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Reversed-Polarity Synthesis of Diaryl Ketones through Palladium-Catalyzed Direct Arylation of 2-Aryl-1,3-dithianes

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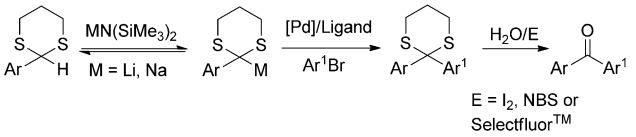
Abstract: An umpolung approach to the synthesis of diaryl ketones has been developed based on in situ generation of acyl anion equivalents and their catalytic arylation. This method entails the base-promoted, palladium-catalyzed direct C-H arylation of 2-aryl-1,3-dithianes with aryl bromides. Use of MN(SiMe$_3$)$_2$ (M = Li, Na) base results in reversible deprotonation of the weakly acidic dithiane. In the presence of a Pd(NiXantphos)-based catalyst and aryl bromide, cross-coupling of the metallated 2-aryl-1,3-dithiane takes place under mild conditions (2 h at rt) with yields as high as 96%. The resulting 2,2-diaryl-1,3-dithianes were converted into diaryl ketones by either molecular iodine, *N*-bromo succinimide (NBS) or Selectfluor in the presence of water. The dithiane arylation/hydrolysis can be performed in a one-pot procedure to yield a variety of diaryl ketones in good to excellent yields. This method is suitable for rapid and large-scale synthesis of diaryl ketones. A one-pot preparation of anti-cholesterol drug fenofibrate (TriCor®) has been achieved on 10.0 mmol scale in 86% yield.

Keywords: C–C bond formation; cross-coupling; dithianes; ketones; palladium; umpolung

Introduction

Synthetic methods based on reversal of functional group polarity, or umpolung methods, constitute a valuable strategy in organic synthesis because they provide unconventional approaches to common structural motifs.[1] Nature also employs the umpolung reactivity to forge C–C bonds.[2] The most widely used umpolung methods involve the generation of acyl anion equivalents to elaborate carbonyl compounds.[3] In the early 1900 s, the cyanide catalyzed homodimerization of aldehydes (benzoin condensation) led to the realization that the polarity of the carbonyl functionality could be reversed.[4] However, the great potential of the umpolung strategy was not broadly recognized until pioneering studies by Corey and Seebach on the use of metallated 1,3-dithianes as masked acyl anion equivalents.[5] To date, C–C bond formation reactions between metallated dithianes – almost always 2-lithio-1,3-dithianes – and various electrophilic reagents such as alkyl halides, epoxides and carbonyl compounds, have been extensively applied to the synthesis of intermediates in route to complex natural products.[6] 2-Lithio-1,3-dithianes can be generated by the action of strong bases (*n*BuLi or *t*BuLi) on dithianes at low temperatures.[7] Despite the widespread and elegant application of lithiated dithiane derivatives in organic synthesis, it is surprising that they have rarely been employed in catalytic reactions as acyl anion equivalents. To the best of our knowledge, there is only one publication claiming the use of dithianes in a catalytic reaction as acyl anion equivalents.[8] This manuscript involves the nickel-catalyzed reaction of preformed 2-lithio-1,3-dithianes with benzoyl halides to form 1,2-diketones derivatives (average yield 46%).[9] The conflicting description in this manuscript makes it unclear if benzoyl chlorides or bromides were actually employed.

Given the synthetic ease of accessing 2-aryl-1,3-dithianes, we wondered if it would be possible to use metallated 2-aryl-1,3-dithianes in palladium catalyzed direct arylation reactions as an umpolung strategy to prepare diaryl ketone derivatives. Rather than using highly reactive organolithium bases generally employed to deprotonate dithianes, we envisioned use of milder bases with the goal of reversibly metallating 2-



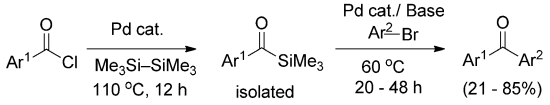
Scheme 1. One-pot synthesis of diaryl ketones by tandem arylation/hydrolysis of dithianes

aryl-1,3-dithianes. Generation of even low concentrations of metallated dithianes could be sufficient for efficient coupling reactions, if transmetallation to palladium is rapid. Herein we report the first direct arylation of dithianes in the presence of a transition metal catalyst and aryl bromides (Scheme 1). This method has been used to produce a diverse range of sterically and electronically differentiated 2,2-diaryl-1,3-dithianes in good to excellent yields. Moreover, we introduce a one-pot arylation of dithianes/hydrolysis to synthesize diaryl ketones with yields of up to 95% (Scheme 1). It is noteworthy that diaryl ketones comprise a common structural core of a large number of biologically relevant compounds and have gained considerable attention as active components of marketed medications, such as Ketoprofen (Oruvail®), Suprofen (Profenal®) and Fenofibrate (TriCor®).[10] We have applied our method to the one-pot synthesis the anticholesterol drug Fenofibrate on 10.0 mmol scale.

Results and Discussion

Background and Approach. Various methods have been introduced for the synthesis of diaryl ketones. Friedel–Crafts acylations and the addition of organometallic reagents to carbonyl compounds followed by oxidation are classic routes for aryl ketone synthesis.[11] These methods typically employ stoichiometric amounts of metal-containing reagents and often perform poorly with heteroaryls or sterically crowded substrates. Transition metal catalyzed carbonylative reactions have also received significant attention and emerged as useful routes to diaryl ketones.[12]

More recent developments in the synthesis of diaryl ketones have focused on acyl anion equivalents. Among them, organometallic acyl reagents such as acylzirconocenes,[13] acylstannanes,[14] and acyl-indiums[15] have been applied in palladium- and copper-catalyzed reactions to prepare various carbonyl compounds. These acyl anion reagents can be challenging to synthesize and to handle.[16] An elegant use of *N-tert*-butylhydrazones as acyl anion equivalents in the palladium catalyzed cross-coupling with aryl bromides has been communicated by Takemiya and Hartwig. The arylated products are easily converted to various ketones via acidic hydrolysis.[17] An innovative example of the umpolung approach to diaryl ketones was



Scheme 2. Two step umpolung synthesis of diaryl ketones.

reported in 2011 by Schmink and Krska and is illustrated in Scheme 2.[18] After a palladium-catalyzed cross-coupling of acyl chlorides and hexamethyldisilane, the resulting acyl silanes were coupled with aryl bromides to furnish the desired diaryl ketones in 21–85% yield (from the acyl silane).

