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Indium(0)-Mediated C_{sp^3}–S/O Cross-Coupling Approach Towards the Regioselective Alkylation of α-Enolic Esters/Dithioesters: A Mechanistic Insight

Sushobhan Chowdhury,[a] Tanmoy Chanda,[a] Ashutosh Gupta,[b] Suvajit Koley,[a] B. Janaki Ramulu,[a] Raymond C. F. Jones,[c] and Maya Shankar Singh*[a]

Keywords: Synthetic methods / Cross-coupling / Regioselectivity / Indium / Alkylation / Allylation

We have reported an indium(0)-mediated C_{sp^3}–S/O cross-coupling approach that leads to the highly regioselective alkylation of α-enolic acetate/dithioacetate systems. This hetero cross-coupling reaction does not require additional co-catalyst or promoter, and the in situ generated organoindium species promotes the reaction by acting as the coupling partner of the α-enolic acetate/dithioacetate substrates. The excellent selectivity for *C*-, *S*-, or *O*-alkylation is solely dependent on the nucleophilic behavior of α-enolic acetate/dithioacetate systems. These results were further supported by DFT calculations of the relative electronic energies of the substrates and products as well as the activation barriers of the respective transformations.

Introduction

During the last century, organometallic reagents such as organolithium, organotin, organozinc, organolead, and organomagnesium compounds have played a key and vital role in the progress of organic synthesis.[1] However, these reactive reagents are highly sensitive to moisture and air and demonstrate poor compatibility towards carbonyl and hydroxy groups, thus, limiting their widespread application in organic synthesis. Consequently, organoindium reagents[2] have recently emerged as an attractive alternative to these organometallic species because of their mild, nontoxic nature, relative stability, and excellent tolerance towards various functional groups. Additionally, the use of organoindium reagents in an aqueous medium is remarkable from both economic and environmental standpoints,[2a] two factors indicative of a successful approach. The attractive features of organoindium reagents lead to better performance and selectivity in comparison to other organometallic reagents, which suffer from significant limitations in organic synthesis. The use of indium(0) metal in allylation, propargylation, and analogous reactions is widely described.[3a–3d] Organoindium compounds as a source of alkyl nucleophiles[3e–3g] have been utilized in several synthetic operations.[4] Moreover, organoindium reagents can act as an effective nucleophilic coupling partner in Pd-catalyzed cross-coupling reactions.[2,5,6] Ranu and co-workers[7] performed a cross-coupling reaction of allylindium reagents with activated benzylic bromides. However, examples of organoindium species in coupling reactions in the absence of other promoters are rare and remain unexplored.

Herein, we disclose a hitherto unreported regioselective alkylation that proceeds through a C_{sp^3}–S/O cross-coupling reaction of an α-enolic acetate/dithioacetate system with an alkylindium reagent. In the initial reaction step, indium(0) forms an organoindium species with the alkyl halide, which undergoes a coupling reaction with the α-enolic ester/dithioester that is present in the system. Upon quenching the reaction, a regioselectively alkylated product is exclusively formed. The regioselectivity of the alkylation step is directed by the relative electronic energies of the respective species and the activation barriers of the transformation, as evident from the DFT calculations of the energies, which were performed on the respective systems.

Results and Discussion

It has been established from spectroscopic (IR and NMR) data and single-crystal X-ray diffraction analysis that a β-oxodithioester solely exists as its enolic tautomer in both the solid[8a] as well as the solution phase. DFT studies that employ the B3LYP method with a 6-31G* basis set also suggest that the α-enolic form is 2.52 kcal mol^{-1} more stable (stabilized by intramolecular hydrogen bonding) than

[a] Department of Chemistry, Faculty of Science, Banaras Hindu University,
Varanasi 221005, India
E-mail: mssinghbhu@yahoo.co.in
http://www.drmssinghchembhu.com/
[b] Department of Chemistry, Udai Pratap Autonomous College, Kashi Vidyapeeth University,
Varanasi 221005, India
[c] Department of Chemistry, Loughborough University,
Loughborough, Leics, LE11 3TU, UK

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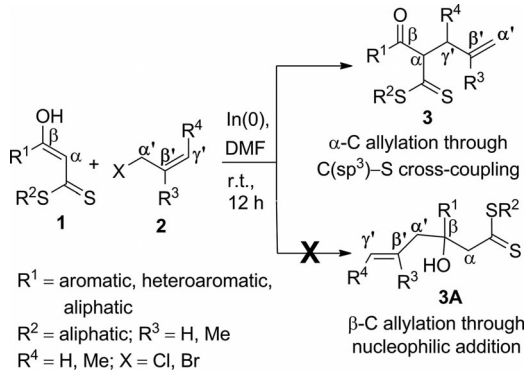
the β-oxo form. Therefore, we began our investigation by assuming that the α-enolic form was the reactive species.

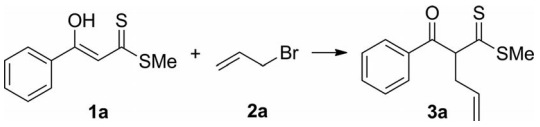
The synthetic utility of α-enolic dithioesters has already been explored by our group,[8b,8c] but we were further interested in the chemistry of their allylated derivatives. In a recent report,[9a] we found that the treatment of an α-enolic dithioester with a Grignard reagent generated a tertiary alcohol through a nucleophilic attack at the enolic β-carbon. Similar results were also observed with alkyllithium reagents.[9b] We, therefore, postulated that the treatment of an α-enolic dithioester with an in situ generated allylic indium species[2,10] should also undergo allylation at the β-carbon of the dithioester through a nucleophilic addition. However, the treatment of α-enolic dithioester **1** with indium(0) powder and allyl halide **2** in *N*,*N*-dimethylformamide (DMF) at room temperature provided the unexpected α-*C*-allylated product **3**, instead of the expected β-*C*-allylated product **3A** (see Scheme 1). Previously, Ila and coworkers[11] performed the α-*C*-allylation of a dithioester with allyl bromide by employing a conventional base-catalyzed nucleophilic substitution pathway. Herein, we achieved the alkylation through C_{sp^3}–S cross-coupling reactions of organoindium species with α-enolic dithioesters. Until now, no examples have been reported of the α-*C*-allylation of a dithioester through a cross-coupling approach, and to the best of our knowledge this is the first of its kind to proceed through an organoindium pathway under neutral, mild reaction conditions.



Scheme 1. Formation of γ′-selective *C*-allylated products **3** from allylic halides **2**.

