Bicatalytic Allylation–Cross-Metathesis Reactions as γ-Carbonyl Cation Equivalents

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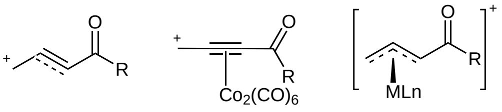
Abstract: The products corresponding to the reactions of arenes and γ-carbonyl cations may be obtained by a one-pot, bicatalytic process involving $InCl_3$-catalyzed arene allylation and cross metathesis with electron-deficient alkenes. The process is successful with electronically neutral and electron-rich arenes, and modestly Lewis basic donor groups are tolerated with an increase in $InCl_3$ loading from 10 mol% to 15 mol%, and in one case, 20 mol%.

Key words: allylation, electrophilic aromatic substitution, indium, metathesis, umpolung

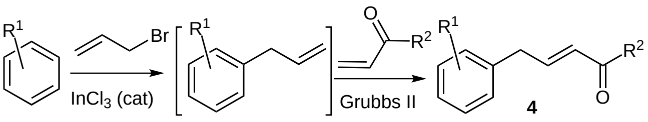
The creation of γ-carbonyl cation equivalents (or 1,5-homo-Michael equivalents) (**1**, Figure 1) is a tactic of increasing importance for functionalizing carbonyl systems by way of umpolung synthons.[1] Among methods not involving rearrangement of the carbon framework,[2] there has been considerable success in the generation and use of γ-carbonyl cationic species stabilized as propargyldicobalt complexes (**2**)[3,4] or iron allyl complexes [**3**, ML_n = $Fe(CO)_4$],[5,6] however, these methods require stoichiometric complexation and decomplexation steps.[7] A number of metal-catalyzed allylation (**3**, M = Pd, Mo, Ir) and propargylation reactions are known, which have been[8] or could be in principle be extended to γ-carbonyl cation equivalents. Unfortunately, these have limited electrophilicity and as such are insufficiently reactive with most arenes.[9] Phosphine-catalyzed γ-nucleophilic attack reactions are known for electron-deficient alkynes or allenes,[10] but these also require strong nucleophiles for successful reaction. Recently, 3,4-allenoates have shown the capability of undergoing gold(I)- or palladium(II)-catalyzed reactions with nucleophiles to give γ-functionalized alkenoates; based on a limited number of cases, strongly activated arene nucleophiles may be employed.[11] In contrast, there have been a number of recent strong Lewis acid catalyzed allylation and propargylation protocols.[12] By far most of these and a few of metal-catalyzed systems[13] require substrates in which the allyl cation is additionally stabilized, rather than being capable of bearing strongly electron-withdrawing groups.

Among the Lewis acid allylation catalysts, indium(III) has been demonstrated recently to be among the most reactive, as they have the ability to induce allylation from substrates with no additional cation stabilizing groups.[14] Fortunately, allylbenzene is an excellent partner in cross metathesis (CM) for carbonyl-substituted alkenes,[15] which are in turn type 2 alkenes with the Grubbs 2nd generation (G2) precatalyst.[16] As a result, we considered it possible that the products corresponding to reaction of γ-carbonyl cations with arenes (**4**, Scheme 1) could be realized by a one-pot, bicatalytic allylation–cross metathesis process involving indium(III). Herein we report our efforts towards this goal.



1 **2** **3**

Figure 1 γ-Carbonyl cations



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Scheme 1 Allylation–cross metathesis protocol

Initial experimentation began with 1,3,5-trimethoxybenzene (**5a**, 3 equiv; Figure 2) as test nucleophile. In the presence of allyl bromide and 4 Å molecular sieves, 10 mol% $InCl_3$ gave conversion to 2-allyl-1,3,5-trimethoxybenzene at reflux in CH_2Cl_2 (20 h), but ceased at 90% conversion. Consequently, 15 mol% $InCl_3$ was employed, to give complete conversion over the same period.[17] At this point, addition of Grubbs II precatalyst and methyl acrylate (**6a**, 3 equiv) showed complete conversion to **4a** at 10 mol% catalyst loading. Unfortunately, the analogous experiments employing methyl vinyl ketone (**6b**) as CM partner afforded no indication of cross metathesis, but rather ^1H NMR spectral analysis revealed the presence of extensive amounts of the product of conjugate addition of 1,3,5-trimethoxybenzene to methyl vinyl ketone (**7**, Figure 3).