Our approach to the synthesis of diaryl ketones stems from a broader program involving C-H functionalization of weakly acidic substrates (pK_a values 28–35 in DMSO). This approach relies on a reversible in situ deprotonation of these substrates to generate reactive organolithium, -sodium, or -potassium intermediates that then undergo transmetallation with a palladium catalyst followed by C–C bond formation. We have found that different phosphine ligands are required (Figure 1, ligands **L1**–**L5**) for the diverse substrate classes and bases we have employed. This method has proven successful for the direct C-H arylation of diarylmethanes (**L1**),[19] benzylic ketimines (**L1**),[20] benzyl thioethers,[21] benzylic phosphine oxides (**L2**),[22] methyl sulfoxides and sulfones (**L3**),[23] amides (**L3**),[24] benzylic phosphonates (**L4**),[25] and allyl benzenes (**L5**).[26]

Development of the direct arylation of 1,3-dithianes. The steps in the deprotonative cross-coupling process (DCCP) in Scheme 1 involve oxidative addition of the aryl bromide to Pd(0), deprotonation of the substrate and transmetallation to palladium followed by reductive elimination. Given that the pK_a of 2-aryl-1,3-dithianes is ~31 in DMSO, the deprotonation was not viewed as the most challenging step. We were more concerned with the transmetallation, because the unfavorable steric interactions necessary to form a fully substituted carbon bound to palladium.

Based on the ability of palladium complexes of van Leeuwen's NiXantphos (**L1**)[27] to effectively cross-

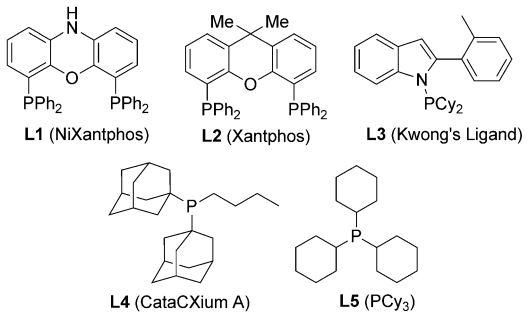


Figure 1. Ligands employed in the deprotonative cross-coupling processes of weakly acidic substrates.

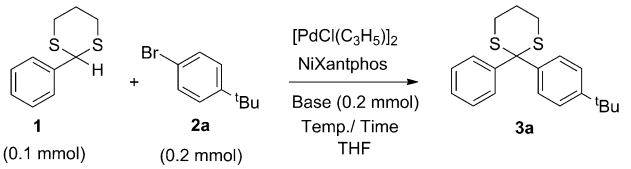
couple organolithium, -sodium, and -potassium organometallics, we examined the reaction of 2-phenyl-1,3-dithiane (**1**) with 1-bromo-4-*tert*-butylbenzene (**2a**) in the presence of dimeric $[PdCl(allyl)]_2$ (20 mol% Pd), NiXantphos (20 mol%) and $LiN(SiMe_3)_2$ (2 equiv) and achieved 71% assay yield of 2,2-diaryl-1,3-dithiane **3a** after 2 h at room temperature (Table 1, entry 1). We next examined three additional bases [$NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, NaO*t*Bu] to increase the yield (entries 2–4). While $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$ each furnished the product in 83% assay yield, NaO*t*Bu was totally ineffective. At this point, we chose $NaN(SiMe_3)_2$ for further optimization of the reaction conditions.

We next explored the possibility of decreasing the catalyst and ligand loading. Using a concentration of 0.1 M and decreasing the palladium loading from 20 mol% to 10 mol% provided the arylated product in 89% assay yield after 2 h at rt (entry 5). Under identical reaction conditions, however, the reaction did not reach completion in 1 h (entry 6). A further decrease of catalyst loading to 5 mol% furnished the desired dithiane in 92% yield in 2 h (entry 7). When the same reaction was carried out in lower concentration (0.07 M) or at higher temperature (60 °C), 93–95% assay yield was observed (entries 8 and 9). Lowering the catalyst loading to 2.5 mol% (entries 10 and 11) resulted in a significant decrease in the assay yield after 2 or 3 h (~37%). Based on these results, we investigated the scope and limitations of this DCCP employing 2.5 mol% $[PdCl(allyl)]_2$ and 5.0 mol% NiXanthphos in THF at room temperature.

Scope of the aryl bromide in the direct arylation of 2-phenyl-1,3-dithianes. Based on the results in Table 1, and the value of the dithiane component, we decided to utilize dithiane derivatives as the limiting reagent with 2 equiv each of aryl bromide and $NaN(SiMe_3)_2$ or $LiN(SiMe_3)_2$. The results of our study are summarized in Tables 2 and 3.

Commercially available 2-phenyl-1,3-dithiane (**1**) underwent DCCP with a wide range of aryl bromides to give the desired 2,2-diaryl-1,3-dithianes (**3a**-**3o**). See Table 2. Alkyl substituted aryl bromides (**2a**-**c**), bromobenzene (**2d**) and 2-bromonaphthalene (**2e**) furnished over 80% yield at room temperature in 2 h. The reaction with sterically encumbered 1-bromonaphthalene (**2f**) required heating to 60 °C for 1 h for full conversion and provided **3f** in 87% yield. Reactions with aryl bromides bearing electron donating 4-*N*,*N*-dimethylamino (**2g**) and 4-methoxy (**2h**) groups were good substrates, producing **3g** and **3h** in 86 and 80% yield, respectively. The reaction with sterically

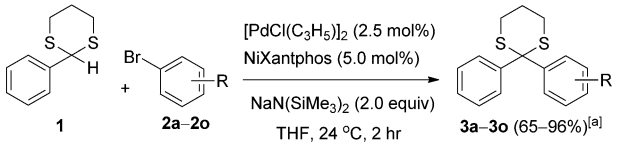
Table 1. Optimization of the direct arylation of 2-phenyl-1,3-dithiane.