Initially, we treated methyl 3-hydroxy-3-phenylprop-2-enedithioate (**1a**, 1.0 mmol), with indium(0) powder (1.2 mmol) and allyl bromide (**2a**, 1.0 mmol) in DMF at room temperature. The reaction afforded α-*C*-allylated product **3a**, that is, methyl 2-allyl-3-oxo-3-phenylpropanedithioate, in 85% yield within 12 h with the full consumption of the starting materials. Encouraged by our initial results, we focused on the optimal reaction conditions (see Table 1). At an elevated temperature of 60 °C, the yield of the desired product decreased along with the generation of some additional compounds, as indicated by the spots on TLC plate (see Table 1, Entry 2). Interestingly, changing the solvent from more polar DMF to the comparatively less polar solvents like tetrahydrofuran (THF), CH_3CN, and EtOH hindered the reaction (see Table 1, Entries 3–8). Obviously, screening the solvents revealed that DMF was the appropriate solvent, as it not only resulted in a shorter reaction time, but also provided the highest yield (see Table 1, Entry 1). Next, $InCl_3$ was used as the mediator instead of In^0 powder. Unfortunately, the efficiency of $InCl_3$ to mediate the reaction was inferior to that of metallic indium (see Table 1, Entries 9 and 10). Consequently, other metals such as Zn and Cu (1.2 mmol in each case) were employed, but they could not promote the reaction (see Table 1, Entries 11 and 12). In the absence of a mediatior, the reaction did not provide any product, even in a trace amount, after 48 h (see Table 1, Entry 13).

Table 1. Optimization of the model allylation reaction.



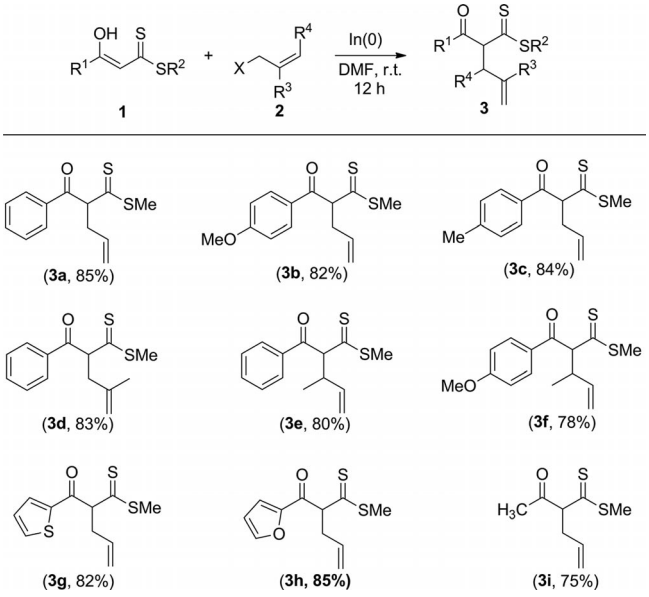
Entry	Mediator [equiv.]	Dithioester/ RX	Solvent	Temp.	Time [h]	% Yield[a]
1	In (1.2)	1:1	DMF	r.t.	12	85
2	In (1.2)	1:1	DMF	60	12	60
3	In (1.2)	1:1	THF	r.t.	24	–[b]
4	In (1.2)	1:1	THF	reflux	24	trace
5	In (1.2)	1:1	CH_3CN	r.t.	24	–[b]
6	In (1.2)	1:1	CH_3CN	reflux	24	10
7	In (1.2)	1:1	EtOH	r.t.	24	–[b]
8	In (1.2)	1:1	EtOH	reflux	24	20
9	$InCl_3$ (1.2)	1:1	DMF	r.t.	24	trace
10	$InCl_3$ (1.2)	1:1	DMF	80 °C	12	40
11	Zn (1.2)	1:1	DMF	r.t.	24	–[b]
12	Cu (1.2)	1:1	DMF	r.t.	24	–[b]
13	none	1:1	DMF	r.t.	48	–[b]
14	In (0.5)	1:1	DMF	r.t.	12	40
15	In (0.75)	1:1	DMF	r.t.	12	60
16	In (1.0)	1:1	DMF	r.t.	12	75
17	In (1.5)	1:1	DMF	r.t.	12	80
18	In (1.2)	1:0.75	DMF	r.t.	12	68
19	In (1.2)	1:1.2	DMF	r.t.	12	82

[a] Isolated pure yields. [b] No reaction.

Next, to optimize the loading of the indium(0), different experiments were performed (see Table 1, Entries 14–17). The optimum loading of indium(0) was determined as 1.2 equiv. Finally, the ratio of allyl bromide to the dithioester was also varied, and a 1:1 ratio led to the maximum yield (see Table 1, Entries 18 and 19). Consequently, the best results were achieved by employing a 1:1:1.2 ratio of the dithioester, allyl bromide, and indium(0) at room temperature for 12 h (for details of the optimization, see Supporting Information).

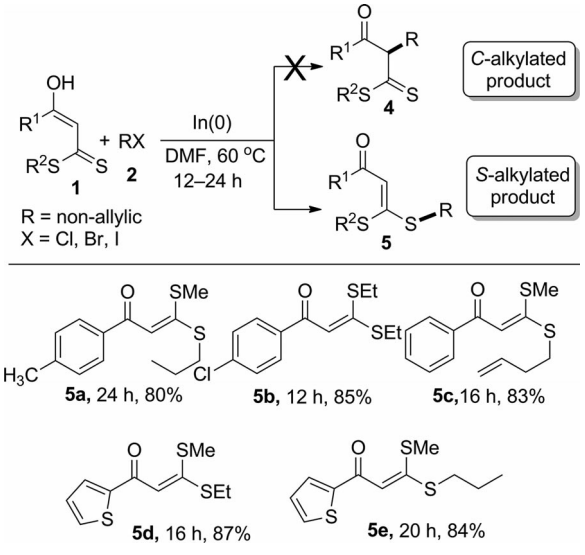
With the optimal reaction conditions in hand, we commenced to explore the substrate scope and diversity of the current protocol (see Table 2). The protocol was found to be γ′ specific, and as observed, a wide range of dithioesters and allyl halides were well tolerated. In all cases, the reactions proceeded smoothly to afford the corresponding products in good yields.