In view of the apparent limitations of this protocol, a number of additives were screened in order to minimize the conjugate addition side reactions caused either by residual indium(III) or by the HBr liberated in the allylation process. It was found that addition of $NaHCO_3$ (3 equiv), prior to the addition of the electron-deficient alkene and G2 precatalyst, enabled the CM reaction with methyl vinyl ketone to proceed to give **4b** with 7.5 mol% G2, and with

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methyl acrylate allowed a reduction in the required amount of Grubbs II precatalyst for conversion to **4a** to 5 mol%.

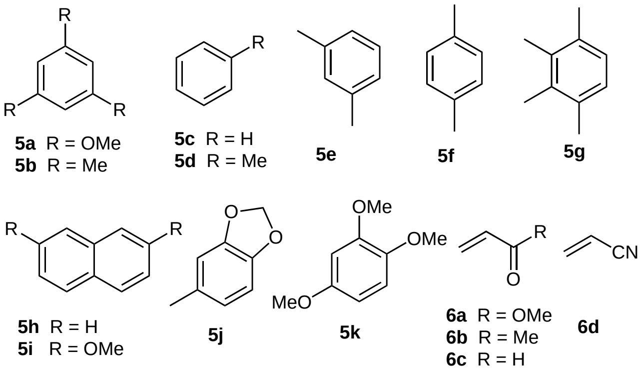

Figure 2 Selected arenes and electron-poor alkenes

Experimentation moved at this point to mesitylene (**5b**), chosen as a nucleophile representative of arenes without Lewis basic groups. In our hands, and consistent with the work of Cook,[14a] complete consumption of allyl bromide now occurred with 10 mol% at room temperature in CH_2Cl_2 (20 h), but instead of simple allylation, only the products of allylation followed by HBr addition to the alkene (**8**, Figure 3) were observed in the ^{1}H NMR spectrum of the reaction mixture. Fortunately, a simple switch in protocol to the addition of solid $NaHCO_3$ (3 equiv, in addition to the 4 Å molecular sieves) prior to the addition of allyl bromide reduced the amount of **8** to at most trace levels, and did not appear to interfere substantially with the allylation rate. As a result, this protocol was adopted as the general one, with modifications in $InCl_3$ and G2 loadings to give complete conversions. In most cases, the amount of nucleophile was fixed at three equivalents, except in the cases of arene nucleophiles sufficiently volatile to be removed readily under vacuum. In those instances larger excesses were employed. Under these conditions the 1,3,5-trimethoxybenzene (**5a**)–methyl acrylate (**6a**) combination afforded **4a** in 67% yield, the 1,3,5-trimethoxybenzene–methyl vinyl ketone (**6b**) combination afforded **4b** in 71% yield, and the mesitylene–methyl acrylate combination gave **4c** in 72% yield (Table 1). Chromatographic separation of each allylation–cross metathesis product was readily accomplished; this is in contrast to the simple allylation intermediates, which were difficult to separate from the arene nucleophile. Each of **4a**–**n** was isolated as exclusively the *E*-isomer, while ^{1}H NMR spectra of the crude reaction products showed prepurification *E*/*Z*-ratios of $\geq$96:4.

One other side product could be observed during this process, during the reactions involving methyl acrylate, which was the formation of small amounts of β-arylalkenoate (cinnamate) **9**. This material was believed to stem from RuH-induced isomerization of the alkene function of the allylated arene into conjugation with the arene, followed by its cross metathesis.[18] In most cases this was quite minimal in amount ($\leq$4% relative to the intended product), and decreased with increasing *ortho*-substitution, but was a substantial by-product in the case of benzene (**5c**, 10 equiv) as nucleophile and methyl acrylate (10% of **8** relative to **4d**). For this case 12 mol% of 1,4-benzoquinone[19] was added to the reaction mixture immediately prior to the 5 mol% G2 precatalyst; this modification reduced the amount of cinnamate by-product to trace amounts (1–1.5% relative to **4d**) and allowed the formation of **4d** in good yield (75%).

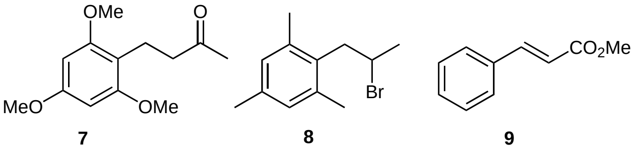

Figure 3 Reaction side-products

The general trends with mesitylene also applied to other arenes lacking Lewis basic functions, in that the $InCl_3$ (10 mol%), $NaHCO_3$ (3 equiv), CH_2Cl_2, room temperature conditions were sufficient for complete allyl bromide consumption (Table 1, Figure 4). Toluene (**5d**, 10 equiv) ultimately afforded **4e** (82% yield) as a mixture of