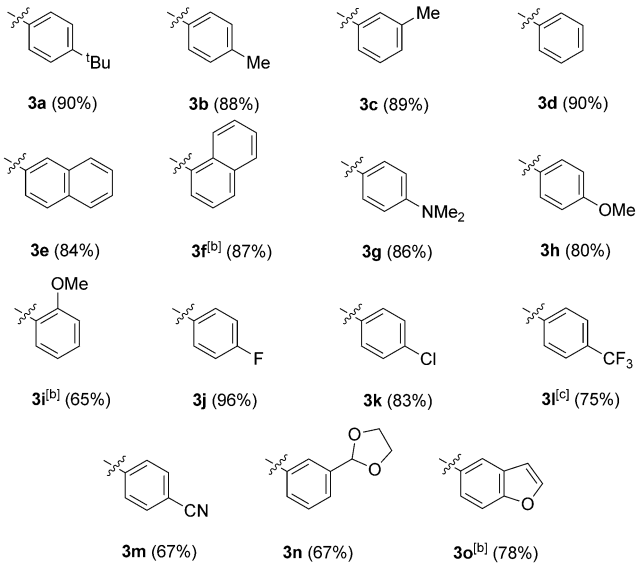


Entry	Base	$[PdCl(C_3H_5)]_2$ mol %	NiXantphos mol %	Temp./Time °C/ h	Yield (%)[a] **3a**
1	$LiN(SiMe_3)_2$	10	20	24 /2	71
2	$NaN(SiMe_3)_2$	10	20	24 /2	83
3	$KN(SiMe_3)_2$	10	20	24 /2	83
4	NaOt-Bu	10	20	24 /2	-
5	$NaN(SiMe_3)_2$	5	10	24 /2	89
6	$NaN(SiMe_3)_2$	5	10	24 /1	79
7	$NaN(SiMe_3)_2$	2.5	5	24 /2	92
8[b]	$NaN(SiMe_3)_2$	2.5	5	24 /2	93
9	$NaN(SiMe_3)_2$	2.5	5	60 /0.5	95
10	$NaN(SiMe_3)_2$	1.25	2.5	24 /2	35
11	$NaN(SiMe_3)_2$	1.25	2.5	24 /3	37

[a] Yield determined by ^{1}H NMR integration of the crude reaction mixture using 0.1 mmol CH_2Br_2 as the internal standard.
[b] Reaction concentration is 0.07 M (entry 8). Reaction concentration for other entries is 0.10 M.

Table 2. Substrate scope of the aryl bromide with 2-phenyl-1,3-dithiane.[a]





[a] Isolated yields.
[b] 60 °C, 1 h reaction time.
[c] $LiN(SiMe_3)_2$ was used as a base.

demanding 2-bromoanisole (**2i**) required heating to 60 °C for 1 h to drive the reaction to completion and afforded diaryl dithiane **3i** in 65 % yield. With 1-bromo-4-fluorobenzene (**2j**), DCCP was particularly successful, providing desired product **3j** in 96 % yield at room temperature.

To test the scalability of the arylation, we performed this reaction with 6.0 mmol 2-phenyl-1,3-dithiane (**1**), 12.0 mmol 1-bromo-4-fluorobenzene (**2j**) and 12.0 mmol $NaN(SiMe_3)_2$ in the presence of 2.5 mol % $[PdCl(allyl)]_2$ and 5.0 mol % NiXanthphos at room temperature. The starting dithiane **1** was consumed after 3 h and the product **3j** was isolated in 85 % yield (1.5 g) after purification by column chromatography.

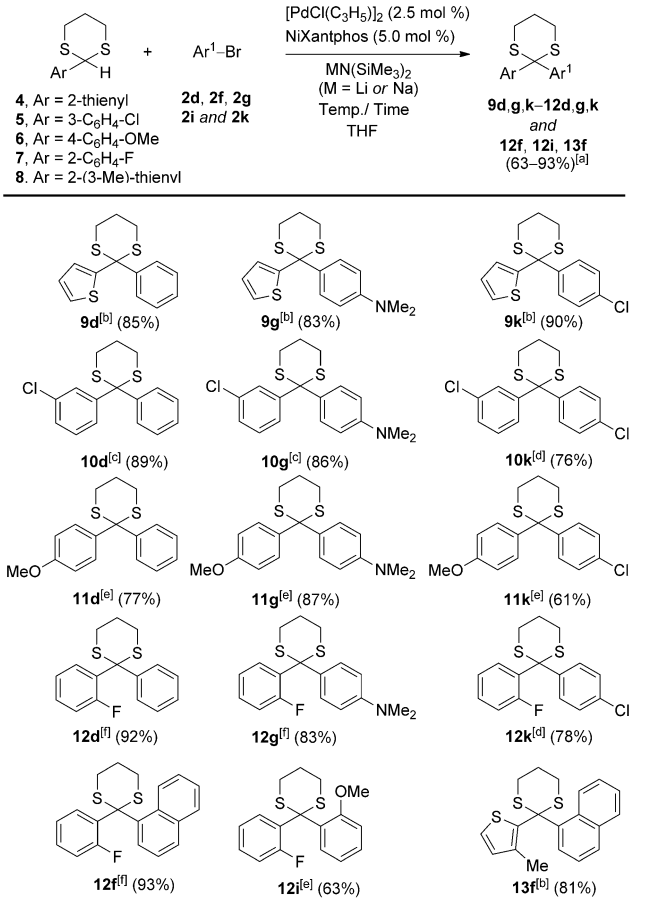
With 1-bromo-4-chlorobenzene (**2k**), the reaction afforded the product **3k** in a good yield (83 %) and high chemoselectivity, despite the known ability of Pd^0(NiXantphos)-based intermediates to oxidatively add aryl chlorides at room temperature.[18a] On the other hand, the reaction with 4-bromobenzotrifluoride (**2l**), having a strongly electron with drawing -CF_3 group, proceeded more efficiently with $LiN(SiMe_3)_2$ and gave the product **3l** in 75 % yield after 2 h at room temperature. Moreover, the sensitive 4-cyano (**2m**) and 3-cyclic acetal (**2n**) functional groups were tolerated reasonably well under our reaction conditions, furnishing arylation products **3m** and **3n** each in 67 % yield. The reaction with 5-bromobenzofuran (**2o**) required heating to 60 °C to afford the diaryl dithiane **3o** in 78 % yield. The successful coupling of a variety of aryl bromides to 2-phenyl-1,3-dithiane inspired us to next examine the scope of the dithiane coupling partner.