Table 2. Substrate scope for the synthesis of *C*-allylated product.[a]



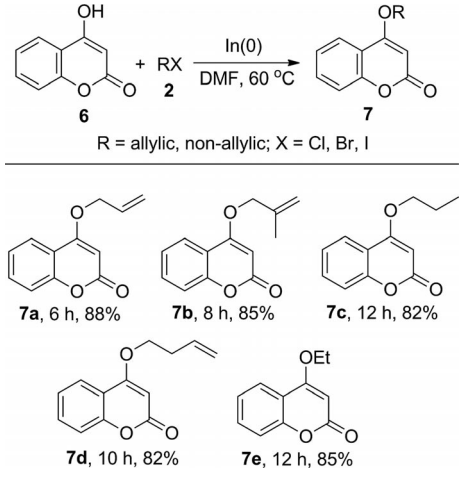
[a] **1** (1.0 mmol) and **2** (1.0 mmol) in presence of indium powder (1.2 mmol).

To broaden the scope of this protocol further, we focused on employing nonallylic halides. Surprisingly, no reaction took place at room temperature. However, a highly regioselective *S*-alkylation reaction took place at 60 °C, and instead of a *C*-alkylation to give **4**, this reaction furnished α-oxoketene-*S*,*S*-acetals **5** in high yield within 12–24 h (see Scheme 2). The structures of all of the α-oxoketene-*S*,*S*-acetals **5** were identified by their IR, ^{1}H NMR, ^{13}C NMR, and HRM spectra and unequivocally confirmed by the X-ray single-crystal diffraction analysis of one of the representative compounds (**5a**).[12a]



Scheme 2. Synthesis of *S*-alkylated product **5** from nonallylic halides.

Prompted by continuous observations of anomalous trends, we attempted a parallel study of the cross-coupling of alkylindium species with 4-hydroxycoumarin (**6**), which is essentially an α-enolic ester that contains a permanent α-enol part and, thus, has a fundamentally similar structure as an α-enolic dithioester. Stunningly, irrespective of the employed alkyl or allyl halide, a regioselective enolic *O*-alkylation took place at 60 °C in all cases to lead to the synthetically useful enol-ether linkage **7** in excellent yields within 6–12 h (see Scheme 3).[12b,13,14]



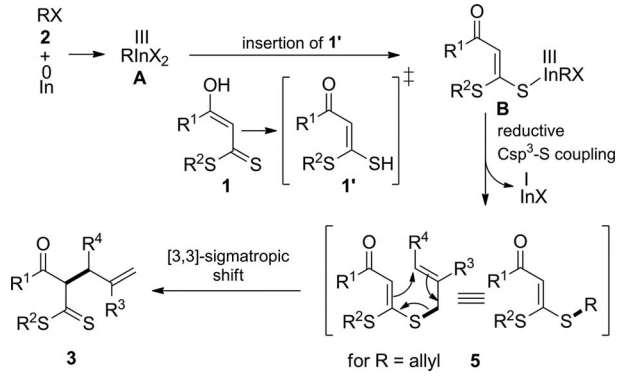
Scheme 3. Regioselective synthesis of *O*-alkylated product **7** from 4-hydroxycoumarin (**6**).

To elucidate the probable structure of the organoindium species, we analyzed the NMR spectra from some of our initial experiments. Methyl 3-hydroxy-3-(*p*-tolyl)prop-2-enedithioate (1.0 mmol) was treated with indium(0) powder (1.2 mmol) in 5 mL of DMF, and the mixture was stirred at room temperature. After 1 h, the NMR spectrum of the reaction mixture was recorded, in which there was no change in the characteristic signals of the dithioester in DMF. This suggested no formation of the initial organo-

indium species with the dithioester (see Supporting Information).

Next, we treated allyl bromide (1.0 mmol) with indium(0) powder (1.2 mmol) in 5 mL of DMF and stirred the mixture at room temperature. In this case, the NMR spectrum of the reaction mixture after 1 h displayed new resonances at δ = 2.12, 4.13, and 4.45 ppm. These signals correspond to the organoindium intermediate allylindium(III) dibromide as revealed by Araki et al.[10b] and also established by Chan et al.[10c] However, other probable intermediates could not be assigned because their corresponding signals were not observed (see Supporting Information). Therefore, according to the observed NMR spectral pattern and literature reports,[10] we considered allylindium(III) dihalide **A** as the active organoindium species to participate in the coupling reaction.

Although available reports of C–S cross-couplings of thiols with alkyl/aryl halides do not provide details about a precise reaction pathway,[15,16] we proposed a tentative mechanism for the coupling phenomenon based on our experimental observations and literature reports (see Scheme 4). The initial step is the formation of organoindium intermediate allylindium(III) dihalide **A**. In the next step, the thioenol form of the dithioester (i.e., **1′**) is inserted into **A** with the halide leaving to form **B**. Consequently, **B** undergoes a reductive C–S coupling to form α-oxoketene dithioacetal **5**. As soon as this is formed, **5** immediately undergoes a facile [3,3] sigmatropic shift of the allylic groups to give *C*-allylated product **3** under the influence of the organoindium species.



Scheme 4. Proposed mechanism based on the spectral evidence.

At this stage, the question with regard to the selectivity of *C*-, *S*-, or *O*-alkylation still remains unanswered. To rationalize this anomaly through a logical thread, we employed DFT calculations. The calculations were performed on isolated molecules without considering indium as part of the system. As regioselectivity is observed in all the cases,[11,13] irrespective of the catalytic and solvent systems, only such an approach can give insight into the inherent electronic properties of the corresponding starting molecules from which the regioselective alkylation occurs.

In case of the α-enolic dithioesters, there are three possible points of alkylation, that is, the enolic oxygen atom, the enolic carbon atom, and the thiocarbonyl sulfur of the dithioacetate. In Figure 1, the DFT calculation shows a large energy difference between the *O*-alkylated product and the *C*-alkylated product (11.69 kcal mol^{-1}), which rules out the possibility of any *O*-alkylation taking place. The *S*-alkylated product, however, shows only a minor energy difference in comparison to the *C*-alkylated product (1.94 kcal mol^{-1}) and is compensated by the greater nucleophilicity and charge density of the S atom over the C atom to favor the exclusive formation of the *S*-alkylated product.