Table 1 Results of the Allylation–Cross Metathesis

Arene (equiv)	$InCl_3$ (mol%)	Temp (°C)	**6**	G2 (mol%)	**4**	Yield (%)
5a (3)	15	40	**6a**	5.0	**4a**	67
5a (3)	15	40	**6b**	7.5	**4b**	71
5b (3)	10	22	**6a**	4.6	**4c**	72
5c (10)	10	22	**6a**	5.0[a]	**4d**	75
5d (10)	10	22	**6a**	5.4	**4e**	82[b]
5e (10)	10	22	**6a**	5.0	**4f**	72[c]
5f (5)	10	22	**6a**	5.0	**4g**	65
5g (10)	10	22	**6a**	5.0	**4h**	61
5h (3)	10	22	**6a**	2.8	**4i**	61[d]
5i (3)	15	40	**6a**	2.4	**4j**	73
5j (3)	15	40	**6a**	3.2	**4k**	61[e]
5k (3)	20[f]	61	**6a**	5.0	**4l**	60
5b (3)	10	22	**6b**	3.7	**4m**	68
5b (3)	10	22	**6c**	8.9	**4n**	61
5b (3)	10	22	**6d**	7.3[g]	**4o**	63[h]

[a] 1,4-Benzoquinone (12 mol%) was added.
[b] **4e**/**4e′**/**4e″** = 60:30:10.
[c] **4f**/**4f′** = 70:30.
[d] **4i**/**4i′** = 87:13.
[e] **4k**/**4k′** = 85:15.
[f] Reaction conditions: $CHCl_3$, reflux, 2 d.
[g] Hoveyda–Grubbs II catalyst was employed
[h] *Z*/*E* = 71:29.

regioisomers (*o*/*p*/*m* [**4e**/**4e′**/**4e″**] = 60:30:10), while *m*-xylene (**5e**, 10 equiv) gave a mixture of 1,2,4- and 1,2,3-substitution products **4f** (1,2,4-/1,2,3- [**4f**/**4f′**] = 70:30) in 72% yield. While *p*-xylene (**5f**, 5 equiv) and 1,2,3,4-tetramethylbenzene (**5g**, 10 equiv) gave **4g** (65% yield) and **4h** (61% yield) in straightforward fashion, naphthalene (**5h**) gave **4i** with a small amount of the C-2 substitution isomer (**4i′**) along with the C-1 isomer (C-1/C-2 [**4i**/**4i′**] = 87:13, 61% yield).

The other alkoxyarenes employed as nucleophiles showed significant similarities to 1,3,5-trimethoxybenzene, in that a higher $InCl_3$ loading (15 mol%) in CH_2Cl_2 at reflux (with 3 equiv $NaHCO_3$) was required for complete consumption of allyl bromide. Under such conditions, 3,4-methylenedioxytoluene (**5i**) and 2,6-dimethoxynaphthalene (**5j**) were converted into **4j** (73% yield) and **4k** (60% yield) following cross metathesis, the latter case predominantly as the C-1 isomer (C-1/C-3 [**4k**/**4k′**] = 85:15). 1,2,4-Trimethoxybenzene (**5k**) reacted more sluggishly, possibly due to the presence of methoxy groups capable of chelation to indium(III), but the use of 20 mol% $InCl_3$ in $CHCl_3$ at reflux (2 d) slowly gave complete consumption of allyl bromide, and ultimately product **4l** (60% yield).

