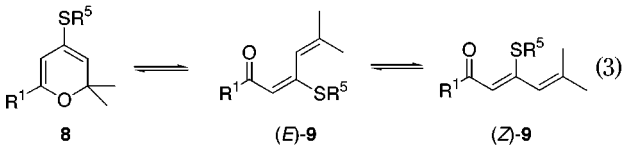
Table 1. Synthesis of Dihydropyran-4-thiones 7a−g

pyranone	R^1	R^2	conditions	thione	yield (%)
1a[a]	Ph	H	rt/4 h	**7a**	100
1b[a]	*t*-Bu	H	rt/6 h	**7b**	100
1c[a]	Me	H	rt/2 h	**7c**	90
1d[a]	H	H	rt/6 h	**7d**[b]	28
1e[c]	Me	Me	rt/4 h	**7e**	79
1f[d]	CO_2n-Bu	H	50 °C/4 h	**7f**	54
1g[a]	Me	CO_2t-Bu	70 °C/4 h	**7g**	66

[a] Synthesized according to ref 20. [b] Extremely volatile and sensitive to hydrolysis. [c] Synthesized according to ref 23. [d] Available from Aldrich.

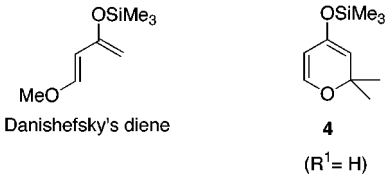
Results and Discussion

Thiones **7a**−**g** were readily available from the corresponding dihydropyranones **1a**−**g** by treatment with Lawesson's reagent[28] (Table 1). Although dihydropyranthiones **7** have a limited shelf life due to the inherent instability of the thione group and should be stored at low temperatures, they could be alkylated with NaH or DBU as bases and a range of different alkyl halides to give cyclic dienes **8a**−**m** (Tables 2 and 3). These intermediates could be isolated but were prone to electrocyclic ring-opening (eq 3) to form linear products of type **9**. Therefore, intermediates **8** were directly reengaged in the CAE reaction as purification on silica gel resulted in a decrease of the overall yields.



(3)

Aromatic sulfides **10**−**25** resulting from CAE reaction of dihydropyranthione-derived dienes and acetylenic ketones **2a**−**f** (Scheme 2) are listed in Table 2. Pyranthione **7c** bearing a methyl group at position 6 was converted into dienes **8h** (R^5 = PMB) and **8i** (R^5 = Bn) and used in CAE reactions without concomitant exo-enolization being observed (entries 12 and 13). In our hands, the unsubstituted pyranthione **7d** representing a precursor for a cyclic analogue of Danishefsky's diene could not be used in CAE reactions.



After alkylation of the thione, electrocyclic ring-opening was predominant and no cycloaddition product was detectable. Danishefsky's diene is thus highly complementary to the cyclic analogues of type **8**. Best results were obtained using dihydropyranthiones bearing bulky and nonenolizable substituents in the 6-position (R^1 = Ph, *t*-Bu). Smaller substituents R^1 (R^1 = Me, H) or electron-withdrawing groups (R^1 = CO_2n-Bu) seem to be less effective in stabilizing the cyclic form of the diene.

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Table 2. Synthesis of Aromatic Sulfides via Thermal CAE Reaction

entry	thione	R^1	R^2	diene	R^5	alkyne	R^3	R^4	temp (°C)	sulfide	yield[a] (%)
1	**7a**	Ph	H	**8a**	PMB[b]	**2c**	CO_2CH_3	Ph	rt	**10**	77
2	**7a**	Ph	H	**8b**	Bn	**2c**	CO_2CH_3	Ph	rt	**11**	89
3	**7a**	Ph	H	**8b**	Bn	**2a**	CO_2CH_3	OCH_3	rt	**12**	100[c]
4	**7a**	Ph	H	**8b**	Bn	**2e**	$CH(OEt)_2$	CF_3	rt	**13**	97
5	**7a**	Ph	H	**8b**	Bn	**2f**	CH_2OTHP	CF_3	rt	**14**	79
6	**7a**	Ph	H	**8a**	PMB	**2a**	CO_2CH_3	OCH_3	rt	**15**	85[d]
7	**7a**	Ph	H	**8c**	1-PhE[e]	**2a**	CO_2CH_3	OCH_3	rt	**16**	85[d]
8	**7a**	Ph	H	**8a**	PMB	**2b**	H	OCH_3	110	**17**	47
9	**7b**	*t*-Bu	H	**8f**	PMB	**2c**	CO_2CH_3	Ph	50	**18**	85
10	**7b**	*t*-Bu	H	**8f**	PMB	**2f**	CH_2OTHP	CF_3	rt	**19**	86
11	**7b**	*t*-Bu	H	**8g**	Bn	**2a**	CO_2CH_3	OCH_3	50	**20**	60
12	**7c**	CH_3	H	**8h**	PMB	**2c**	CO_2CH_3	Ph	rt	**21**	42
13	**7c**	CH_3	H	**8i**	Bn	**2c**	CO_2CH_3	Ph	rt	**22**	74
14	**7e**	CH_3	CH_3	**8k**	PMB	**2c**	CO_2CH_3	Ph	rt	**23**	27
15	**7f**	CO_2n-Bu	H	**8l**	Bn	**2c**	CO_2CH_3	Ph	110	**24**	71[f]
16	**7g**	CH_3	CO_2t-Bu	**8m**	PMB	**2c**	CO_2CH_3	Ph	100	**25**	40

[a] Isolated yield [%] over two steps. [b] *p*-Methoxybenzyl. [c] Neat, yield based on purified and isolated diene. [d] Neat. [e] 1-Phenylethyl. [f] Yield based on isolated diene.

Table 3. Synthesis of Aromatic Sulfides via Et_2AlCl-Catalyzed CAE Reaction of Thione 7a

entry	diene	R^1	R^2	R^5	alkyne	R^3	R^4	temp (°C)/amt of Et_2AlCl (equiv)	sulfide	yield (%)[a]
1	**8a**	Ph	H	PMB[b]	**2b**	H	OCH_3	rt/3	**17**	90
2	**8a**	Ph	H	PMB	**2d**	$CH(OEt)_2$	Ph	rt/0.2	**26**	79
3	**8d**	Ph	H	Hex	**2g**	CO_2CH_3	CH_3	0/0.5	**27**	93[c]
4	**8d**	Ph	H	Hex	**2c**	CO_2CH_3	Ph	0/0.5	**28**	98
5	**8a**	Ph	H	PMB	**2h**	$SiMe_3$	Ph	rt/0.2	**29**	86
6	**8a**	Ph	H	PMB	**2i**	Br	$Ph(OMe)_3$	rt/0.2	**30**	64
7	**8d**	Ph	H	Hex	**2k**	Br	OCH_3	rt/1	**31**	44
8	**8e**	Ph	H	CH_3	**2k**	Br	OCH_3	rt/1.25	**32**	60
9	**8d**	Ph	H	Hex	**2l**	Br	CH_3	−10/1	**33**	44
10	**8e**	Ph	H	CH_3	**2h**	$SiMe_3$	Ph	0/1	**34**	73
11	**8d**	Ph	H	Hex	**2h**	$SiMe_3$	Ph	0/1	**35**	55

[a] Isolated yield over two steps. [b] *p*-Methoxybenzyl. [c] 95:5 mixture of regioisomers.