For similar reasons, the *S*-allylation will occur first in the allylation of the dithioester. In the next step, because of the lability of the C–S bond, the *S*-allylated product will pass through the comparatively low energy barrier of 22.30 kcal mol^{-1} and undergo a [3,3] sigmatropic shift at room temperature to give the lower energy *C*-allylated product **3** (see Figure 1). This type of [3,3] sigmatropic shift

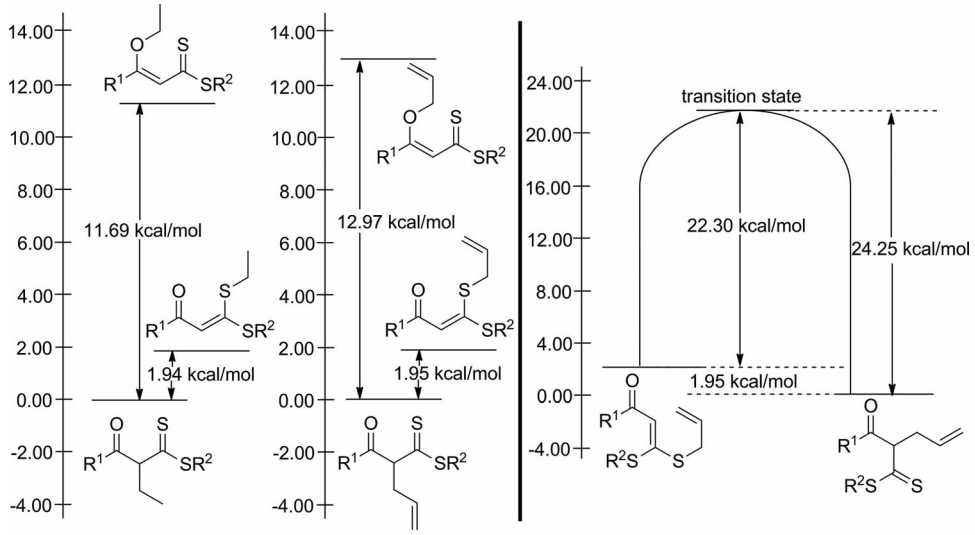


Figure 1. Relative electronic state energies of ethylated and allylated products as well as the activation energy barrier of [3,3] sigmatropic shift for α-enolic dithioesters **1**.

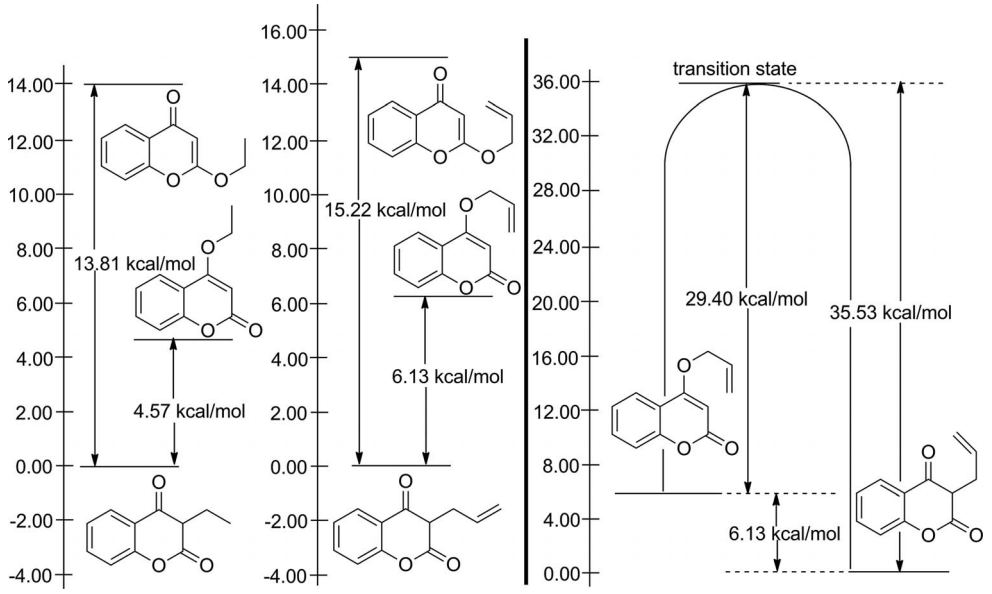


Figure 2. Relative electronic state energies of ethylated and allylated products as well as activation energy barrier of [3,3] sigmatropic shift for 4-hydroxycoumarin (**6**).

cannot occur with nonallylic groups, and, in this case, the reaction would, therefore, terminate at the *S*-alkylation step to give corresponding *S*-alkylated product.

In the case of the alkylation of 4-hydroxycoumarin, the energy difference between the enolic *O*-alkylated product and the *C*-alkylated product is 4.57 kcal mol^{-1}. Thus, here also the charge density factor predominates to guide the reaction towards an enolic *O*-alkylation. The huge energy difference of the product obtained by *O*-alkylation of the ester carbonyl group (13.81 kcal mol^{-1}), however, makes it energetically more unstable, which rules out any possibility of ester *O*-alkylation (see Figure 2). The stability of the allylated product of 4-hydroxycumarin also follows the same trend as the alkylation. Here, the possibility of a [3,3] sigmatropic shift has been ruled out because of the greater stability of C–O bond and relatively high activation energy barrier of 29.40 kcal mol^{-1} (see Figure 2). Therefore, in case of 4-hydroxycumarin, both the alkylation and allylation reactions terminated at the enolic *O*-alkylation step.

Conclusions

In summary, we have developed a facile indium(0)-mediated regioselective alkylation protocol for α-enolic ester/dithioester systems that proceeds through a C_{sp^3}–S/O cross-coupling reaction of alkylindium reagents and α-enolic esters/dithioesters. A reasonable mechanism that describes the overall reaction pathway has also been documented. The alkylation trend was solely dependent on the structural and chemical behavior of the substrate and alkylating reagent, which was revealed by theoretical investigations done on their relative electronic energies as well as the activation barrier of the transformation. Thus, the concept of chemoelectronic guidance, which was observed throughout the entire course of the alkylation study, will certainly help chemists to deal with such systems. The allylated adducts have been further employed in the syntheses of different thioheterocycles, which will be published at a later date.

Experimental Section

General Methods: Commercially available alkyl and allyl halides, indium powder, 4-hydroxycoumarin, and DMF were used as received without further purification. The β-oxodithioesters were prepared according to the literature procedure.[17] DFT studies were performed by employing the B3LYP (Becke-3-parameter-Lee–Yang–Parr) method with the 6-31G(d) basis set implemented in Gaussian 09 for all structures. Geometrical parameters of reactants, intermediates, transition states (TS), and products were fully optimized in the gas phase (for isolated molecules). Thin layer chromatography was performed with silica gel 60 F_{254} precoated plates. Column chromatography was performed with 100–200 mesh silica gel. Infrared spectra were recorded as KBr pellets, and the frequencies are reported in cm^{-1}. The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a spectrometer that operated at either 300 or 400 MHz and 75.5 or 100 MHz, respectively. Chemical shifts (δ) are given in parts per million (ppm) by using the residual solvent peaks as the reference relative to TMS. Coupling constant (J) values are given in Hz. Mass spectra were recorded using electrospray ionization mass spectrometry.