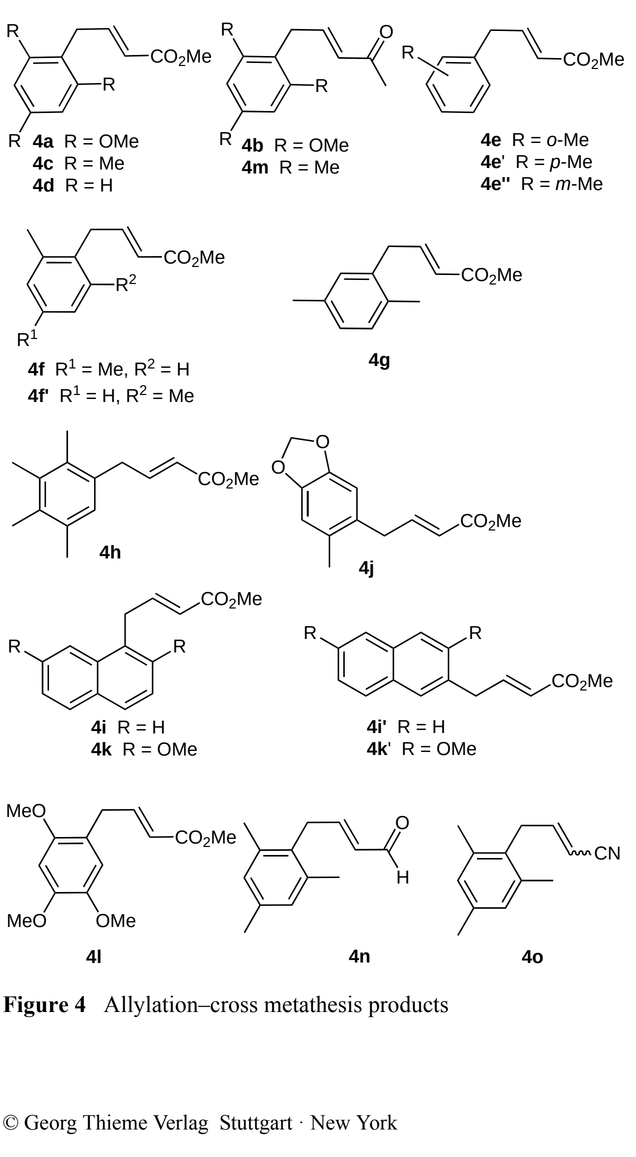

Figure 4 Allylation–cross metathesis products

Finally, a small number of electron-deficient alkenes other than methyl acrylate were investigated in conjunction with mesitylene (**5b**) for the allylation–cross metathesis protocol. Use of methyl vinyl ketone (**6b**) gave **4m** (68% yield) readily, and in contrast to the case employing 1,3,5-trimethoxybenzene, required only 4 mol% of G2 for completion of the CM step. Acrolein (**6c**) also served as suitable partner in the allylation–cross metathesis process, although an increased amount of G2 (9 mol%) was required to obtain **4n** in 61% yield. Finally, the use of acrylonitrile (**6d**) and Hoveyda–Grubbs II precatalyst (HG2) (7 mol%) enabled the formation of **4o** (63% yield). As is established in CM reactions with acrylonitrile with HG2, the *Z*-isomer of **4o** predominated (*Z*/*E* = 71:29).[20]

In summary, we have demonstrated that a bicatalytic, one-pot indium(III) allylation–cross metathesis protocol can afford the products corresponding to the reaction of γ-carbonyl cations with arene nucleophiles.[21] Relative to the complementary Nicholas reaction chemistry, arenes of somewhat more modest nucleophilicity, including benzene, may be employed in the current work. In comparison to other catalytically generated γ-carbonyl cation equivalents, the current protocol may employ far less reactive nucleophiles. Moderately Lewis basic substituents are tolerated in the allylation step, although somewhat more aggressive conditions are required.

Future work will be concerned with the use of substituted allyls for the goal of creating products with γ-substitution, and with other nucleophiles compatible with the bicatalytic allylation–CM protocol.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) (a) **Representative Procedure**: To a suspension of InCl$_3$ (0.0216 g, 0.098 mmol, 15 mol%) and 4 Å molecular sieves (ca. 0.4 g) in CH$_2$Cl$_2$ (6 mL) were added 1,3,5-trimethoxybenzene (0.328 g, 1.95 mmol), NaHCO$_3$ (0.164 g, 1.95 mmol), and allyl bromide (55.0 μL, 0.650 mmol). The mixture was heated to reflux for 20 h. The mixture was removed from the heating source, at which time methyl acrylate (0.18 mL, 2.0 mmol) and Grubbs II precatalyst (0.0143 g, 0.0168 mmol, 2.6 mol%) were added. Following heating to reflux for 10 h, removal of the volatiles under reduced pressure and preparative TLC (PE–Et$_2$O, 2:1) afforded **4a** as a colorless solid; yield: 0.1167 g (0.438 mmol, 67%). IR (neat): 3000 (m), 2949 (m), 1716 (s), 1652 (s) cm^{-1}. ^{1}H NMR (500 MHz): $\delta = 7.05$ (dt, $J = 15.6$, 6.4 Hz, 1 H), 6.14 (s, 2 H), 5.72 (dt, $J = 15.6$, 1.6 Hz, 1 H), 3.82 (s, 3 H), 3.79 (s, 6 H), 3.69 (s, 3 H), 3.46 (dd, $J = 6.4$, 1.6 Hz, 2 H). ^{13}C NMR (125 MHz): $\delta = 167.5$, 160.0, 158.7, 148.4, 120.1, 106.4, 90.5, 55.6, 53.3, 51.2, 25.5. MS: $m/z = 266$ [M$^+$]. HRMS (EI): m/z calcd for C$_{14}$H$_{18}$O$_5$: 266.1154; found: 266.1144.