Acetylenes bearing strong electron-withdrawing substituents were most efficient in the CAE reaction. Prolonged heating was necessary in reactions with less reactive dienophiles such as methyl propiolate which was incompatible with the limited thermal stability of some of the dienes **8**.

To overcome the problem of insufficient reactivity and to broaden the range of acetylenic ketones amenable to the CAE reaction, we explored the use of a Lewis acid catalyst to increase the reactivity of the dienophiles. After having screened several Lewis acids which are known to catalyze cycloaddition reactions,[29−36] we found that Et_2AlCl indeed efficiently accelerated the CAE reaction. Aromatic sulfides synthesized using Et_2AlCl catalysis are summarized in Table 3.

The reaction with methyl propiolate under Lewis acid-catalyzed reaction conditions gave sulfide **17** in 90% yield (Table 3, entry 1). In contrast, the uncatalyzed reaction gave the desired sulfide **17** in 47% yield (Table 2, entry 8) along with significant amounts of noncharacterized byproducts, complicating the purification of the final products.

Under Lewis acid-catalyzed conditions the reaction of brominated or silylated actylenic ketones **2h**−**l** (R^3 = Br, $SiMe_3$) became feasible (Table 3, entries 5−11). Thus, products **19**−**35** (Table 3, entries 5−11) with R^3 = TMS and Br constitute synthetically especially useful intermediates for further derivatization reactions such as ipso-substitutions and Pd-catalyzed cross-coupling reactions. Without the use of Et_2AlCl these dienophiles either were too unreactive for the CAE reaction or underwent numerous side reactions.

The amount of Lewis acid catalyst necessary for the reaction depended largely on the nature of the alkyne. α-Alkynyl ketones needed less than 1 equiv of catalyst for completion of the reaction whereas propiolic esters required stoichiometric amounts or more. In the latter case, the aluminum appeared to coordinate tightly with the products, which prevented the release of the catalyst.

CAE reactions of dienes derived from thiones bearing electron-withdrawing groups such as **7f** and **7g** (Tables 1 and 2) could not be catalyzed, probably due to the fact that the catalyst was deactivating the diene by coordination to the ester function. Those reactions were carried out at 100−110 °C in a sealed tube without a Lewis acid catalyst present.

Different reaction protocols allowing a simple workup procedure were screened in order to use the CAE reaction for combinatorial and parallel synthesis. Among the several successful alkylation protocols amenable to the alkylation of dihydropyranthiones **7**, best results were

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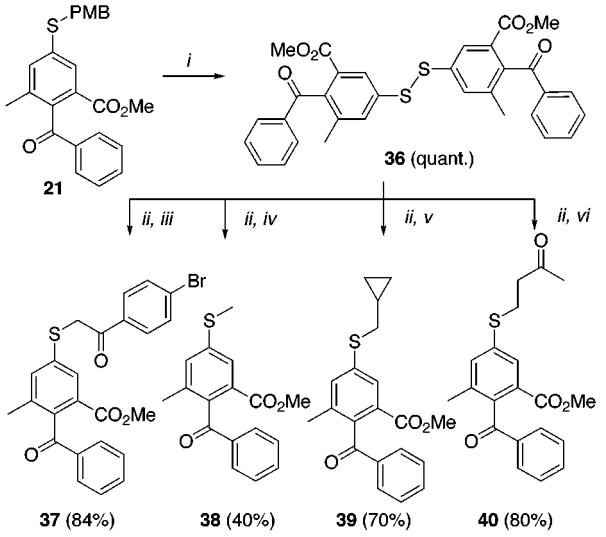
Scheme 3



Reagents and conditions: *i*) NBS, MeCN; *ii*) PS-PPh_2;[37] *iii*) 4-Br-$C_6H_4COCH_2Br$; *iv*) CH_3I; *v*) $C_3H_5CH_2Br$; *iv*) methyl vinyl ketone

obtained by treatment either with an alkyl halide and NaH in DMF (general procedure A) or with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane (general procedure B). The former procedure required aqueous workup for the isolation of the diene, whereas in the latter a simple filtration over a small plug of silica gel efficiently removed the byproducts. Obviously, method B was more appropriate for parallel synthesis. In the subsequent cycloaddition reaction the excess of α-alkynyl ketone (1.05−2.0 equiv) was trapped with a polymer-supported thiol.[37] Thus, the polymer-bound 1,4-adducts could be easily removed by simple filtration.

The aromatic sulfides generated by CAE reactions of dihydropyranthiones with acetylenic ketones were further derivatized. Additional molecular diversity on the sulfur atom could be introduced by a trans-alkylation protocol as depicted in Scheme 3. Treatment of the *p*-methoxybenzyl thioether **21** with *N*-bromosuccinimide (NBS) resulted in quantitative formation of disulfide **36**. Reductive cleavage of the disulfide using polymer-bound triphenylphosphine and subsequent alkylation of the intermediate thiophenols with different electrophiles in a one-pot procedure[37] gave sulfides **37**−**40**. Again, the use of solid-supported reagents facilitated workup and isolation of the final products.

Another interesting derivatization consisted in a direct transformation of the aromatic sulfides into sulfonamides. Traditionally, sulfonamides are synthesized via the corresponding sulfonic acids and sulfonyl chlorides, requiring rather harsh reaction conditions. To synthesize a wide range of aromatic sulfonamides, we developed a simple two-step procedure to convert aromatic *p*-methoxybenzyl sulfides into sulfonamides (Scheme 4, Chart 1). The reaction sequence involved thioether cleavage with sulfuryl chloride as reported by Kharasch et al.[39] to form the highly reactive and easily hydrolizable