General Procedure for the Synthesis of α-Allyl-β-oxodithioacetates 3a–3i: To a solution of α-enolic dithioester **1** (1.0 mmol) in DMF (5 mL) were added indium powder (1.2 mmol) and allyl halide **2** (1.0 mmol), and the resulting mixture was stirred at room temperature for 12 h. Upon completion, the reaction was treated with dilute HCl solution followed by brine, and the mixture was extracted with ethyl acetate (2× 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude reaction mixture was purified by column chromatography (hexane) to afford the pure α-allyl-β-oxodithioacetates **3**.

Methyl 2-Benzoylpent-4-enedithioate (3a): Red oil (212 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.2 Hz, 2 H,

Ar), 7.53 (t, *J* = 7.2 Hz, 1 H, Ar), 7.44–7.39 (m, 2 H, Ar), 5.86–5.73 (m, 1 H, vinylic CH), 5.31 (t, *J* = 7.2 Hz, 1 H, tertiary CH), 5.14–5.00 (m, 2 H, vinylic CH_2), 3.09–2.99 (m, 1 H, CH_2), 2.83–2.74 (m, 1 H, CH_2), 2.58 (s, 3 H, SMe) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 231.7 (C=S), 193.2 (C=O), 136.0, 134.4, 133.2, 128.7, 128.5, 117.4, 67.6 (tertiary CH), 38.3 (CH_2), 19.9 (SMe) ppm. IR (KBr): $\tilde{\nu}$ = 2978, 2916, 1688, 1447, 1231, 921, 688 cm^{-1}. HRMS: calcd. for 251.0559 $[M + H]^+$; found 251.0571.

Methyl 2-(4-Methoxybenzoyl)pent-4-enedithioate (3b): Red oil (228 mg, 82% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.7 Hz, 2 H, Ar), 6.91 (d, *J* = 9.0 Hz, 2 H, Ar), 5.83–5.74 (m, 1 H, vinylic CH), 5.29 (t, *J* = 7.2 Hz, 1 H, tertiary CH), 5.14–5.00 (m, 2 H, vinylic CH_2), 3.85 (s, 3 H, OMe), 3.05–3.01 (m, 1 H, CH_2), 2.83–2.76 (m, 1 H, CH_2), 2.60 (s, 3 H, SMe) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 232.2 (C=S), 191.7 (C=O), 163.6, 134.6, 131.2, 129.0, 117.3, 113.7, 67.6 (tertiary CH), 55.4 (OMe), 38.4 (CH_2), 19.9 (SMe) ppm.

Methyl 2-(4-Methylbenzoyl)pent-4-enedithioate (3c): Red oil (221 mg, 84% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.1 Hz, 2 H, Ar), 7.23 (d, *J* = 8.1 Hz, 2 H, Ar), 5.86–5.72 (m, 1 H, vinylic CH), 5.29 (t, *J* = 7.2 Hz, 1 H, tertiary CH), 5.13–5.00 (m, 2 H, vinylic CH_2), 3.08–2.95 (m, 1 H, CH_2), 2.88–2.65 (m, 1 H, CH_2), 2.59 (s, 3 H, SMe), 2.38 (s, 3 H, tolyl CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 232.0 (C=S), 193.0 (C=O), 144.3, 134.6, 133.6, 129.3, 129.0, 117.4, 67.7 (tertiary CH), 38.4 (CH_2), 21.6 (tolyl CH_3), 20.0 (SMe) ppm.

Methyl 2-Benzoyl-4-methylpent-4-enedithioate (3d): Red oil (218 mg, 83% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.5 Hz, 2 H, Ar), 7.55 (t, *J* = 7.2 Hz, 1 H, Ar), 7.47–7.42 (m, 2 H, Ar), 5.51 (t, *J* = 7.2 Hz, 1 H, tertiary CH), 4.73 (d, *J* = 19.2 Hz, 2 H, vinylic CH_2), 3.09–3.02 (m, 1 H, CH_2), 2.78–2.71 (m, 1 H, CH_2), 2.59 (s, 3 H, SMe), 1.78 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 232.1 (C=S), 193.4 (C=O), 141.9, 136.1, 133.3, 128.9, 128.6, 112.7, 66.2 (tertiary CH), 42.0 (CH_2), 22.7 (CH_3), 20.1 (SMe) ppm.

Methyl 2-Benzoyl-3-methylpent-4-enedithioate (3e): Red oil (210 mg, 80% yield, diastereomeric mixture). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.04 (m, 2 H, Ar), 7.56–7.43 (m, 3 H, Ar), 5.78–5.66 (m, 1 H, vinylic CH), 5.31–5.22 (m, 1 H, CH), 5.12–4.92 (m, 2 H, vinylic CH_2), 3.52–3.42 (m, 1 H, CH), 2.58 (d, *J* = 17.7 Hz, 3 H, SMe), 1.76 (q, *J* = 6.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 230.4 (C=S), 193.4 (C=O), (140.3, 139.3), (136.7, 136.7), (133.5, 133.3), (129.0, 129.0), (128.6, 128.6), (115.7, 115.3), (74.1, 74.0), (42.7, 41.8), (20.2, 20.0, SMe), (18.9, 17.1, CH_3) ppm.

Methyl 2-(4-Methoxybenzoyl)-3-methylpent-4-enedithioate (3f): Red oil (229 mg, 78% yield, diastereomeric mixture). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.01 (m, 2 H, Ar), 6.91–6.86 (m, 2 H, Ar), 5.76–5.64 (m, 1 H, vinylic CH), 5.24–5.16 (m, 1 H, CH), 5.08–4.88 (m, 2 H, vinylic CH_2), 3.81 (d, *J* = 2.7 Hz, 3 H, OMe), 3.44–3.38 (m, 1 H, CH), 2.53 (d, *J* = 17.1 Hz, 3 H, SMe), 1.06–1.00 (m, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 230.9 (C=S), (191.6, 191.5, C=O), 163.7, (140.4, 139.3), (131.3, 131.3), 129.6, (115.4, 115.1), (113.7, 113.7, 113.5, 113.4), (74.0, 73.9), (55.3, 55.3, 55.3, OMe), (42.5, 41.5), (20.0, 19.8, SMe), (18.7, 17.0, CH_3) ppm. MS: *m*/*z* (%) = 295 (10) $[M + 1]^+$, 317 (55) $[M + 23]^+$.