Scope of 2-aryl-1,3-dithianes in the direct arylation. We next explored the DCCPs of sterically and electronically diverse 2-aryl-1,3-dithianes (**4**-**8**) with various aryl bromides (Table 3). Straightforward procedures for the synthesis of a variety of 2-aryl-1,3-dithiane derivatives have been reported.[28] For example, Chakraborti and coworkers reported that 2-thienyl-1,3-dithiane (**4**) and 2-(4-methoxyphenyl)-1,3-dithiane (**6**) could be prepared in quantitative yields from their respective aldehydes and 1,3-dithiopropane with a one-minute reaction time under solvent-free, copper-catalyzed reaction conditions.[28a]

For the reactions of 2-aryl-1,3-dithianes with aryl bromides, we initially employed $NaN(SiMe_3)_2$ in the presence of 2.5 mol % $[PdCl(allyl)]_2$ and 5.0 mol % NiXanthphos in THF at room temperature for 2 h. If necessary, we modified the conditions to increase the yield. For instance, the reaction of 2-thienyl-1,3-dithiane (**4**) with bromobenzene (**2d**) gave dithiane **9d** in only 49 % yield when $NaN(SiMe_3)_2$ was used. The yield could be increased to 85 % with $LiN(SiMe_3)_2$ under otherwise the identical conditions (Table 3). 2-Thienyl-1,3-dithiane (**4**) afforded good yield with 1-bromo-4-*N*,*N*-dimethylaminobenzene (83 %) and 1-bromo-4-chlorobenzene (90 %) with $LiN(SiMe_3)_2$. Similarly, 2-(3-chlorophenyl)-1,3-dithiane (**5**) underwent DCCPs with bromobenzene (**2d**), 1-bromo-4-*N*,*N*-dimethylaminobenzene (**2g**) and 1-bromo-4-chlorobenzene (**2k**) more effectively in the presence of $LiN(SiMe_3)_2$, producing dithianes **10d**, **10g** and **10k** in 89, 86 and 76 % yields, respectively. It is noteworthy that use of $LiN(SiMe_3)_2$ in these reactions required heating to 60 °C. On the other hand, for reactions of less acidic 2-(4-methoxyphenyl)-1,3-dithiane (**6**), use of $NaN(SiMe_3)_2$ at 60 °C for 1 h was necessary to obtain higher yields of dithianes **11d**, **11g** and **11k** (77, 87, and 61 % yields, respectively).

Reactions of 2-fluorophenyl substituted dithiane **7** with aryl bromides were particularly efficient. Dithianes **12d** and **12g** were obtained by coupling bromobenzene (**2d**) and 1-bromo-4-*N*,*N*-dimethylamino-

Table 3. Substrate scope of 2-aryl-1,3-dithiane and aryl bromides.



[a] Isolated yields.
[b] $LiN(SiMe_3)_2$, 24 °C, 2 h.
[c] $LiN(SiMe_3)_2$, 60 °C, 1 h.
[d] $LiN(SiMe_3)_2$, 60 °C, 2 h.
[e] $NaN(SiMe_3)_2$, 60 °C, 1 h.
[f] $NaN(SiMe_3)_2$, 24 °C, 2 h

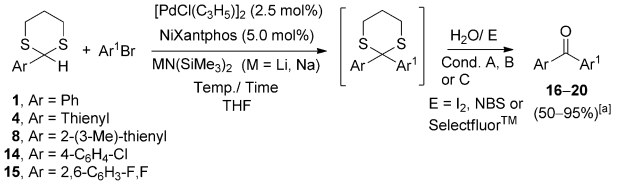
benzene (**2g**) with 2-(2-fluorophenyl)-1,3-dithiane (**7**) in 92 and 83% yields, respectively, using $NaN(SiMe_3)_2$ at room temperature in 2 h. Reaction of dithiane **7** with 1-bromo-4-chlorobenzene (**2k**) was rather sluggish, however, and reaction had to be performed in the presence of $LiN(SiMe_3)_2$ at 60 °C to furnish **12k** in 78% yield in 2 h. Recently, the synthesis of diaryl ketones bearing *ortho*-substituents on both aryl groups under mild conditions has gained importance,[29] because many biologically active diaryl ketones are sterically congested.[10c–e] To explore the potential of our method for the construction of more hindered ketone precursors, 2-fluorophenyl substituted dithiane **7** was coupled with 1-bromonaphthalene (**2f**) and 2-bromoanisole (**2i**) to achieve dithianes **12f** (93%) and **12i** (63%), respectively. Furthermore, sterically more crowded 3-methylthiophene containing dithiane **8** was coupled with 1-bromo naphthalene to afford **13f** in 81% yield. Taken together, the results in Tables 2 and 3 indicate that the DCCP of 2-aryl-1,3-dithianes with aryl bromides is a general and mild method for the synthesis of diaryl dithianes.

Development of a one-pot umpolung synthesis of diaryl ketones. Having demonstrated the direct arylation of 2-aryl-1,3-dithiane derivatives, we set out to develop a one-pot arylation/hydrolysis procedure. There are numerous protocols for the hydrolysis of dithianes. In the tandem arylation/ketone release, we explored three oxidative methods for the hydrolysis (Table 4). Thus, upon complete consumption of the 2-aryl-1,3-dithiane starting material in the DCCP, water (0.5 mL) and electrophile (I_2, NBS or Selectfluor™) were added in procedures A, B, and C, respectively (Table 4). The reaction mixtures were stirred for 1 h at rt before workup. In general, all three procedures gave diaryl ketone derivatives in good yields. Furthermore, in most cases, we observed that the scope of aryl bromides and 2-aryl-1,3-dithianes described in Tables 2 and 3 readily translated to the one-pot procedure. Simple alkyl (**16a**), amino (**16g**) and halogen (**18j**, **k**) substituted diaryl ketones were obtained in moderate to excellent yields (66–95%). Likewise, sterically encumbered diaryl ketones (**19i** and **20f**, **20i**) formed in 75–95%. This sequential procedure tolerated different functionalities, although 4-*N*,*N*-dimethylamino (**16g**, 66% and **17g**, 57%) and 4-cyano (**16m**, 50%) substituted diaryl ketones exhibited noticeably lower yields than their corresponding dithianes **3g** (86%), **9g** (83%) and **3m** (67%).

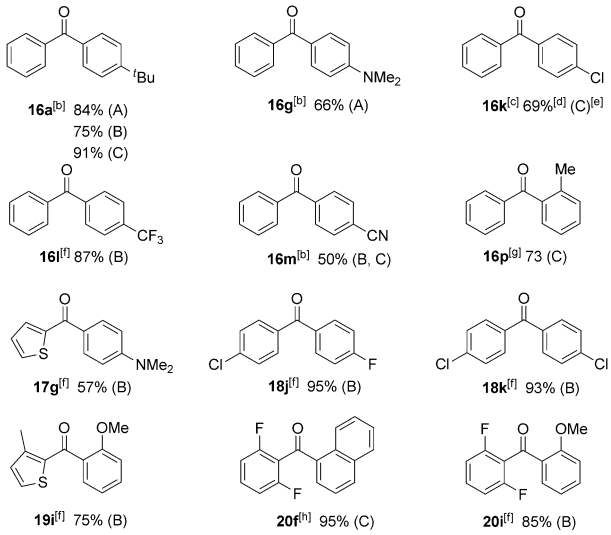
On the other hand, trifluoromethyl substituted diaryl ketone **16l** was obtained in higher yield (87%) compared to its corresponding dithiane **3l** (75%). Moreover, *o*-tolyl substituted ketone **16p** was synthesized in 73% yield in this one-pot procedure. In contrast, its corresponding dithiane **3p** was rather unstable to column chromatography and it could not be isolated in pure form. We have also tested the scalability of this process with the 6.0 mmol scale synthesis of chloro substituted benzophenone **16k** in 69% isolated yield (0.89 g). The reaction of dithiane **14** with carbonyl containing substrate methyl 4-bromobenzoate in the presence of $LiN(SiMe_3)_2$ at room temperature failed in the first step. Dithiane **14** was partially recovered from the reaction mixture.