Scheme 4

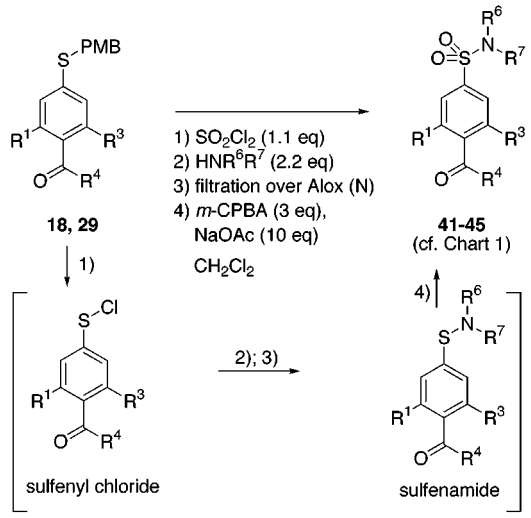
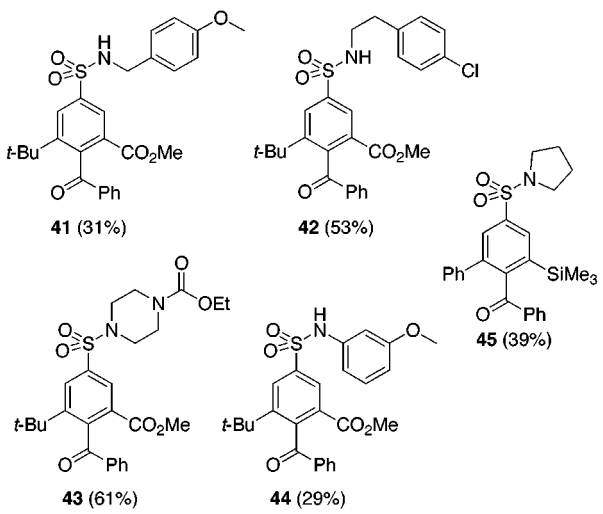


Chart 1



sulfenyl chloride derivatives. In our case, isolation of the sulfenyl chlorides was not necessary, and direct substitution with primary or secondary amines gave the intermediate, rather unstable sulfenamide derivatives which after filtration over a thin plug of aluminum oxide (N) were oxidized with *m*-CPBA under buffered conditions to give sulfonamides **41**−**45** in 30−60% overall yields. Reaction conditions were not optimized, and disulfide formation remained an important side reaction. Nevertheless, this protocol represents a mild alternative for the synthesis of aromatic sulfonamides.

Summary

On the basis of the carbonyl−alkyne exchange reaction of 2,2-dimethyl-2,3-dihydro-4*H*-pyran-4-thione-derived cyclic dienes **8** and electron-deficient acetylenes, a novel synthesis of aromatic sulfides has been developed. The procedure allows the synthesis of highly substituted benzenes with great potential for variation of functional groups starting from readily available, highly reactive building blocks under very mild conditions and in high yields. The use of Et_2AlCl as a Lewis acid catalyst

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substantially increased the range of applicable acetylenic dienophiles as also enolizable acetylenic ketones could be employed. Reaction conditions were developed suitable for automated parallel synthesis using a polymer-bound thiol as trapping agent for the capture of excess dienophile. The resulting aromatic sulfides could be efficiently transformed by a reductive transalkylation procedure using a polymer-bound phosphine either into products **37**−**40** (Scheme 3) or into sulfonamides **41**−**45** as depicted in Scheme 4. Hence, the described aromatic sulfides **10**−**35** constitute platforms for further chemical transformations into pharmacologically interesting molecules.

Experimental Section

General Procedures. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 0.25 mm plates. Visualization was accomplished using ultraviolet light or one of the following stains: (a) 1% $KMnO_4$, 2% $NaHCO_3$ in H_2O or (b) *o*-toluidine (320 mg), acetic acid (60 mL), and KI (2 g) dissolved in H_2O (1 L). Chromatography was performed using E. Merck silica gel 60 (230−400 mesh). Solvent systems are reported as volume percent mixtures. Chloroform was filtered over alox prior to use. CH_2Cl_2 was distilled from CaH and stored under Ar. Liquid reagents were distilled prior to use. All other reagents were purchased from Fluka or Aldrich and used without further purification. Highly loaded PS−PPh_2 and PS−CH_2SH resins were purchased from Polyphor Ltd. Acetylenic ketones **2a**−**l** were synthesized in analogy to literature procedures.[20,40−43]

Synthesis of 2,2-Dimethyl-2,3-dihydropyran-4-thiones 7. General Procedure. To a stirred solution of dihydropyranone **1** (10 mmol) in toluene (10 mL) was added Lawesson's reagent (0.6 equiv). The reaction mixture was stirred under Ar as indicated. Purification by filtration over silica gel (120 g) with hexane/CH_2Cl_2 gave purple thiones **7** which are rather unstable but can be stored at −20 °C for at least a month.

2,2-Dimethyl-6-phenyl-2,3-dihydropyran-4-thione (7a). Quantitative. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, 2 H, J = 3.1); 7.51−7.49 (m, 1 H); 7.45−7.41 (m, H); 6.99 (s, 1 H); 2.97 (s, 2 H); 1.52 (s, 2 CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 222.7; 160.4; 133.2; 131.8; 128.8; 127.1; 114.4; 80.4; 54.4; 25.8. IR (NJL): 1665; 1582; 765 cm^{-1}. MS (EI): *m*/*z* 218 (86, $[M]^+$); 203 (68, $[M - CH_3]^+$); 105 (100, $[Ph - CO]^+$); 77 (53, $[C_6H_5]^+$).

6-*tert*-Butyl-2,2-dimethyl-2,3-dihydropyran-4-thione (7b). Quantitative. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.44 (s, 1 H); 2.88 (s, 2 H); 1.38 (s, 6 H, 2 CH_3); 1.18 (s, 6 H, *t*-Bu). IR (KBr): 1554m; 1257; 1156; 1088 cm^{-1}. MS (EI): *m*/*z* 198 (100, $[M]^+$); 183 (32, $[M - CH_3]^+$); 141 (95, $[M - t\text{-Bu}]^+$); 85 (55).

2,2,5,6-Tetramethyl-2,3-dihydropyran-4-thione (7e). 79%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.00 (s, 2 H); 2.09 (s, 3 H); 2.04 (s, 3 H); 1.36 (s, 6 H, 2 Me). MS (EI): *m*/*z* 170 (98, M^+); 155 (100, $[M - CH_3]^+$).

***n*-Butyl 6,6-Dimethyl-4-thioxo-5,6-dihydro-4*H*-pyran-2-carboxylate (7f).** 54%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.92 (s, 1 H); 4.28 (t, 2 H, J = 6.6); 2.95 (s, 2 H); 1.8−1.6 (m, 2 H); 1.5−1.3 (m, 2 H); 1.47 (s, 6 H, 2 Me); 0.96 (t, 3 H, J = 7.3). IR (MIR): 1734s; 1567m; 1288s; 1260m; 1236s; 1218 s; 1087s cm^{-1}. MS (EI): *m*/*z* 242 (72, M^+); 141(82); 125 (100); 115 (60); 57 (64).

***tert*-Butyl 2,6,6-Trimethyl-4-thioxo-5,6-dihydro-4*H*-pyran-3-carboxylate (7g).** 66%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.91 (s, 2 H); 2.03 (s, 3 H); 1.52 (s, 9 H, *t*-Bu); 1.40 (s, 6 H, 2 Me). MS (EI): *m*/*z* 256 (48, M^+); 200 (100, $[M - C_4H_8]^+$); 185 (36); 167 (42); 154 (30); 139 (18).