Methyl 2-(Thiophene-2-carbonyl)pent-4-enedithioate (3g): Red oil (208 mg, 82% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 3.6 Hz, 1 H, Ar), 7.66 (d, *J* = 4.5 Hz, 1 H, Ar), 7.11 (t, *J* = 4.5 Hz, 1 H, Ar), 5.82–5.73 (m, 1 H, vinylic CH), 5.18–5.01 (m, 3 H, tertiary CH, vinylic CH_2), 3.06–2.99 (m, 1 H, CH_2), 2.85–2.78 (m, 1 H, CH_2), 2.62 (s, 3 H, SMe) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 231.1 (C=S), 186.0 (C=O), 143.3, 134.8, 134.2, 133.1, 128.2, 117.7, 69.2 (tertiary CH), 38.2 (CH_2), 20.1 (SMe) ppm.

Methyl 2-(Furan-2-carbonyl)pent-4-enedithioate (3h): Red oil (204 mg, 85% yield, diastereomeric mixture). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (br., 1 H, Ar), 7.33 (d, *J* = 3.6 Hz, 1 H, Ar), 6.53 (br., 1 H, Ar), 5.83–5.70 (m, 1 H, vinylic CH), 5.14–5.01 (m, 3 H, tertiary CH, vinylic CH_2), 3.06–2.97 (m, 1 H, CH_2), 2.83–2.74 (m, 1 H, CH_2), 2.62 (s, 3 H, SMe) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 230.9 (C=S), 181.8 (C=O), 151.6, 147.0, (134.2, 134.1), 118.9, 117.6, (112.5, 112.3), (67.8, 67.6, CH), 37.6 (allylic CH_2), 20.0, (SMe) ppm. IR (KBr): $\tilde{\nu}$ = 2921, 2852, 1585, 1475, 1235, 1071, 780 cm^{-1}.

Methyl 2-Acetylpent-4-enedithioate (3i): Red oil (141 mg, 75% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.73–5.62 (m, 1 H, vinylic CH), 5.13–4.99 (m, 3 H, tertiary CH, vinylic CH_2), 4.35 (t, *J* = 7.2 Hz, 1 H, tertiary CH), 2.91–2.66 (m, 5 H, CH_2 and SMe), 2.20 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 223.9 (C=S), 201.1 (C=O), 134.1, 117.5, 73.4, 37.0 (CH_2), 27.9 (CH_3), 20.1 (SMe) ppm.

General Procedure for the Synthesis of α-Oxoketene-*S*,*S*-acetals 5a–5e: To a solution of α-enolic dithioester **1** (1.0 mmol) in DMF (5 mL) were added indium powder (1.2 mmol) and alkyl halide **2** (1.0 mmol), and the mixture was stirred at 60 °C for the stipulated period of time. Upon completion, the reaction was treated with dilute HCl solution followed by brine, and the resulting mixture was extracted with ethyl acetate (2× 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude reaction mixture was purified by column chromatography (increasing amounts of ethyl acetate in hexane) to afford the pure α-oxoketene-*S*,*S*-acetals **5**.

3-(Methylthio)-3-(propylthio)-1-(*p*-tolyl)prop-2-en-1-one (5a): Yellow solid (212 mg, 80% yield); m.p. 76–77 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.1 Hz, 2 H, Ar), 7.22 (d, *J* = 8.1 Hz, 2 H, Ar), 6.82 (s, 1 H, dithioacetal CH), 2.99 (t, *J* = 7.2 Hz, 2 H, CH_2 of SPr), 2.51 (s, 3 H, SMe), 2.39 (s, 3 H, tolyl CH_3), 1.85–1.75 (m, 2 H, CH_2 of SPr), 1.09 (t, *J* = 7.2 Hz, 3 H, CH_3 of SPr) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 185.4 (C=O), 164.8, 142.1, 136.6, 129.0, 127.7, 110.2, 36.0, 21.5, 20.9 (SMe), 15.2, 13.5 ppm. IR (KBr): $\tilde{\nu}$ = 2969, 2932, 1602, 1477, 1180, 781 cm^{-1}. HRMS: calcd. for 268.0872 $[M + H]^+$; found 268.0935.

3-(Methylthio)-1-phenyl-3-(prop-2-yn-1-ylthio)prop-2-en-1-one (5b): Yellow sticky solid (243 mg, 85% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.1 Hz, 2 H, Ar), 7.38 (d, *J* = 8.1 Hz, 2 H, Ar), 6.73 (s, 1 H, dithioacetal CH), 3.11–3.01 (m, 4 H, 2 CH_2 of SEt), 1.45–1.34 (m, 6 H, 2 CH_3 of SEt) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 184.1 (C=O), 165.7, 137.8, 137.6, 129.0, 128.6, 109.5, 28.3 (CH_2 of SEt), 25.6 (CH_2 of SEt), 13.7 (CH_3 of SEt), 12.4 (CH_3 of SEt) ppm.

3-(But-3-en-1-ylthio)-3-(methylthio)-1-phenylprop-2-en-1-one (5c): Yellow gel (218 mg, 83% yield, diastereomeric mixture). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.88 (m, 2 H, Ar), 7.48–7.40 (m, 3 H, Ar), 6.79 (d, *J* = 25.2 Hz, 1 H, dithioacetal CH), 5.90–5.79 (m, 1 H, vinylic CH), 5.19–5.05 (m, 2 H, vinylic CH_2), 3.14–3.05 (m, 2 H, CH_2), 2.54–2.46 (m, 5 H, CH_2, SMe) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 185.4 (C=O), 165.0, 139.1, (135.7, 135.1), (132.1, 132.0, 131.6), 128.3, (127.6, 127.5), (117.1, 116.5), (110.2, 109.6), (33.3, 32.9), (31.4, 30.4), (17.3, 15.1) ppm.

3-(Ethylthio)-3-(methylthio)-1-(thiophen-2-yl)prop-2-en-1-one (5d): Yellow sticky solid (213 mg, 87% yield, diastereomeric mixture). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 1 H, Ar), 7.52 (d,

J = 4.8 Hz, 1 H, Ar), 7.09–7.06 (m, 1 H, Ar), 6.62 (d, J = 24.9 Hz, 1 H, dithioacetal CH), 3.10–2.99 (m, 2 H, CH_2 of SEt), 2.53–2.49 (m, 3 H, SMe), 1.45–1.33 (m, 3 H, CH_3 of SEt) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = (178.1, 177.9, C=O), (165.0, 164.9), (146.1, 146.1), (131.8, 131.7), (129.4, 129.4), 127.7, (109.7, 109.1), (28.1, 25.4), (17.1, 15.1), (13.6,12.3) ppm.

