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An S_N2' displacement approach to allenyl acetates

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ABSTRACT

Reaction of cuprates derived from $R^3MgBr/CuI/LiBr$ (R^3 = *n*-alkyl) with $R^1C{\equiv}CCH(O_2CR^2)_2$ (R^1 = sp^2 hybridised substituent, R^2 = mainly Me, alkyl, Ph) provides access to allenyl esters $R^1R^3C{=}C{=}CH(O_2CR^2)$ (51–88%). Such species are not accessible via rearrangement of precursor propargylic $R^1R^3C(O_2CR^2)C{\equiv}CH$.

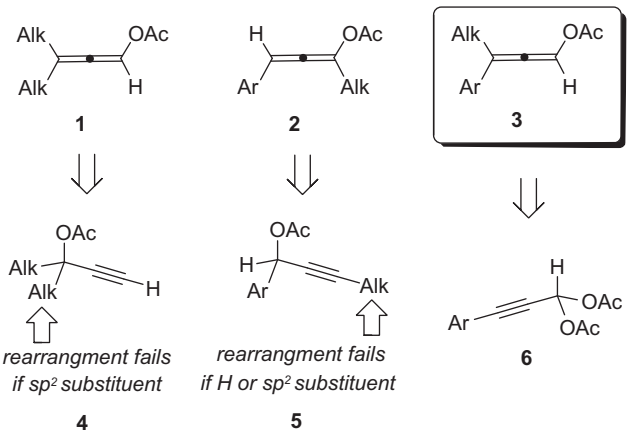
As part of a mechanistic study we recently needed access to the specifically substituted allenyl acetates **3** (Scheme 1) that are not present in the primary literature. Typically, allenylic acetates are prepared by rearrangement of propargylic precursors **4** or **5**. For example, dialkyl substituted **4** under Cu-[1] (or better Rh-[2] or Ag-catalysis[3]) provides **1** in good yields. Unfortunately, this methodology fails if one or both of the alkyl units are replaced by an aryl or vinyl unit.[4] Similarly, Ag-catalysed rearrangement of **5** to give **2** proceeds in high yields.[5] However, terminal propargylic systems (as required for the preparation of **3**) cannot be used—they either result in oligomerisation or cyclisation of **5** under Au-NHC ligand/$AgBF_4$ catalysis.[5a]

In the absence of a viable propargylic rearrangement strategy we considered an S_N2' displacement of one of the acetates within **6** using a suitable organometallic.[6] While the propargylic diacetates **6** are inordinately rare,[7] formation of such derivatives from more general RCHO units and Ac_2O under Lewis acid catalysis is well precedented.[8] However, such procedures often require use of excess Ac_2O which we found co-elutes with **6** on chromatography. A short optimisation study[4] indicated that catalytic $FeCl_3$ provided a chemoselective process giving synthetically viable yields of **6** when using only 1 equiv of anhydride (Table 1).[9]

In the case of a *p*-methoxy substituent (**6d**) the reaction was much slower leading to lower yields, presumably due to electronic deactivation of the intermediate onium species. Pivalic anhydride and benzoic anhydrides were also tolerated in the reaction but they were not as efficient as Ac_2O.

Optimisation of S_N2' additions was carried out on substrate **6a**. While cuprate reagents derived from organolithium reagents gave only traces of **3**, those from RMgBr generated significant yields (24–72%) at 0 °C in the presence of LiBr (Table 2). Lowering the temperature to −10 °C and changing the Grignard solvent provided the highest amount of **3** while EtMgBr proved to be a superior nucleophile to its methyl analogue.