Synthesis of fenofibrate. To demonstrate the utility of the method presented herein, we synthesized marketed drug fenofibrate (TriCor by Abbott) used for the treatment of hypercholesterolemia and hyper-triglyceridemia (Scheme 3).[30] Initial optimization involved 0.2 mmol scale reactions with 2.0, 1.2, 1.1 and 1.0 equiv of aryl bromide having hindered carbonyl functionality **2r**, 1.0 equiv of 2-(4-chlorophenyl)-1,3-dithiane (**14**), and 2.0 equiv of $LiN(SiMe_3)_2$ at room temperature with 2.5 mol% catalyst. Selectfluor™ (4.0 equiv) was used in the hydrolysis step. Reactions with 2.0 and 1.2 equiv of **2r** gave fenofibrate in 86% and 90% yields, respectively. However, the yield of

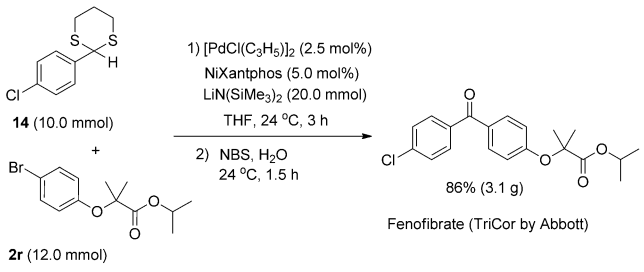
Table 4. Substrate scope of the one-pot umpolung synthesis of diaryl ketones



Cond: (A) I_2, $CaCO_3$, H_2O; 24 °C, 1 h; (B) NBS, H_2O; 24 °C, 1 h; (C) Selectfluor™, H_2O; 24 °C, 1 h.



[a] Isolated yields.
[b] $NaN(SiMe_3)_2$, 24 °C, 2 h.
[c] $NaN(SiMe_3)_2$, 24 °C, 3 h.
[d] Yield of 6.00 mmol scale reaction (0.89 g).
[e] 24 °C, 3.5 h (for the 2nd step).
[f] $LiN(SiMe_3)_2$, 24 °C, 2 h.
[g] $NaN(SiMe_3)_2$, 60 °C, 1 h.
[h] $NaN(SiMe_3)_2$, 60 °C, 2 h



Scheme 3. One-pot umpolung synthesis of fenofibrate

fenofibrate decreased gradually with the use of 1.1 (82%) and 1.0 equiv (77%) of aryl bromide **2r**. The efficiency of hydrolysis step was examined employing more economical NBS in the tandem arylation/hydrolysis reaction using 2.0 equiv of **2r**. This reaction produced fenofibrate in very good yield (92%).

With the successful optimization of the small scale reactions, we tested the scalability of the DCCP for the one-pot synthesis of fenofibrate. We conducted the large scale reaction without using a drybox and employed commercially available 1.0 M solution of $LiN(SiMe_3)_2$ in THF to simplify the method. The arylation was performed with 10.0 mmol 2-(4-chlorophenyl)-1,3-dithiane, 12.0 mmol aryl bromide **2r** and 20.0 mmol $LiN(SiMe_3)_2$ in the presence of 2.5 mol% $[PdCl(C_3H_5)]_2$ and 5.0 mol% NiXanthphos in THF at room temperature for 3 h. Once the arylation was complete (as judged by TLC), 4.5 equiv of NBS were added to the arylation reaction mixture and the reaction stirred for 1.5 h at rt before workup and purification of the product on silica gel. This one-pot procedure resulted in the isolation of over 3 g fenofibrate in 86% yield.

Conclusions

Umpolung carbonyl reactivity with metallated dithianes has evolved over 40 years and is now a mainstay in synthetic chemistry. In particular, recent applications of metallated dithianes as acyl anion equivalents have achieved new levels of sophistication through "anion relay chemistry" (ARC), enabling the synthesis of architecturally complex molecular frameworks. Despite the remarkable advances in dithiane chemistry, high yielding applications of dithianes as masked acyl anion equivalents in transition metal catalyzed reactions have not been previously achieved.

Herein, we disclose a versatile method for the reversed polarity synthesis of diaryl ketones through palladium-catalyzed direct sp^3-C-H arylation of 2-aryl-1,3-dithianes. Keys to the success of this method are the in situ deprotonation of dithianes under catalytic reaction conditions and the identification of a catalyst to couple the resulting lithio- and sodio-based metallated dithianes with aryl bromides. The benefits of this method are that it proceeds at room temperature, is usually complete in 1–3 h, requires simple experimental techniques, and provides various dithianes in good to excellent yields. Moreover, the arylation reaction can be performed in a tandem fashion to release the carbonyl functionality in the presence of readily available oxidants. This tandem process enables the synthesis of diaryl ketones on multigram scales without use of a drybox. Based on these attributes, we expect that this method will be suitable for applications in medicinal chemistry.

Experimental Section

General Procedure A: Preparation of 2-aryl-1,3-dithianes 5, 7, 8 and 15 according to modified literature procedure:[28a]

An oven-dried 10 mL reaction vial equipped with a stirring bar was charged with a benzaldehyde derivative (8.4 mmol, 1.0 equiv) and $Cu(BF_4)_2.xH_2O$ (0.169 mmol, 2.0 mol%). To the neat stirred aldehyde, 1,3-propanedithiol (10 mmol, 1.0 mL) was added and the vial was closed with a rubber septum. The vial was placed into the preheated (60 °C) oil bath and the reaction mixture stirred at this temperature for 1 h. After cooling to room temperature, the reaction mixture was diluted with in 20 mL CH_2Cl_2 and washed with water (2×10 mL). The organic phase was dried over $MgSO_4$, filtrated and the solvent was removed in a rotary evaporator. The solid white residue was recrystallized from hexanes to give 2,2-diaryl-1,3-dithianes.