3-(Methylthio)-3-(propylthio)-1-(thiophen-2-yl)prop-2-en-1-one (5e): Yellow viscous liquid (217 mg, 84% yield, diastereomeric mixture). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (br., 1 H, Ar), 7.54–7.52 (m, 1 H, Ar), 7.09 (br., 1 H, Ar), 6.64 (d, J = 26.4 Hz, 1 H, dithioacetal CH), 3.05–2.97 (m, 2 H, CH_2 of SPr), 2.52 (d, J = 16.8 Hz, 3 H, SMe), 1.85–1.71 (m, 2 H, CH_2 of SPr), 1.14–1.03 (m, 3 H, CH_3 of SPr) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1 (C=O), 165.2, 146.1, 131.8, 129.4, 127.8, 109.7, 35.9, 20.8, 15.2, 13.6 ppm.

General Procedure for the Synthesis of 4-Alkoxy-2*H*-chromen-2-ones 7a–7e: To a solution of 4-hydroxycoumarin (**6**, 1.0 mmol) in DMF (5 mL) were added indium powder (1.2 mmol) and alkyl/allyl halides **2** (1.0 mmol), and the mixture was stirred at 60 °C for the stipulated period of time. Upon completion, the reaction was treated with dilute HCl solution followed by brine, and the resulting mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude reaction mixture was purified by column chromatography (increasing amounts of ethyl acetate in hexane) to afford the pure 4-alkoxy-2*H*-chromen-2-ones **7**.

4-(Allyloxy)-2*H*-chromen-2-one (7a): White solid (179 mg, 88% yield); m.p. 114–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.8 Hz, 1 H, Ar), 7.54 (t, J = 7.8 Hz, 1 H, Ar), 7.32–7.24 (m, 2 H, Ar), 6.13–6.04 (m, 1 H, vinylic CH), 5.69 (s, 1 H), 5.53–5.40 (m, 2 H, vinylic CH_2), 4.69 (d, J = 5.4 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.1, 162.7, 153.3, 132.3, 130.6, 123.8, 123.0, 119.5, 116.7, 115.6, 90.9, 69.7 ppm. IR (KBr): $\tilde{\nu}$ = 3082, 1720, 1399, 1247, 940, 844, 768 cm^{-1}. HRMS: calcd. for 203.0703 $[M + H]^+$; found 203.0702.

4-[(2-Methylallyl)oxy]-2*H*-chromen-2-one (7b): White sticky solid (182 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.8 Hz, 1 H, Ar), 7.54 (t, J = 7.8 Hz, 1 H, Ar), 7.32–7.25 (m, 2 H, Ar), 5.68 (s, 1 H), 5.13 (d, J = 17.1 Hz, 2 H, vinylic CH_2), 4.59 (s, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.1, 162.8, 153.3, 138.4, 132.3, 123.8, 122.9, 116.7, 115.7, 114.5, 90.9, 72.6, 19.3 ppm.

4-Propoxy-2*H*-chromen-2-one (7c): White solid (168 mg, 82% yield); m.p. 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.5 Hz, 1 H, Ar), 7.54 (t, J = 7.5 Hz, 1 H, Ar), 7.32–7.24 (m, 2 H, Ar), 5.66 (s, 1 H), 4.09 (t, J = 6.3 Hz, 2 H, CH_2 of OPr), 1.97–1.88 (m, 2 H, CH_2 of OPr), 1.11 (t, J = 7.2 Hz, 3 H, CH_3 of OPr) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.6, 162.9, 153.3, 132.2, 123.7, 122.9, 116.7, 115.8, 90.3, 70.7, 21.9, 10.4 ppm. IR (KBr): $\tilde{\nu}$ = 2967, 2881, 1708, 1624, 1240, 928, 781 cm^{-1}.

4-(But-3-en-1-yloxy)-2*H*-chromen-2-one (7d): Highly viscous liquid (177 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 4.8 Hz, 1 H, Ar), 7.54 (t, J = 7.2 Hz, 1 H, Ar), 7.31–7.24 (m, 2 H, Ar), 5.95–5.86 (m, 1 H, vinylic CH), 5.67 (s, 1 H), 5.26–5.16 (m, 2 H, vinylic CH_2), 4.17 (t, J = 6.6 Hz, 2 H, CH_2), 2.70–2.66 (m, 2 H, CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.4, 162.9, 153.1, 133.2, 132.2, 123.8, 122.8, 118.0, 116.6, 115.6, 90.3, 68.2, 32.7 ppm.

4-Ethoxy-2*H*-chromen-2-one (7e): White solid (161 mg, 85% yield); m.p. 106–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.8 Hz, 1 H, Ar), 7.53 (t, J = 7.5 Hz, 1 H, Ar), 7.32–7.23 (m, 2 H, Ar), 5.66 (s, 1 H), 4.20 (q, J = 6.9 Hz, 2 H, CH_2 of OEt), 1.57–1.54 (m, 3 H, CH_3 of OEt) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.5, 153.3, 132.2, 123.7, 123.0, 116.6, 115.7, 100.5, (90.3, 90.2), 65.1, 14.0 ppm.

Supporting Information (see footnote on the first page of this article): Detailed experimental methods, optimization chart, NMR study, crystal structures, copies of ^{1}H and ^{13}C NMR spectra, and computational details.

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[1] P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, Germany, **2005**.

[2] For reviews on indium chemistry, see: a) Z.-L. Shen, S.-Y. Wang, Y.-K. Chok, Y.-H. Xu, T.-P. Loh, *Chem. Rev.* **2013**, *113*, 271–401; b) J. S. Yadav, A. Antony, J. George, B. V. Subba Reddy, *Eur. J. Org. Chem.* **2010**, 591–605; c) U. K. Roy, S. Roy, *Chem. Rev.* **2010**, *110*, 2472–2535; d) J. A. J. Pardoe, A. J. Downs, *Chem. Rev.* **2007**, *107*, 2–45.