The optimised conditions were applied to a representative range of diacetate starting materials **6** (Table 3)[10] allowing us to attain the desired substitution pattern in allene **3** on up to gram scales at least. The following limitations were found: addition of MeMgBr gave lower yields compared to higher *n*-alkyl Grignards, presumably due to the high bond strength of M-Me derivatives.[11] In the present system *sec*- and aromatic Grignard reagents led to unsatisfactory yields. Attempts to make the process catalytic in copper were thwarted by the propensity of **3** to undergo further coupling reactions.[12] Allenyl carboxylates are distinctly electron-rich due to their enol-like structure. This leads to an upfield shift of their central allene carbons (e.g., those in **1** typically show δ_C 189–190 compared to the more normal 205–215 ppm range expected for substituted allenes[13]). For the compounds **3** isolated herein the equivalent range was δ_C 192–193 for the central allene carbon. To ensure that the desired substitution pattern had been attained, a crystallographic study of one representative example **3fb** was carried out which confirmed the connectivity (Fig. 1).[14]



Scheme 1. Disconnections for the preparation of allenyl acetates (Alk = sp^3 substituent, Ar = sp^2 substituent).

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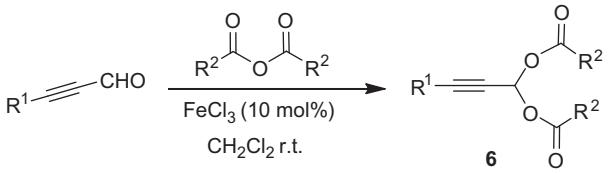
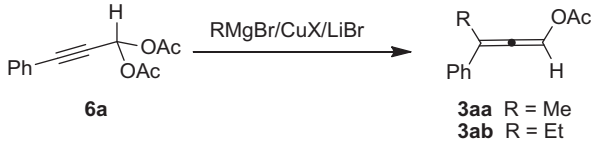
Table 1
Preparation of diacetates **6** using 1 equiv of anhydrides



Product	R^1	R^2	Time (h)	Yield (%)[a] (brsm)[b]
6a	Ph	Me	1	75 (86)
6b	*p*-MeC_6H_4	Me	2	63 (89)
6c	*m*-MeC_6H_4	Me	3	72
6d	*p*-$MeOC_6H_4$	Me	24	26 (54)
6e	1-Cyclohexenyl	Me	24	49 (70)
6f	$(CH_2)_2Ph$	Me	5	62 (79)
6g	Phenanthrenyl	Me	18	51 (77)
6h	Ph	*t*-Bu	0.5	46
6i	Ph	Ph	6	20

[a] Isolated yield.
[b] Yield based on recycled starting material.

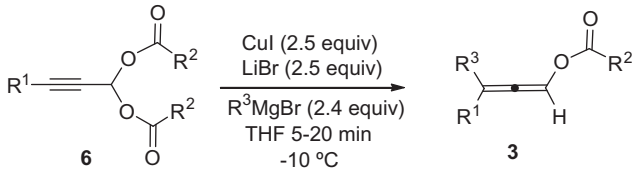
Table 2
Optimisation of RMgBr/CuX/LiBr addition to **6**



RMgBr (equiv)	CuX (equiv)	LiBr (equiv)	Solvent	Temp (°C)	Yield **3** (%)[a]
MeMgBr (2.4)	CuI (2.5)	2.5	THF	0	30
MeMgBr (2.4)	CuCN (2.5)	5	THF	0	24
EtMgBr (4.8)	CuI (5.0)	5	Et_2O	0	35
EtMgBr (4.9)	CuI (5.0)	5	THF	0	52
EtMgBr (2.4)	CuI (2.5)	2.5	THF	0	72
EtMgBr (2.4)[b]	CuI (2.5)	2.5	THF	−10	88

[a] Isolated yield.
[b] Grignard as a 1.0 M solution in MTBE; all other cases 3.0 M in Et_2O.

Table 3
Preparation of allenes **3** by S_N2' displacement with RMgBr



Product	R^1	R^2	R^3	Yield **3** (%)[a]
3ab	Ph	Me	Et	88
3aa	Ph	Me	Me	30
3ac	Ph	Me	*n*-Bu	65
3ad	Ph	*t*-Bu	Et	78
3ae	Ph	Ph	Et	74
3bb	*p*-Tolyl	Me	Et	81
3cb	*m*-Tolyl	Me	Et	46
3db	1-Cyclohexene	Me	Et	67
3eb	$(CH_2)_2Ph$	Me	Et	51
3fb	Phenanthrenyl	Me	Et	51

[a] Isolated yield.