Alkylation of 2,2-Dimethyl-2,3-dihydropyran-4-thiones 7. General Procedure A. To a stirred solution of thione **7** (0.5 mmol) in DMF (1.5 mL) at 0 °C under Ar were added alkyl halide (1.2 equiv) and NaH dispersion (55%, 1.2 equiv). The reaction mixture was stirred at 0 °C as indicated, poured onto saturated NH_4Cl solution, and extracted with ether. The combined organic fractions were dried ($MgSO_4$) and the solvents evaporated. The crude dienes **8** were used without further purification or analysis.

Alkylation of 2,2-Dimethyl-2,3-dihydropyran-4-thiones 7. General Procedure B. To a stirred solution of thione **7** (0.5 mmol) in CH_2Cl_2 (2 mL) at room temperature under Ar were added alkyl halide (1.2 equiv) and DBU (1.2 equiv). The reaction mixture was stirred at room temperature as indicated and filtered over silica gel (2 g), and the solvents were removed under reduced pressure. The crude dienes **8** were used without further purification or analysis.

Uncatalyzed CAE Reactions of Cyclic Dienes 8 with Acetylenic Ketones 2. General Procedure. To a solution of the crude diene **8** (0.5 mmol) in toluene (500 μL) was added acetylene **2** (1.2−2 equiv). The mixture was stirred as indicated until all the diene was consumed. Polystyrene-bound thiol[37,42] was added and the mixture stirred at room temperature until the excess dienophile was trapped. Filtration and chromatography on silica gel gave analytically pure products.

Catalyzed CAE Reactions of Cyclic Dienes 8 with Acetylenic Ketones 2. General Procedure. To a solution of the crude diene **8** (0.5 mmol) in toluene (500 μL) were added acetylene **2** (1.2−2 equiv) and dropwise a solution of Et_2AlCl in toluene (1.8 M, 0.1−3 equiv). The mixture was stirred at room temperature as indicated until disappearance of **8**. Polystyrene-bound thiol[37,42] was added and the mixture stirred at room temperature until the excess dienophile was trapped. Filtration and chromatography on silica gel gave analytically pure products.

Methyl 2-Benzoyl-5-(4-methoxybenzylsulfanyl)biphenyl-3-carboxylate (10). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2c** (24 h at room temperature). Yellow oil. 77%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.98 (d, 1 H, J = 1.8); 7.6−7.5 (m, 2 H); 7.45−7.3 (m, 1 H); 7.3−7.2 (m, 4 H); 7.2−7.05 (m, 5 H); 6.7−6.6 (m, 2 H); 4.20 (s, 2 H); 3.80 (s, 3 H, COOMe); 3.67 (s, 3 H, OMe). IR (film): 1727s; 1677s cm^{-1}. MS (EI): *m*/*z* 468 (12, M^+); 121 (100, $[CH_2C_6H_4 - OMe]^+$).

Methyl 2-Benzoyl-5-(benzylsulfanyl)biphenyl-3-carboxylate (11). Alkylation of **7a** according to general procedure B (3 h). CAE reaction with **2c** (3.5 h at room temperature). Recrystallization from hexane/ether (3:1). 89%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.98 (d, 1 H, J = 1.9); 7.6−7.5 (m, 2 H); 7.42 (d, 1 H, J = 1.9); 7.4−7.05 (m, 13 H); 4,24 (s, 2 H); 3.67 (s, 3 H, OMe). IR (KBr): 1727s; 1665s cm^{-1}. MS (EI): *m*/*z* 438 (100, M^+); 406 (7); 361 (12); 91(15). Anal. Calcd for $C_{28}H_{22}O_3S$ (438.54): C, 76.69; H, 5.06; S, 7.31. Found: C, 76.60; H, 5.04; S, 7.18.

Dimethyl 5-(Benzylsulfanyl)biphenyl-2,3-dicarboxylate (12). Alkylation of **7a** according to general procedure A (3 h). CAE reaction with **2a** (neat DMAD, 18 h). Yellow oil. Quantitative. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.69 (d, 1 H, J = 1.9); 7.4−7.25 (m, 11 H); 4,18 (s, 2 H); 3.89 (s, 3 H, OMe); 3.64 (s, 3 H, OMe). IR (film): 1732s cm^{-1}. MS (EI): *m*/*z* 392 (100, M^+); 361 (20, $[M - OCH_3]^+$).

1-[5-(Benzylsulfanyl)-3-(diethoxymethyl)biphenyl-2-yl]-2,2,2-trifluoroethanone (13). Alkylation of **7a** according to general procedure A (3 h). CAE reaction with **2e** (2 equiv) (45 min at room temperature). Yellow oil. 97%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.5 (d, 1 H, J = 1.9); 7.4−7.2 (m, 11 H); 5.61 (s, 1 H); 4.21 (s, 2 H); 3.52 (q, 4 H); 1.19 (t, 6 H). IR (film): 1735s; 1580 cm^{-1}. MS (EI): *m*/*z* 474 (20, M^+); 429 (20, $[M - OCH_2CH_3]^+$); 331 (18); 91 (100, Bn^+).

1-[5-(Benzylsulfanyl)-3-(tetrahydropyran-2-yloxymethyl)biphenyl-2-yl]-2,2,2-trifluoroethanone (14). Alkylation of **7a** according to general procedure A (3 h). CAE reaction

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with **2f** (2 equiv) (3 h at room temperature). Yellow oil. 79%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.4−7.2 (m, 12 H); 4.73 (d, 1 H, J = 12.6); 4.65−4.55 (m, 1 H); 4.48 (d, 1 H, J = 12.6); 4.22 (s, 2 H); 4.85−4.7 (m, 1 H); 3.6−3.45 (m, 1 H); 1.8−1.5 (m, 6 H). IR (film): 1732s; 1579s cm^{-1}. MS (EI): m/z 486 (5, M^+); 386 (40, $[M - THP]^+$); 263 (38); 91 (100, Bn^+).

Dimethyl 5-(4-Methoxybenzylsulfanyl)biphenyl-2,3-dicarboxylate (15). Alkylation of **7a** according to general procedure A (2 h). CAE reaction with DMAD (**2a**, 200 μL) (5 h at room temperature). Yellow oil. 85%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.88 (d, 1 H, J = 1.9); 7.4−7.2 (m, 8 H); 6.9−6.8 (m, 2 H); 4.15 (s, 2 H); 3.89 (s, 3 H); 3.79 (s, 3 H); 3.64 (s, 3 H). IR (film): 1731s; 1609s; 1205 cm^{-1}. MS (EI): m/z 422 (5, M^+); 391 (4, $[M - OCH_3]^+$); 121 (100, $[CH_2C_6H_4 - OMe]^+$).