[3] a) A. N. Pae, Y. S. Cho, *Curr. Org. Chem.* **2002**, *6*, 715–737; b) J. Podlech, T. C. Maier, *Synthesis* **2003**, 633–655; c) V. Nair, S. Ros, C. N. Jayan, B. S. Pillai, *Tetrahedron* **2004**, *60*, 1959–1982; d) R. B. Kargbo, G. R. Cook, *Curr. Org. Chem.* **2007**, *11*, 1287–1309; e) S. Araki, T. Shimizu, P. S. Johar, S.-J. Jin, Y. Butsugan, *J. Org. Chem.* **1991**, *56*, 2538–2542; f) V. J. Bryan, T.-H. Chan, *Tetrahedron Lett.* **1997**, *38*, 6493–6496; g) J. Yoo, K. E. Oh, G. Keum, S. B. Kang, Y. Kim, *Polyhedron* **2000**, *19*, 549–551.

[4] a) L. C. Chao, R. D. Rieke, *J. Org. Chem.* **1975**, *40*, 2253–2255; b) S. Araki, H. Ito, Y. Butsugan, *Synth. Commun.* **1988**, *18*, 453–458; c) S. Araki, Y. Butsugan, *J. Chem. Soc., Chem. Commun.* **1989**, 1286–1287; d) N. Fujiwara, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 4095–4101.

[5] a) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236–2239; *Angew. Chem.* **2009**, *121*, 2270; b) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648–7651; *Angew. Chem.* **2008**, *120*, 7760; c) Z.-L. Shen, Y.-C. Lai, C. H. An Wong, K. K. K. Goh, Y.-S. Yang, H.-L. Cheong, T.-P. Loh, *Org. Lett.* **2011**, *13*, 422–425; d) K. Takami, H. Yorimitsu, H. Shinokubo, S. Matsubara, K. Oshima, *Org. Lett.* **2001**, *3*, 1997–1999; e) K. Lee, J. Lee, P. H. Lee, *J. Org. Chem.* **2002**, *67*, 8265–8268; f) J.-Y. Lee, P. Ho Lee, *J. Org. Chem.* **2008**, *73*, 7413–7416; g) P. Ho Lee, S.-Y. Sung, K. Lee, *Org. Lett.* **2001**, *3*, 3201–3204; h) D. Rodriguez, J. P. Sestelo, L. A. Sarandeses, *J. Org. Chem.* **2004**, *69*, 8136–8139, and references cited therein.

[6] a) N. H. Werstiuk, *Tetrahedron* **1983**, *39*, 205–268; b) Z.-L. Shen, K. K. K. Goh, H.-L. Cheong, C. H. An Wong, Y.-C. Lai, Y.-S. Yang, T.-P. Loh, *J. Am. Chem. Soc.* **2010**, *132*, 15852–15855; c) P. H. Lee, Y. Park, S. Park, E. Lee, S. Kim, *J. Org. Chem.* **2011**, *76*, 760–765; d) J. Mo, D. Eom, S. H. Kim, P. H. Lee, *Chem. Lett.* **2011**, *40*, 980–982.

[7] B. C. Ranu, S. Banerjee, L. Adak, *Tetrahedron Lett.* **2007**, *48*, 7374–7379.

[8] a) I. Garcia-Orozco, M. C. Ortega-Alfaro, J. G. Lopez-Cortes, R. A. Toscano, C. Alvarez-Toledano, *Inorg. Chem.* **2006**, *45*, 1766–1773; b) M. S. Singh, G. C. Nandi, T. Chanda, *RSC Adv.* **2013**, *3*, 14183–14198; c) S. Chowdhury, T. Chanda, S. Koley, B. J. Ramulu, R. C. F. Jones, M. S. Singh, *Org. Lett.* **2013**, *15*, 5386–5389.

[9] a) S. Chowdhury, T. Chanda, G. C. Nandi, S. Koley, B. J. Ramulu, S. K. Pandey, M. S. Singh, *Tetrahedron* **2013**, *69*, 8899–8903; b) S. Masson, A. Thuillier, *Tetrahedron Lett.* **1982**, *23*, 4087–4090.

[10] For different proposed structures of organoindium complexes, see: a) M. J. S. Gynane, I. J. Worrall, *J. Organomet. Chem.* **1974**, *81*, 329–334, and references cited therein; b) S. Araki, H. Ito, Y. Butsugan, *J. Org. Chem.* **1988**, *53*, 1831–1833; c) T. H. Chan, Y. Yang, *J. Am. Chem. Soc.* **1999**, *121*, 3228–3229, and references cited therein; d) M. Yasuda, M. Haga, Y. Nagaoka, A. Baba, *Eur. J. Org. Chem.* **2010**, 5359–5363.

[11] S. Apparao, S. S. Bhattacharjee, H. Ila, H. Junjappa, *J. Chem. Soc. Perkin Trans. 1* **1985**, 641–645, and references cited therein.

[12] a) CCDC-894933 (for **1b**) and -908493 (for **5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif; b) CCDC-938934 (for **7c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] a) J. G. Deshmukh, M. H. Jagdale, R. B. Mane, M. M. Salunkhe, *J. Indian Chem. Soc.* **1986**, *63*, 442–443; b) A. A. Avetisyan, A. G. Alvandzhyan, *Russ. J. Org. Chem.* **2006**, *42*, 1063–1067; c) K. C. Majumdar, A. Biswas, P. P. Mukhopadhyay, *Can. J. Chem.* **2005**, *83*, 2046–2051; d) A. Patra, A. K. Mukhopadhyay, A. K. Mitra, *Indian J. Chem. Sect. B* **1986**, *25*, 1167–1170, and references cited therein.

[14] a) A. Srivastava, V. Mishra, P. Singh, R. Kumar, *J. Appl. Polym. Sci.* **2012**, *126*, 395–407; b) C. Supuran, S. Dedhar, F. Carta, J.-Y. Winum, P. C. McDonald, PCT Int. Patent Appl. 2012070024, **2012**; c) F. Carta, A. Maresca, A. Scozzafava, C. T. Supuran, *Bioorg. Med. Chem.* **2012**, *20*, 2266–2273.

[15] a) V. P. Reddy, K. Swapna, A. V. Kumar, K. Rama Rao, *J. Org. Chem.* **2009**, *74*, 3189–3191; b) V. P. Reddy, A. V. Kumar, K. Swapna, K. Rama Rao, *Org. Lett.* **2009**, *11*, 1697–1700.

[16] T. H. Chan, C. J. Li, M. C. Lee, Z. Y. Wei, *Can. J. Chem.* **1994**, *72*, 1181–1192, and references cited therein.

[17] R. Samuel, C. V. Asokan, S. Suma, P. Chandran, S. Retnamma, E. R. Anabha, *Tetrahedron Lett.* **2007**, *48*, 8376.

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