General Procedure B: Arylation of 2-Aryl-1,3-dithianes:

An oven-dried 10 mL reaction vial equipped with a stirring bar was charged with 2-aryl-1,3-dithiane (0.2 mmol, 1.0 equiv) and aryl bromide (0.4 mmol, 2.0 equiv), if it is a solid, and the vial was put into a glovebox. The reaction vial was charged with base [$LiN(SiMe_3)_2$ or $NaN(SiMe_3)_2$] (0.4 mmol, 2.0 equiv), 1.4 mL THF, 0.4 mL THF solution (0.025 M) of NiXantphos and 0.2 mL THF solution of (0.025 M) $[PdCl(allyl)]_2$, respectively. The vial was sealed with a rubber septum, wrapped with a strip of Parafilm, and taken out of the glovebox. The sealed vial was charged with aryl bromide (0.4 mmol, 2.0 equiv), if it was liquid, by a syringe. The resulting solution was stirred for the given time at the stated temperature. The reaction mixture was quenched with 0.1 mL of water and filtered through a small pad of Celite. The pad was then rinsed with additional CH_2Cl_2. The combined organic solution was mixed with 0.5 g of deactivated silica gel and the solvent was removed in a rotary evaporator. The remaining solid residue was loaded onto a deactivated silica gel column and purified by flash chromatography. The silica gel was deactivated by flushing with 5% triethylamine/hexanes solution (3 times) followed by 20:1 hexanes/ethyl acetate solution (3 times) to remove excess triethylamine.

General Procedure C: One-pot Umpolung Synthesis of Diaryl Ketones:

An oven-dried 10 mL reaction vial equipped with a stirring bar was charged with 2-aryl-1,3-dithiane (0.2 mmol, 1.0 equiv) and aryl bromide (0.4 mmol, 2.0 equiv), if it was solid, and then the vial was put into a glovebox. The reaction vial was charged with base [$LiN(SiMe_3)_2$ or $NaN(SiMe_3)_2$] (0.4 mmol, 2.0 equiv), 1.4 mL THF, 0.4 mL THF solution (0.025 M) of NiXantphos and 0.2 mL THF solution of (0.025 M) $[PdCl(allyl)]_2$, respectively. The vial was sealed with a rubber septum wrapped with a strip of Parafilm and removed from the glovebox. The sealed vial was charged with aryl bromide (0.4 mmol, 2.0 equiv), if it was liquid, by syringe. After having stirred the mixture for the given time at the stated temperature, the vial was cooled to rt (if the reaction was carried out 60 °C) and opened to air; then 0.5 mL H_2O, I_2 (1.2 mmol, 0.3 g), and $CaCO_3$ (1.6 mmol, 0.16 g) were added (Method A) [or 0.5 mL H_2O and NBS (1.0 mmol, 0.18 g) (Method B); or 0.5 mL H_2O and Selectfluor™ (0.79 mmol, 0.28 g) (Method C)]. The resulting mixture stirred at rt for 1 h. The reaction mixture was taken up in 10 mL CH_2Cl_2 and washed with water (2×5 mL). The aqueous phase was extracted with 10 mL CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$), filtrated and mixed with 0.5 g of silica gel. The solvent was then removed in a rotary evaporator. The remaining solid residue was loaded onto a silica gel column and purified by flash chromatography.

General Procedure D: Preparation of 10.0 mmol Scale One-pot Umpolung Synthesis of Fenofibrate:

An oven-dried 250 mL two-neck, round-bottomed reaction flask equipped with a stirring bar and a glass stopcock adapter connected to a Schlenk line was charged with 2-(4-chlorophenyl)-1,3-dithiane (**14**, 10 mmol, 2.31 g), isopropyl 2-(4-bromophenoxy)-2-methylpropanoate (**2r**, 12 mmol, 3.61 g), NiXantphos (5.0 mol%, 276 mg) and $[PdCl(allyl)]_2$ (2.5 mol%, 91 mg), respectively. The open neck was closed with a rubber septum and sealed with a strip of Parafilm. The flask was evacuated by vacuum and then refilled with nitrogen gas. This process was repeated 3 times and 80 mL dry THF was added through the septum by syringe. The resulting solution was stirred at room temperature for 3 min and a solution of $LiN(SiMe_3)_2$ (20 mmol, 20 mL of a 1.0 M of THF solution) was added by syringe under a nitrogen atmosphere. The flask was removed from the Schlenk line and the reaction mixture was stirred under a nitrogen atmosphere at room temperature. After complete consumption (3 h) of 2-(4-chlorophenyl)-1,3-dithiane (**14**), 25 mL H_2O and NBS (45 mmol, 8.0 g) were added and the flask was closed with a rubber septum. The reaction mixture was stirred for 1.5 h at rt and added to a separatory funnel with 250 mL CH_2Cl_2 and washed with water (2×50 mL). The aqueous phase was extracted with 250 mL CH_2Cl_2, and combined organic phases were dried ($MgSO_4$), filtrated and mixed with 5 g of silica gel. The solvent was removed in a rotary evaporator. The remaining solid residue was loaded onto a silica gel column and purified by flash chromatography on silica gel using 20:1 hexanes/ethyl acetate as eluent to yield the product **fenofibrate** (3.1 g, 86%) as a white solid. The NMR spectral data match with the previously published data.[30]

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References

[1] a) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511–3522; b) T. Opatz, *Synthesis* **2009**, 1941–1959; c) N. Marion, S. Diez-Gonzáles, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000; *Angew. Chem.* **2007**, *119*, 3046–3058; d) J. S. Johnson, *Angew. Chem.* **2004**, *116*, 1348–1350; *Angew. Chem. Int. Ed.* **2004**, *43*, 1326–1328; e) D. Seebach, *Angew. Chem.* **1979**, *91*, 259–278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–336.

[2] a) S. Eymur, M. Göllü, C. Tanyeli, *Turk. J. Chem.* **2013**, *37*, 586–609; b) B. Shen, D. M. Makley, J. N. Johnston, *Nature* **2010**, *465*, 1027–1032; c) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534–541; d) M. Pohl, B. Lingen, M. Müller, *Chem. Eur. J.* **2002**, *8*, 5288–5295.

[3] a) O. Miyata, T. Miyoshi, M. Ueda, *ARKIVOC* **2013**, *ii*, 60–81; b) A. R. Katrizky, K. Kirichenko, *ARKIVOC* **2006**, *iv*, 119–151; c) B.-T. Gröbel, D. Seebach, *Synthesis* **1977**, 357–402.

[4] a) A. Lapworth, *J. Chem. Soc. Trans.* **1903**, *83*, 995–1005; b) A. Lapworth, *J. Chem. Soc. Trans.* **1904**, *85*, 1206–1214.