In addition to accessing **3** as a general class of reagents we had need of one example which was appreciably enriched in one enantiomer. Fortunately, compound **3ab** undergoes enzymatic kinetic resolution (Scheme 2) using a supported lipase attained from *Burkholderia cepacia* (referred to here as PS Amano SD). Addition of an excess of this material, in small portions, to (±)-**3ab** gave a 54% isolated yield of *E*/*Z*-**7** (an approximate 1:1 mixture) leading to recovery of 45% isolated yield of (+)-**3ab** in 85% ee as determined by chiral GC within 1.5 h.[15] Extending the reaction time to 2 h led to a slight increase in selectivity to 88% ee but a significant drop in the amount of (+)-**3ab** recovered (31%). Based on literature precedents[16] using this lipase, we tentatively suggest that (+)-**3ab** corresponds to the (*S*)-enantiomer.[16] Attempts to confirm this via crystalline **3fb** were thwarted by an apparent size restriction in the lipase active site, even a moderate increase in the size of the aryl group was not tolerated, for example, (±)-**3bb** gave only a 45% ee at >75% conversion with the equivalent hydrolysis products **7′** as an *E*/*Z* mixture.

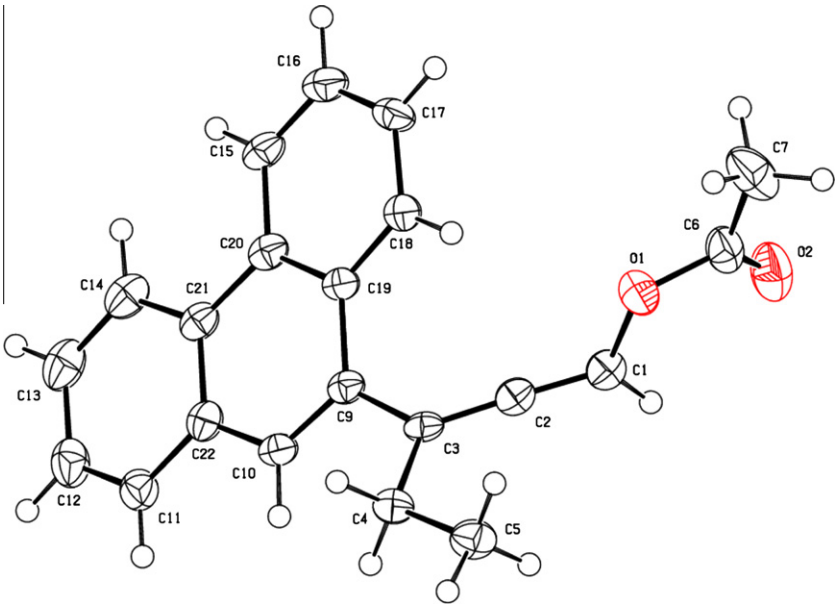
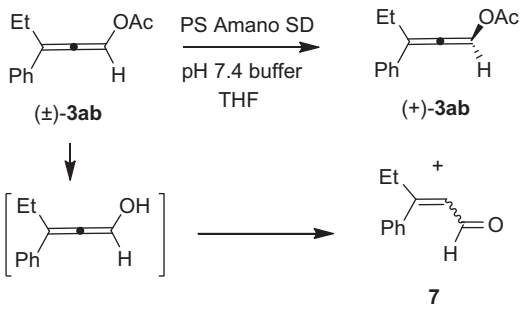


Figure 1. Structure of **3fb**. Key bond distances C1–C2 1.289 Å, C1–O1 1.407 Å, C2–C3 1.311 Å, C3–C4 1.514 Å, C3–C9 1.495 Å, C6–O2 1.201 Å.



Scheme 2. Lipase-promoted kinetic resolution of allenyl acetate (±)-**3ab**.

In conclusion a new S_N2' displacement strategy allows access to allenyl acetates of the structure ArRC═C═CH(OAc) that are not attainable from traditional routes employing rearrangement of propargylic acetates. In some cases the resulting acetates undergo lipase-promoted kinetic resolution resulting in enantiomerically enriched species (45–88% ee). The scope and range of materials are presently under investigation in our laboratory as is their use as mechanistic probes in transition metal promoted catalysis.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.013.