Dimethyl 5-(1-Phenylethylsulfanyl)biphenyl-2,3-dicarboxylate (16). Alkylation of **7a** according to general procedure A (2 h). CAE reaction with DMAD (**2a**, 200 μL) (4 h at room temperature). Yellow oil. 85%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.88 (d, 1 H, J = 1.9); 7.4−7.2 (m, 11 H); 4.46 (q, 1 H, J = 7.0); 3.88 (s, 3 H); 3.64 (s, 3 H); 1.67 (d, 3 H, J = 7.0). IR (film): 1730s; 1577; 1203 cm^{-1}. MS (EI): m/z 406 (8, M^+); 375 (8, $[M - OCH_3]^+$); 302 (24); 270 (48); 105 (100, $[CH_3CHC_6H_5]^+$).

Methyl 5-(4-Methoxybenzylsulfanyl)biphenyl-2-carboxylate (17). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with methyl propiolate (**2b**, 6 equiv) and Et_2AlCl (1.8 M in toluene, 3 equiv) (2 h at room temperature). Recrystallization from hexane. 90%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.75 (d, 1 H, J = 8.7); 7.4−7.2 (m, 10 H); 6.83 (d, 2 H, J = 8.7); 4.16 (s, 2 H); 3.79 (s, 3 H); 3.61 (s, 3 H). IR (KBr): 1727s; 1609; 1585; 1107 cm^{-1}. MS (EI): m/z 364 (12, M^+); 121 (100, $[CH_2C_6H_4 - OMe]^+$). Anal. Calcd for $C_{22}H_{20}O_3S$ (364.46): C, 72.50; H, 5.53; S, 8.80. Found: C, 72.45; H, 5.77; S, 8.84.

Methyl 2-Benzoyl-3-*tert*-butyl-5-(4-methoxybenzylsulfanyl)benzoate (18). Alkylation of **7b** according to general procedure A (2.5 h). CAE reaction with **2c** (1.1 equiv) (3 h at 50 °C). Yellow oil. 85%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.3−7.55 (br, 2 H); 7.82 (d, 1 H, J = 1.9); 7.58 (d, 1 H, J = 1.9); 7.55−7.3 (m, 3 H); 7.3−7.2 (m, 2 H); 6.9−6.8 (m, 2 H); 4.16 (s, 2 H); 3.79 (s, 3 H); 3.51 (s, 3 H); 1.21 (s, 9 H). IR (film): 1727s; 1679s cm^{-1}. MS (EI): m/z 448 (5, M^+); 121 (100, $[CH_2C_6H_4OMe]^+$).

1-[2-*tert*-Butyl-4-(4-methoxybenzylsulfanyl)-6-(tetrahydropyran-2-yloxymethyl)phenyl]-2,2,2-trifluoroethanone (19). Alkylation of **7b** according to general procedure A (3 h). CAE reaction with **2f** (2 equiv) (6 h at room temperature). Yellow oil. 86%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.3−7.25 (m, 4 H); 6.9−6.8 (m, 2 H); 4.65−4.55 (m, 2 H); 4.3−4.2 (m, 1 H); 4.13 (s, 2 H); 3.85−3.7 (m, 1 H); 3.79 (s, 3 H); 3.6−3.45 (m, 1 H); 1.75−1.45 (m, 6 H); 1.27 (s, 9 H). IR (film): 1738s; 1610; 1580 cm^{-1}. MS (EI): m/z 496 (3, M^+); 121 (100, $[CH_2C_6H_4OMe]^+$).

Dimethyl 3-*tert*-Butyl-5-(4-methoxybenzylsulfanyl)-phthalate (20). Alkylation of **7b** according to general procedure A (2 h). CAE reaction with DMAD (**2a**, 2 equiv) (6 h at 50 °C). Yellow oil. 60%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.77 (d, 1 H, J = 1.9); 7.48 (d, 1 H, J = 1.9); 7.3−7.2 (m, 2 H); 6.9−6.8 (m, 2 H); 4.11 (s, 2 H); 3.87 (s, 3 H); 3.86 (s, 3 H); 3.78 (s, 3 H); 1.32 (s, 9 H). IR (film): 1734s; 1664s; 1075 cm^{-1}. MS (EI): m/z 402 (7, M^+); 371 (5, $[M - OMe]^+$); 121 (100, $[CH_2C_6H_4OMe]^+$).

Methyl 2-Benzoyl-5-(4-methoxybenzylsulfanyl)-3-methylbenzoate (21). Alkylation of **7c** according to general procedure B (2 h). CAE reaction with **2c** (1.2 equiv) (3 h at room temperature). Yellow oil. 42%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.85 (s, 1 H); 7.75−7.7 (m, 2 H); 7.6−7.5 (m, 1 H); 7.5−7.4 (m, 2 H); 7.33 (s, 1 H); 7.3−7.25 (m, 2 H); 6.85−6.8 (m, 2 H); 4.17 (s, 2 H); 3.80 (s, 3 H); 3.64 (s, 3 H); 2.11 (s, 3 H). IR (film): 1724s; 1676s; 1610; 1597; 1584 cm^{-1}. MS (EI): m/z 406 (40, M^+); 375 (10, $[M - OCH_3]^+$); 257 (12); 121 (100).

Methyl 2-Benzoyl-5-(benzylsulfanyl)-3-methylbenzoate (22). Alkylation of **7c** according to general procedure B (2.5 h). CAE reaction with **2c** (1.2 equiv) (3 h at room temperature). Yellow oil. 74%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.88 (d, 1 H, J = 1.9); 7.8−7.7 (m, 2 H); 7.6−7.5 (m, 1 H); 7.5−7.2 (m, 8 H); 4.21 (s, 2 H); 3.64 (s, 3 H); 2.11 (s, 3 H). IR (MIR): 1721s; 1674s; 1583; 1267 cm^{-1}. MS (EI): m/z 376 (58, M^+); 91 (100).

Methyl 2-Benzoyl-5-(4-methoxybenzylsulfanyl)-3,4-dimethylbenzoate (23). Alkylation of **7e** according to general procedure B (1 h). CAE reaction with **2c** (1.2 equiv) (24 h at room temperature). Yellow oil. 27%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.91 (s, 1 H); 7.8−7.7 (m, 2 H); 7.6−7.45 (m, 1 H); 7.45−7.35 (m, 2 H); 7.3−7.2 (m, 2 H); 6.9−6.8 (m, 2 H); 4.14 (s, 2 H); 3.80 (s, 3 H); 3.65 (s, 3 H); 2.34 (s, 3 H); 2.07 (s, 3 H). IR (MIR): 1715s; 1672s; 1511; 1165 cm^{-1}. MS (EI): m/z 420 (14, M^+); 389 (3, $[M - OCH_3]^+$); 121 (100).