[5] a) E. J. Corey, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075–1077; *Angew. Chem.* **1965**, *77*, 1134–1135; b) E. J. Corey, D. Seebach, *Angew. Chem.* **1965**, *77*, 1136–1137; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1077–1078; c) D. Seebach, *Synthesis* **1969**, 17–36.

[6] a) S. Geum, H.-Y. Lee, *Org. Lett.* **2014**, *16*, 2466–2469; b) M. Z. Chen, O. Gutierrez, A. B. Smith III, *Angew. Chem. Int. Ed.* **2014**, *53*, 1279–1282; *Angew. Chem.* **2014**, *126*, 1303–1306; c) B. Melillo, A. B. Smith III, *Org. Lett.* **2013**, *15*, 2282–2285; d) A. B. Smith III, H. Han, W.-S. Kim, *Org. Lett.* **2011**, *13*, 3328–3331; e) A. B. Smith III, R. Tong, *Org. Lett.* **2010**, *12*, 1260–1263; f) A. B. Smith III, M. A. Folyey, S. Dong, A. Orbin, *J. Org. Chem.* **2009**, *74*, 5987–6001; g) A. B. Smith III, J. M. Cox, N. Furuichi, C. S. Kenesky, J. Zheng, W. M. Wuest, *Org. Lett.* **2008**, *10*, 5501–5504; h) A. B. Smith III, W. M. Wuest, *Chem. Commun.* **2008**, 5883–5895; i) A. B. Smith III, W.-S. Kim, W. M. Wuest, *Angew. Chem.* **2008**, *120*, 7190–7194; *Angew. Chem. Int. Ed.* **2008**, *47*, 7082–7086; j) A. B. Smith III, T. Tomioka, C. A. Risatti, J. B. Sperry, C. Sfouggatakis, *Org. Lett.* **2008**, *10*, 4359–4362; k) A. B. Smith III, D. Lee, *J. Am. Chem. Soc.* **2007**, *129*, 10957–10962; l) A. B. Smith III, C. M. Adams, *Acc. Chem. Res.* **2004**, *37*, 365–377; m) A. B. Smith III, S. M. Condon, J. A. McCauley, *Acc.*

Chem. Res. **1998**, *31*, 35–46; n) M. Yus, C. Nájera, F. Foubelo, *Tetrahedron* **2003**, *59*, 6147–6212.

[7] Metallated dithianes having cations other than lithium are rarely applied in the literature, see; a) D. Seebach, H. F. Leitz, V. Ehrig, *Chem. Ber.* **1975**, *108*, 1924–1945; b) R. Weil, N. Collignon, *Bull. Soc. Chim. Fr.* **1974**, 253; c) E. L. Eliel, A. A. Hartmann, *J. Org. Chem.* **1972**, *37*, 505–506.

[8] For some applications of dithianes in catalytic reactions where they do not behave as acyl anion equivalents, see: a) W. Du, L. Tian, J. Lai, X. Huo, X. Xie, X. She, S. Tang, *Org. Lett.* **2014**, *16*, 2470–2473; b) X. Zhao, Z. Zhong, L. Peng, W. Zhang, J. Wang, *Chem. Commun.* **2009**, 2535–2537; c) E. Morita, M. Iwasaki, S. Yoshida, H. Yorimitsu, K. Oshima, *Chem. Lett.* **2009**, *38*, 624–625; d) T.-Y. Luh, C.-F. Lee, *Eur. J. Org. Chem.* **2005**, 3875–3885; e) B. Breit, *Angew. Chem.* **1998**, *110*, 467–470; *Angew. Chem. Int. Ed.* **1998**, *37*, 453–456; f) Y. Horikawa, M. Watanabe, T. Fujiwara, T. Takeda, *J. Am. Chem. Soc.* **1997**, *119*, 1127–1128; g) T.-Y. Luh, *Acc. Chem. Res.* **1991**, *24*, 257–263. For non-transition metal catalyzed reactions see:h) S. E. Denmark, L. R. Cullen, *Org. Lett.* **2014**, *16,* 70–73; i) M. Michida, T. Mukaiyama, *Chem. Asian J.* **2008**, *3*, 1592–1600.

[9] C. Malanga, L. A. Aronica, L. Lardicci, *Tetrahedron Lett.* **1995**, *36*, 9185–9188.

[10] a) J. R. Luque-Ortega, P. Reuther, L. Rivas, C. Dardonville, *J. Med. Chem.* **2010**, *53*, 1788–1798; b) S. K. Vooturi, C. M. Cheung, M. J. Rybak, S. M. Firestine, *J. Med. Chem.* **2009**, *52*, 5020–5031; c) Y. Deng, C. Young-Won, H. Chai, W. J. Keller, A. D. Kinghorn, *J. Nat. Prod.* **2007**, *70*, 2049–2052; d) M. Pecchio, P. N. Solís, J. L. López-Pérez, Y. Vásquez, N. Rodríguez, D. Olmedo, M. Correa, A. S. Feliciano, M. P. Gupta, *J. Nat. Prod.* **2006**, *69*, 400–413; e) J. W. Lampe, C. K. Biggers, J. M. Defauw, R. J. Foglesong, S. E. Hall, J. M. Heerding, S. P. Hollinshead, H. Hu, P. F. Hughes, G. E., Jr. Jagdmann, M. G. Johnson, Y.-S. Lai, C. T. Lowden, M. P. Lynch, J. S. Mendoza, M. M. Murphy, J. W. Wilson, L. M. Ballas, K. Carter, J. W. Darges, J. E. Davis, F. R. Hubbard, M. L. Stamper, *J. Med. Chem.* **2002**, *45*, 2624–2643.

[11] a) A. A. Khan, F. Kamena, M. S. M. Timmer, B. L. Stocker, *Org. Biomol. Chem.* **2013**, *11*, 881–885; b) J. H. Poupaert, P. Depreux, C. R. McCurdy, *Monatshefte für Chemie*, **2003**, *134*, 823–830; c) S. Ushijima, S. Dohi, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 1436–1442; d) S. Dohi, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 6557–6564.