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9. Typical procedure: anhydrous $FeCl_3$ (0.24 g, 1.5 mmol, 10 mol%) was suspended in CH_2Cl_2 (150 ml) and left to stir for 15 min before addition of RC≡CCHO (15 mmol) in 10 ml of CH_2Cl_2 followed by Ac_2O (1.4 ml, 15 mmol). After 3 h the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (100 ml) and washed with $NaHCO_3$ until neutral. The washings were back extracted with CH_2Cl_2 (50 ml). The combined organic fractions were dried ($MgSO_4$), evaporated and purified by flash column chromatography (30:1–10:1 petroleum ether:EtOAc). Representative data, **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51–7.48 (m, 3*H*), 7.38–7.31 (m, 3*H*), 2.15 (s, 6*H*); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ_C 168.1, 132.1, 129.5, 128.3, 81.4, 80.0, 20.7; IR ν_{max} 3620, 3478, 3010, 2976, 2895, 2240, 1826, 1767, 1372, 1245, 1126, 1046, 956, 877; MS *m*/*z* (ESI) for $C_{13}H_{12}O_4Na$ [M+Na] calcd 255.0628, found 255.0624.
10. Typical procedure: Dry CuI (0.62 g, 3.3 mmol, 2.5 equiv) and LiBr (0.28 g, 3.3 mmol, 2.5 equiv) under argon were cooled to −10 °C and 25 ml of THF was added. A solution of EtMgBr (1 M in MTBE, 3.2 ml, 3.2 mmol, 2.4 equiv) was added slowly and after 10 min, diacetate **6** (1.3 mmol) was added in THF (5 ml). After 30 min, the reaction was quenched with saturated aqueous NH_4Cl/NH_3 solution. The mixture was diluted with Et_2O (150 ml), the organic phase was separated and washed with NH_4Cl/NH_3 solution three, four times or until the aqueous phase was no longer blue. The organic fraction was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, evaporated and purified by flash column chromatography (30:1 *n*-pentane:Et_2O) to give the products as yellow oils (except **3fb** which was a colourless solid). Representative data, **3ab**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (t, 1*H*, *J* = 2.6 Hz), 7.48–7.45 (m, 2*H*), 7.37–7.27 (m, 3*H*), 2.65–2.51 (m, 2*H*), 2.17 (s, 3*H*), 1.18 (t, 3*H*, *J* = 7.8 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ_C 192.5, 168.7, 128.4, 128.0, 126.6, 121.8, 113.4, 24.3, 20.9, 12.2; IR ν_{max} 3010, 1750, 1372, 1240; MS *m*/*z* (ESI) for $C_{13}H_{14}O_2Na$ [M+Na] calcd 225.0886, found 225.0893.
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14. Compound **3fb** crystallises from *i*-PrOH: $C_{21}H_{18}O_2$, *M* = 302.35, monoclinic, *a* = 8.380(2), *b* = 7.611(2), *c* = 24.952(7) Å, *β* = 94.366(5), *U* = 1586.8(7) Å^3, *T* = 150(2) K, space group $P2_1/c$ (no. 14), *Z* = 4. Full crystal data for (**3fb**) have been deposited with the Cambridge Crystallographic Data Centre (CCDC reference number 760895). These data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/data_request/cif.
15. To (±)-3-phenylpenta-1,2-dienyl acetate **3ab** (105 mg, 0.52 mmol) were added THF (0.2 ml) and phosphate buffer (15 ml, pH 7.4) with vigorous stirring. PS Amano SD lipase (400 mg) was added with vigorous stirring in small portions. After 2 h, the reaction mixture was extracted with Et_2O (5 × 5 ml) and the combined organics were concentrated under reduced pressure. The product was purified by flash column chromatography (30:1 *n*-pentane:Et_2O). A sample of **3ab** with 88% ee (confirmed by chiral GC) gave $[\alpha]_D$ +83.9 (*c* = 0.65, $CHCl_3$).
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