1-Butyl-3-methyl 2-benzoyl-5-(methylsulfanyl)isophthalate (24). Alkylation of **7f** according to general procedure B (1 h). Isolation of the diene by chromatography. CAE reaction with **2c** (3 h at 110 °C). Yellow oil. 71%. IR (film): 1729s; 1681s; 1598; 1583 cm^{-1}. MS (EI): m/z 386 (68, M^+); 330 (26, $[M - C_4H_8]^+$); 313 (18); 253 (100); 221 (92); 105 (50).

4-*tert*-Butyl 1-Methyl 2-Benzoyl-5-(4-methoxybenzylsulfanyl)-3-methylterephthalate (25). Alkylation of **7g** according to general procedure B (1 h). CAE reaction with **2c** (1.2 equiv) (5 h at 100 °C). Yellow oil. 40%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.84 (s, 1 H); 7.8−7.7 (m, 2 H); 7.65−7.5 (m, 1 H); 7.5−7.35 (m, 2 H); 7.3−7.2 (m, 2 H); 6.9−6.8 (m, 2 H); 4.14 (s, 2 H); 3.79 (s, 3 H); 3.64 (s, 3 H); 2.11 (s, 3 H); 1.61 (s, 9 H). IR (film): 1726s; 1678s; 1610; 1512 cm^{-1}. MS (EI): m/z 506 (12, M^+); 449 (52, $[M - C_4H_8]^+$); 121 (100).

[3-(Diethoxymethyl)-5-(4-methoxybenzylsulfanyl)biphenyl-2-yl]phenylmethanone (26). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2d** (1.2 equiv) and Et_2AlCl (0.2 equiv) (24 h at room temperature). Yellow oil. 79%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.69 (d, 1 H, J = 1.8); 7.55−7.45 (m, 2 H); 7.35−7.05 (m, 11 H); 6.9−6.8 (m, 2 H); 5.57 (s, 1 H); 4.19 (s, 2 H); 3.80 (s, 3 H); 3.6−3.3 (br, 4 H); 1.2−0.8 (br, 6 H). IR (film): 1665s; 1610; 1597 cm^{-1}. MS (EI): m/z 512 (10, M^+); 483 (4, $[M - C_2H_5]^+$); 467 (6, $[M - OC_2H_5]^+$); 437 (12); 121 (100).

Methyl 2-Acetyl-5-(hexylsulfanyl)biphenyl-3-carboxylate (27). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2g** (1.2 equiv) and Et_2AlCl (0.5 equiv) (2 h at 0 °C). Yellow oil. 93% (ratio of regioisomers 95:5). ^{1}H NMR (250 MHz, $CDCl_3$) (major isomer): δ 7.82 (d, 1 H, J = 1.9); 7.5−7.2 (m, 6 H); 3.88 (s, 3 H); 2.99 (t, 2 H, J = 7.2); 2.07 (s, 3 H); 1.75−1.55 (m, 2 H); 1.5−1.2 (m, 6 H); 0.95−0.8 (m, 3 H). IR (film) (major isomer): 1727s; 1704s; 1582; 1574; 1092 cm^{-1}. MS (EI) (major isomer): m/z 370 (28, M^+); 355 (100, $[M - CH_3]^+$); 271 (10).

Methyl 2-Benzoyl-5-(hexylsulfanyl)biphenyl-3-carboxylate (28). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2c** (1.05 equiv) and Et_2AlCl (0.5 equiv) (2 h at 0 °C). Crystallization from methanol. 98%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.94 (d, 1 H, J = 1.9); 7.65−7.55 (m, 2 H); 7.5−7.2 (m, 3 H); 7.44 (d, 1 H, J = 1.9); 7.17 (s, 5 H); 3.67 (s, 3 H); 3.03 (t, 2 H, J = 7.2); 1.8−1.6 (m, 2 H); 1.55−1.25 (m, 6 H); 0.95−0.8 (m, 3 H). IR (KBr): 1727s; 1678s; 1582 cm^{-1}. MS (EI): m/z 432 (100, M^+); 355 (82, $[M - C_6H_5]^+$); 271 (24); 105 (20). Anal. Calcd for $C_{27}H_{28}O_3S$ (432.59): C, 74.97; H, 6.52; S, 7.41. Found: C, 74.91; H, 6.59; S, 7.51.

[5-(4-Methoxy-benzylsulfanyl)-3-(trimethylsilanyl)biphenyl-2-yl]phenylmethanone (29). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2h** (1.2 equiv) and Et_2AlCl (0.2 equiv) (5 h at room temperature). Crystallization from methanol. 86%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.52 (d, 1 H, J = 1.8); 7.45−7.4 (m, 2 H); 7.3−7.25 (m, 4 H); 7.2−7.05 (m, 7 H); 6.9−6.8 (m, 2 H); 4.16 (s, 2 H); 3.80 (s, 3 H); 0.14 (s, 9 H). IR (KBr): 1663s; 1558; 1267 cm^{-1}. MS (EI): m/z 482 (4, M^+); 467 (40, $[M - CH_3]^+$); 346 (10); 121 (100). Anal. Calcd for $C_{30}H_{30}O_2SSi$ (482.71): C, 74.65; H, 6.26; S, 6.64. Found: C, 74.48; H, 6.02; S, 6.59.

[3-Bromo-5-(4-methoxybenzylsulfanyl)biphenyl-2-yl]-(3,4,5-trimethoxyphenyl)methanone (30). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2i** (1.2 equiv) and Et_2AlCl (0.2 equiv) (5 h at room temperature). Crystallization from hexane. 64%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.54 (d, 1 H, J = 1.8); 7.3−7.1 (m, 8 H); 6.9−6.8 (m, 4 H); 4.18 (s, 2 H); 3.87 (s, 3 H); 3.80 (s, 3 H); 3.76 (s, 6 H). IR

(KBr): 1667s; 1615; 1582 cm^{-1}. MS (EI): *m/z* 578 (18, M^+, 1 Br); 429 (10, 1 Br); 121 (100).

Methyl 3-Bromo-5-(hexylsulfanyl)biphenyl-2-carboxylate (31). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2k** (2 equiv) and Et_2AlCl (1 equiv) (2 h at room temperature). White solid. 44%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.45 (d, 1 H, $J = 1.9$); 7.45−7.3 (m, 5 H); 7.19 (d, 1 H, $J = 1.9$); 3.64 (s, 3 H); 2.95 (t, 2 H, $J = 7.2$); 1.75−1.55 (m, 2 H); 1.5−1.2 (m, 6 H); 0.95−0.8 (m, 3 H). IR (film): 1737s; 1582s; 1574 cm^{-1}. MS (EI): *m/z* 406 (100, M^+, 1 Br); 375 (12, $[M - OMe]^+$, 1 Br); 322 (40, 1 Br); 291 (50, 1 Br).