[12] a) A. R. Hajipour, R. Pourkaveh, *Synlett* **2014**, *25*, 1101–1105; b) Y. Li, W. Lu, D. Xue, C. Wang, Z.-T. Liu, J. Xia, *Synlett* **2014**, *25*, 1097–1100; c) T.-S. Jiang, G.-W. Wang, *Adv. Synth. Catal.* **2014**, *356*, 369–373; d) A. Maji, S. Rana, Akansha, D. Maiti, *Angew. Chem. Int. Ed.* **2014**, *53*, 2428–2432; *Angew. Chem.* **2014**, *126*, 2460–2464; e) K. Kunchithapatham, C. C. Eichman, J. P. Stambuli, *Chem. Commun.* **2011**, 47,12679–12681; f) X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009; g) K. Kobayashi, Y. Nishimura, F. Gao, K. Gotoh, Y. Nishihara, K. Takagi, *J. Org. Chem.* **2011**, *76*, 1949–1952; h) H. Li, M. Yang, Y. Qi, J. Xue, *Eur. J. Org. Chem.* **2011**, 2662–2667; i) C. Qin, J. Chen, H. Wu, J. Cheng, Q. Zhang, B. Zuo, W. Su, J. Ding, *Tetrahedron Lett.* **2008**, *49*, 1884–1888; j) H. Neumann, A. Brennführer, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2437–2442; k) M. Pucheault, S. Darses, J-P. Genet, *J. Am. Chem. Soc.* **2004**, *126*, 15356–15357; l) C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem.* **2004**, *116*, 3028–3030; *Angew. Chem. Int. Ed.* **2004**, *43*, 2968–2970; m) Y.-C. Huang, K. K. Majumdar, C.-H. Cheng, *J. Org. Chem.* **2002**, *67*, 1682–1684; n) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 3229–3231; o) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000**, *122*, 11260–11261.

[13] a) Y. Hanzawa, K. Narita, M. Yabe, T. Taguchi, *Tetrahedron* **2002**, *58*, 10429–10435; b) Y. Hanzawa, N. Tabuchi, T. Taguchi, *Tetrahedron Lett.* **1998**, *39*, 6249–6252.

[14] Y. Obora, M. Nakanishi, M. Tokunaga, Y. Tsuji, *J. Org. Chem.* **2002**, *67*, 5835–5837.

[15] D. Lee, T. Ryu, Y. Park, H. P. Lee, *Org. Lett.* **2014**, *16*, 1144–1147.

[16] a) A. Capperucci, A. Degl'Innocenti, C. Faggi, G. Reginato, A. Ricci, P. Dembech, G. Seconi, *J. Org. Chem.* **1989**, *54*, 2966–2968; b) K. Yamamoto, A. Hayashi, S. Suzuki, J. Tsuji, *Organometallics* **1987**, *6*, 974–979.

[17] A. Takemiya, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 14800–14801.

[18] J. R. Schmink, S. W. Krska, *J. Am. Chem. Soc.* **2011**, *133*, 19574–19577.

[19] a) J. Zhang, A. Bellomo, N. Trongsiriwat, T. Jia, P. J. Carroll, S. D. Dreher, M. T. Tudge, H. Yin, J. R. Robinson, E. J. Schelter, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 6276–6287; b) A. Bellomo, J. Zhang, N. Trongsiriwat, P. J. Walsh, *Chem. Sci.* **2013**, *4*, 849–857; c) J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2012**, *134*, 13765–13772.

[20] M. Li, B. Yücel, J. Adrio, A. Bellomo, P. J. Walsh, *Chem. Sci.* **2014**, *5*, 2383–2391.

[21] G. Frensch, N. Hussain, F. A. Marques, P. J. Walsh, *Adv. Synth. Catal.* **2014**, 2517–2524.

[22] S. Montel, T. Jia, P. J. Walsh, *Org. Lett.* **2014**, *16*, 130–133.

[23] a) T. Jia, A. Bellomo, K. EL Baina, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2013**, *135*, 3740–3743; b) B. Zheng, T. Jia, P. J. Walsh, *Org. Lett.* **2013**, *15*, 1690–1693.

[24] a) B. Zheng, T. Jia, P. J. Walsh, *Adv. Synth. Catal.* **2014**, *356*, 165–178; b) B. Zheng, T. Jia, P. J. Walsh, *Org. Lett.* **2013**, *15*, 4190–4193.

[25] S. Montel, L. Raffier, Y. He, P. J. Walsh, *Org. Lett.* **2014**, *16*, 1446–1449.

[26] N. Hussain, G. Frensch, J. Zhang, P. J. Walsh, *Angew. Chem. Int. Ed.* **2014**, *53*, 3693–3697; *Angew. Chem.* **2014**, *126*, 3767–3771.

[27] a) M.-N. Birkholz, Z. Freixa, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2009**, *38*, 1099–1118; b) P. W. N. M. Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741–2769; c) L. A. van der Veen, P. H. Keeven, G. C. Schoemaker, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, M. Lutz, A. L. Speek, *Organometallics* **2000**, *19*, 872–883.

[28] a) R. C. Besra, S. Rudrawar, A. K. Chakraborti, *Tetrahedron Lett.* **2005**, *46*, 6213–6217; b) S.-S. Weng, S.-C. Chang, T.-H. Chang, J.-P. Chyn, S.-W. Lee, C.-H. Lin,

F.- K. Chen, *Synthesis* **2010**, 1493–1499; c) S. Rudrawar, R. C. Besra, A. K. Chakraborti, *Synthesis* **2006**, 2767–2771; d) M. H. Ali, M. G. Gomes, *Synthesis* **2005**, 1326–1332; e) D. Dong, Y. Ouyang, H. Yu, Q. Liu, J. Liu, M. Wang, J. Zhu, *J. Org. Chem.* **2005**, *70*, 4535–4537; f) S. K. De, *Synthesis* **2004**, 2837–2840; g) S. K. De, *Tetrahedron Lett.* **2004**, *45*, 2339–2341; h) H. Firouzabadi, N. Iranpoor, H. Hazarkhani, *J. Org. Chem.* **2001**, *66*, 7527–7529; i) S. Samajdar, M. K. Basu, F. F. Becker, B. K. Banik, *Tetrahedron Lett.* **2001**, *42*, 4425–4427.

[29] a) H.-H. Cho, S.-H. Kim, *Bull. Korean Chem. Soc.* **2012**, *33*, 3083–3086; b) M. J. Lo Fiego, G. F. Silbestri, A. B. Chopa, M. T. Lockhart, *J. Org. Chem.* **2011**, *76*, 1707–1714; c) B. M. O'Keefe, N. Simmons, S. F. Martin, *Tetrahedron* **2011**, *67*, 4344–4351; d) O. Chuzel, A. Roesch, J.-G. Genet, S. Darses, *J. Org. Chem.* **2008**, *73*, 7800–7802; e) B. M. O'Keefe, N. Simmons, S. F. Martin, *Org. Lett.* **2008**, *10*, 5301–5304.

[30] For very recent synthesis of fenofibrate see: K. M. Bjerglund, T. Skrydstrup, G. A. Molander, *Org. Lett.* **2014**, *16*, 1888–1891.