Methyl 3-Bromo-5-(methylsulfanyl)biphenyl-2-carboxylate (32). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2k** (1.2 equiv) and Et_2AlCl (1.25 equiv) (2 h at room temperature). 60%. Crystallization from methanol. ^1H NMR (250 MHz, $CDCl_3$): δ 7.45−7.3 (m, 6 H); 7.15 (d, 1 H, $J = 1.9$); 3.64 (s, 3 H); 2.51 (s, 3 H). IR (KBr): 1732s; 1583s; 1574 cm^{-1}. MS (EI): *m/z* 336 (100, M^+, 1 Br); 305 (76, $[M - OMe]^+$, 1 Br); 226 (18); 183 (16); 139 (18).

1-(3-Bromo-5-(hexylsulfanyl)biphenyl-2-yl)ethanone (33). Alkylation of **7a** according to general procedure B (2.5 h). CAE reaction with **2l** (1.2 equiv) and Et_2AlCl (1 equiv) (1.5 h at −10 °C). Amorphous solid. 44%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.46 (d, 1 H, $J = 1.7$); 7.45−7.3 (m, 3 H); 7.3−7.25 (m, 2 H); 7.19 (d, 1 H, $J = 1.7$); 2.96 (t, 2 H, $J = 7.2$); 2.05 (s, 3 H); 1.75−1.55 (m, 2 H); 1.5−1.2 (m, 6 H); 0.95−0.8 (m, 3 H). IR (KBr): 1709s; 1581s; 1573 cm^{-1}. MS (EI): *m/z* 390 (62, M^+, 1 Br); 375 (100, $[M - CH_3]^+$, 1 Br); 291 (20, 1 Br); 212 (10); 184 (12).

(5-(Methylsulfanyl)-3-(trimethylsilanyl)biphenyl-2-yl)-phenylmethanone (34). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2h** (1.2 equiv) and Et_2-AlCl (1 equiv) (1 h at 0 °C). Yellow oil. 73%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.55 (d, 1 H, $J = 1.9$); 7.5−7.4 (m, 2 H); 7.55−7.0 (m, 9 H); 2.56 (s, 3 H); 0.19 (s, 9 H). IR (film): 1664s; 1597; 1581 cm^{-1}. MS (EI): *m/z* 376 (5, M^+); 361 (100, $[M - CH_3]^+$).

(5-(Hexylsulfanyl)-3-(trimethylsilanyl)biphenyl-2-yl)-phenylmethanone (35). Alkylation of **7a** according to general procedure A (2.5 h). CAE reaction with **2h** (1.2 equiv) and Et_2-AlCl (1 equiv) (2 h at 0 °C). Yellow oil. 55%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.57 (d, 1 H, $J = 1.9$); 7.5−7.4 (m, 2 H); 7.55−7.0 (m, 9 H); 3.0 (t, 2 H, $J = 7.3$); 1.8−1.6 (m, 2 H); 1.55−1.25 (m, 6 H) 0.9−0.8 (m, 3 H); 0.19 (s, 9 H). IR (KBr): 1665s; 1597; 1560 cm^{-1}. MS (EI): *m/z* 446 (5, M^+); 431 (100, $[M - CH_3]^+$).

4,4′-Dibenzoyl-3,3′-dimethyl-5,5′-disulfanediyldibenzoic Acid Dimethyl Ester (36). To a solution of **21** (240 mg, 0.59 mmol) in acetonitrile (10 mL) at room temperature was added NBS (116 mg, 1.1 equiv). After 1 h, the solvent was evaporated and the product purified by chromatography on SiO_2 (20 g, hexane/ether, 2:1) to give 170 mg (quantitative) of **36** as a slightly brown oil which solidifies upon standing. ^1H NMR (250 MHz, $CDCl_3$): δ 8.09 (s, 2 H); 7.8−7.7 (m, 4 H); 7.60 (s, 2 H); 7.6−7.5 (m, 2 H); 7.5−7.4 (m, 4 H); 3.67 (s, 6 H); 2.18 (s, 6 H). IR (film): 1716s; 1678s; 1610; 1582 cm^{-1}. MS (EI): *m/z* 570 (27, M^+); 539 (8, $[M - OCH_3]^+$); 506 (36, $[M - S_2]^+$); 300 (24), 253 (100); 209 (34); 165 (33); 105 (80); 77 (62).

Methyl 2-Benzoyl-5-[2-(4-bromophenyl)-2-oxoethylsulfanyl]-3-methylbenzoate (37). From **36** and 4-bromophenacyl bromide according to literature procedures.[38] 84%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.91 (s, 1 H); 7.9−7.8 (m, 2 H); 7.8−7.7 (m, 2 H); 7.7−7.6 (m, 2 H); 7.6−7.5 (m, 1 H); 7.5−7.4 (m, 2 H); 4.34 (s, 2 H); 3.64 (s, 3 H); 2.14 (s, 3 H). IR (MIR): 1717s; 1683s; 1672; 1581 cm^{-1}. MS (EI): *m/z* 482 (66, M^+, 1 Br); 451 (10, $[M - OCH_3]^+$, 1 Br); 267 (12); 183 (100, 1 Br).

Methyl 2-Benzoyl-3-methyl-5-(methylsulfanyl)benzoate (38). From **36** and methyl iodide according to literature procedures.[38] White amorphous solid. 40%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.8−7.7 (m, 3 H); 7.65−7.5 (m, 1 H); 7.5−7.35 (m, 2 H); 7.31 (s, 1 H); 3.65 (s, 3 H); 2.55 (s, 3 H); 2.16 (s, 3 H). IR (KBr): 1722s; 1674s; 1588 cm^{-1}. MS (EI): *m/z* 300 (76, M^+); 267 (77); 223 (100); 165 (10); 105 (14); 77 (10).

Methyl 2-Benzoyl-5-(cyclopropylmethylsulfanyl)-3-methylbenzoate (39). From **36** and (bromomethyl)cyclopropane according to literature procedures.[38] 70%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.87 (s, 1 H); 7.8−7.7 (m, 2 H); 7.65−7.5 (m, 1 H); 7.5−7.35 (m, 3 H); 3.65 (s, 3 H); 2.93 (d, 2 H, $J = 7.0$); 2.15 (s, 3 H); 1.2−1.0 (m, 1 H); 0.7−0.55 (m, 2 H); 0.35−0.25 (m, 2 H). IR (film): 1724s; 1676s; 1583 cm^{-1}. MS (EI): *m/z* 340 (100, M^+); 307 (18); 267 (25); 254 (64); 105 (24); 77 (10); 55 (16).

Methyl 2-Benzoyl-3-methyl-5-(3-oxobutylsulfanyl)benzoate (40). From **36** and methyl vinyl ketone according to literature procedures.[38] 80%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.85 (s, 1 H); 7.8−7.7 (m, 2 H); 7.6−7.5 (m, 1 H); 7.5−7.35 (m, 3 H); 3.66 (s, 3 H); 3.22 (t, 2 H, $J = 7.1$); 2.83 (t, 2 H, $J = 7.1$); 2.20 (s, 3 H); 2.15 (s, 3 H). IR (KBr): 1723s; 1667s; 1582 cm^{-1}. MS (EI): *m/z* 356 (76, M^+); 323 (24); 281 (100); 279 (60, $[M - C_6H_5]^+$); 253 (29); 209 (35); 105 (28); 77 (25); 43 (32).

Synthesis of Sulfonamides. General Procedure. For Primary Amines. To a solution of *p*-methoxybenzyl thioether (0.2 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) was added SO_2Cl_2 (1.1 equiv) to form the sulfenyl chloride (15 min). This yellow solution was added dropwise to a solution of primary amine (2.2 equiv) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 2−3 h before being filtered over a short Alox (N) column (ca. 2 g). The sulfenamide was washed down the column with $CHCl_3$, the solvents were evaporated, and the residue was dissolved in CH_2Cl_2. NaOAc (10 equiv) and *m*-CPBA (3 equiv) were added, and the reaction mixture was stirred at room temperature for 2−3 h, poured onto $NaHCO_3$-(satd), and extracted with ether. The products were purified by chromatography on silica gel.

For Secondary Amines. To a solution of *p*-methoxybenzyl thioether (0.2 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) was added SO_2Cl_2 (1.1 equiv) to form the sulfenyl chloride. After 15 min, the amine (2.2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 2−3 h before being filtered over a short Alox (N) column (ca. 2 g). The sulfenamide was washed down the column with $CHCl_3$, the solvents were evaporated, and the residue was dissolved in CH_2Cl_2. NaOAc (10 equiv) and *m*-CPBA (3 equiv) were added, and the reaction mixture was stirred at room temperature for 2−3 h, poured onto $NaHCO_3$(satd), and extracted with ether. The products were purified by chromatography on silica gel.

Methyl 2-Benzoyl-3-*tert*-butyl-5-(4-methoxybenzylsulfamoyl)benzoate (41). From **18** and 4-methoxybenzylamine. 31%. ^1H NMR (250 MHz, $CDCl_3$): δ 8.30 (d, 1 H, $J = 2.1$); 8.21 (d, 1 H, $J = 2.1$); 8.25−7.7 (br, 2 H); 7.6−7.3 (m, 3 H); 7.15−7.05 (m, 2 H); 6.85−6.75 (m, 2 H); 4.79 (t, 1 NH, $J = 6$); 4.20 (d, 2 H, $J = 6$); 3.77 (s, 3 H); 3.59 (s, 3 H); 1.29 (s, 9 H). IR (film): 1730s; 1681s; 1612; 1597; 1584; 1165 cm^{-1}. MS (ISP): *m/z* 518 ($[M + Na]^+$); 513 ($[M + NH_4]^+$); 496 ($[M + H]^+$); 464 ($[M - OCH_3]^+$).

Methyl 2-Benzoyl-3-*tert*-butyl-5-[2-(4-chlorophenyl)-ethylsulfamoyl]benzoate (42). From **18** and 2-(4-chlorophenyl)ethylamine. 53%. ^1H NMR (250 MHz, $CDCl_3$): δ 8.30 (d, 1 H, $J = 2.1$); 8.23 (d, 1 H, $J = 2.1$); 8.2−7.3 (br, 5 H); 7.3−7.2 (m, 2 H); 7.1−7.0 (m, 2 H); 4.45 (t, 1 NH, $J = 6.5$); 3.59 (s, 3 H); 3.30 (q, 2 H, $J = 6.5$); 2.82 (t, 2 H, $J = 6.5$); 1.30 (s, 9 H). IR (film): 1730s; 1681s; 1495 cm^{-1}. MS (ISP): *m/z* 531 ($[M + NH_4]^+$, 1 Cl); 514 ($[M + H]^+$, 1 Cl); 482 ($[M - OCH_3]^+$, 1 Cl).

Ethyl 4-[4-Benzoyl-3-*tert*-butyl-5-(methoxycarbonyl)-benzenesulfonyl]piperazine-1-carboxylate (43). From **18** and 1-(ethoxycarbonyl)piperazine. 61%. ^1H NMR (250 MHz, $CDCl_3$): δ 8.23 (d, 1 H, $J = 2.1$); 8.13 (d, 1 H, $J = 2.1$); 8.2−7.3 (br, 5 H); 4.13 (q, 2 H, $J = 7.1$); 3.7−3.5 (m, 4 H); 3.60 (s, 3 H); 3.1−2.95 (m, 4 H): 1.32 (s, 9 H); 1.25 (t, 3 H, $J = 7.1$). IR (film): 1731s; 1702s; 1596 cm^{-1}. MS (EI): *m/z* 516 (2, M^+); 485 (5, $[M - OCH_3]^+$); 452 (12, $[M - SO_2]^+$); 296 (18); 264 (33); 157 (100).

Methyl 2-Benzoyl-3-*tert*-butyl-5-(3-methoxyphenylsulfamoyl)benzoate (44). From **18** and 3-methoxyaniline. 29%. ^1H NMR (250 MHz, $CDCl_3$): δ 8.35 (d, 1 H, $J = 2.1$); 7.99 (d, 1 H, $J = 2.1$); 8.2−7.0 (br m, 7 H); 6.75−6.55 (m, 3 H); 6.49 (br, NH); 3.77 (s, 3 H); 3.58 (s, 3 H); 1.16 (s, 9 H). IR (film): 1730s; 1681s; 1606; 1596; 1291; 1154 cm^{-1}. MS (EI): *m/z* 481 (100, M^+); 385 (48); 372 (72); 370 (88); 340 (15); 105 (28).

Phenyl[5-(pyrrolidine-1-sulfonyl)-3-(trimethylsilanyl)-biphenyl-2-yl]methanone (45). From **29** and pyrrolidine. 61%. ^1H NMR (250 MHz, $CDCl_3$): δ 8.10 (d, 1 H, $J = 1.8$);

7.86 (d, 1 H, $J = 1.8$); 7.5−7.4 (m, 2 H); 7.4−7.3 (m, 1 H); 7.2−7.05 (m, 7 H); 3.35−3.25 (m, 4 H); 1.9−1.8 (m, 4 H); 0.2 (s, 9 H). MS (ISP): *m*/*z* 481 (100, $[M + NH_4]^+$); 464 (10, $[M + H]^+$).

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Supporting Information Available: Copies of ^{1}H NMR spectra of a selection of CAE reaction products (compounds **11**, **13**, **15**, **18**, **21**−**23**, **25**, **29**, **30**, and **32**−**35**). This material is available free of charge via the Internet at http://pubs.acs.org.

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