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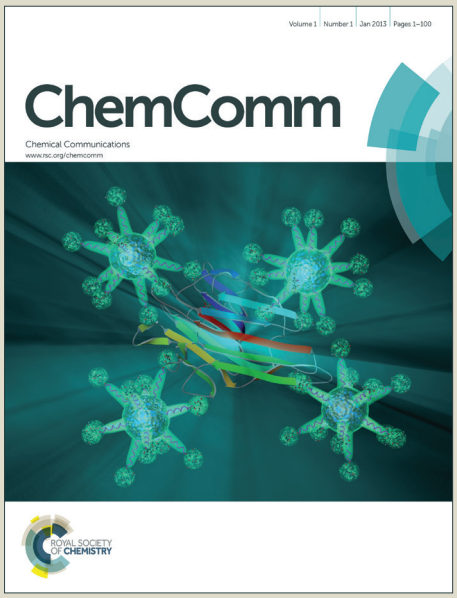

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Rhodium-catalysed alkoxylation/ acetalization of diazo compounds: One-step synthesis of highly functionalised quaternary carbon centres

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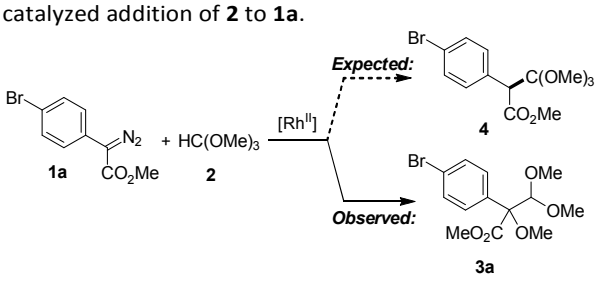
Jola Pospech,[a] Alastair J. J. Lennox[a] and Matthias Beller[a]*

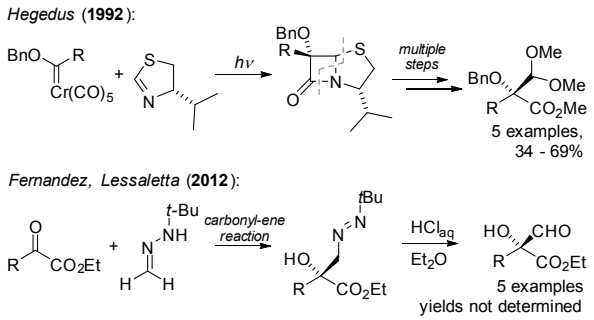
An intermolecular tandem reaction for the rapid build-up of densely functionalised α-alkoxy-β-oxo-esters has been developed. This novel process applies the easy to handle trimethyl orthoformate as a C1-building block in the rhodium(II)-catalysed alkoxylation/acetalization of donor-acceptor substituted diazo compounds. The concomitant C–O/C–C bond formation reaction gives products with unique quaternary carbon centers, substituted by groups of different oxidation level (ester, protected aldehyde and alkoxide).

Rhodium(II) mediated C–C and C–X bond forming reactions have proven to be a powerful approach to the functionalization of organic molecules. Opportunities provided by rhodium(II)-catalysed C–C coupling chemistry have been unravelled by the groups of Doyle,[1] Padwa[2] and Davies.[3] Since exploration in the field began, this strategy has been applied to the synthesis of natural products and pharmaceuticals, which has recently been extensively reviewed.[4] However, with limited exceptions,[5] there remain gaps in the use of C1-building blocks to construct functionalised molecules in a controlled manner. Towards this end, we attempted to implement C1-building blocks into molecular scaffolds applying the logic of C-H bond functionalization.[6] In terms of rhodium(II)-catalysis we reasoned that an adequate C1-source had to possess an electronically stabilised and sterically accessible C-H bond, such as an unsubstituted acetal. We thus considered a protocol employing trimethyl orthoformate as a potential precursor, where the insertion of a rhodium carbenoid into the isolated central C–H bond would grant access to synthetically valuable derivatives.

We selected the readily accessible 4-bromophenyl diazoacetate (**1a**) as a model substrate. At ambient temperature, it was reacted with trimethyl orthoformate (**2**) in **Scheme 1.** Unexpected reaction outcome in the Rh-catalyzed addition of **2** to **1a**.



Scheme 2. Upper: Multi-step synthesis of chiral α-(alk)oxy-β-oxo esters. Lower: Synthesis of unstable α-hydroxy-β-oxo esters.



the presence of a suitable Rh(II)catalyst. Having expected direct insertion into the carbenoid, leading to orthoester **4**, (Scheme 1), we were surprised to isolate a different compound. Full characterisation (^{1}H- and ^{13}C-NMR, HRMS, X-ray crystallography[7]) of the resulting crystalline material revealed that in place of C–H bond cleavage in the ortho ester, a tandem alkoxylation/acetalization sequence occurred, yielding a tertiary α-alkoxy-β-oxo-ester (**3a**) as the major product.

Densely functionalized α-alkoxy-β-oxo-esters, such as **3a**, are versatile and potentially important structures in synthetic chemistry. Extensive studies and noteworthy advances have

[a] Leibniz-Institute for Catalysis at the University of Rostock, Albert-Einstein-Strasse 29a, D-18059 Rostock, Germany.

† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization for all new compounds, copies of ^{1}H and ^{13}C NMR spectra and X-ray data for compounds **3a**, **9** and **11**. See DOI: 10.1039/x0xx00000x

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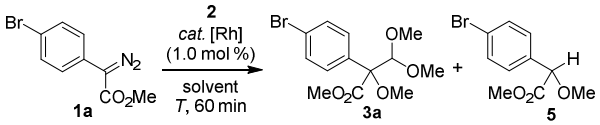
Table 1. Optimization of reaction conditions in the rhodium(II)-catalyzed alkoxylation/acetalization (masked formylation) of diazo compound **1a**.



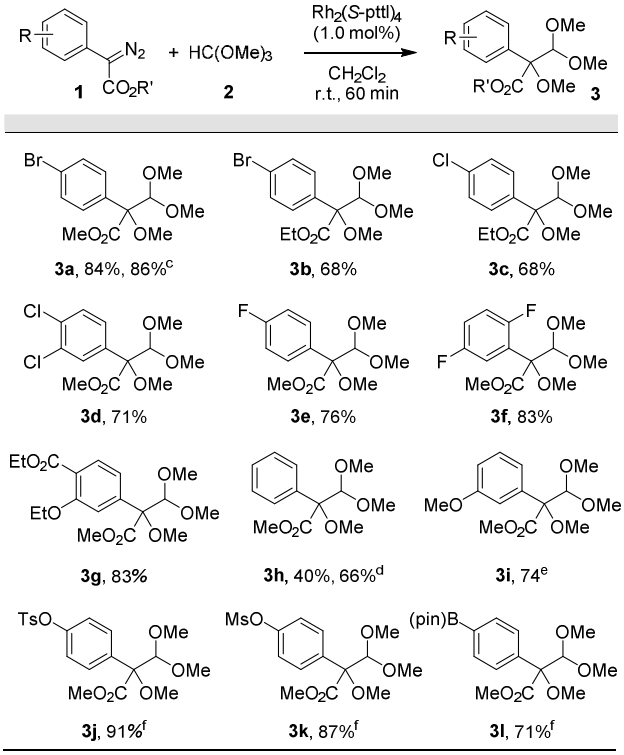
entry[a]	Rh(II) cat.	solvent	*T* [°C]	conv. [%][b]	ratio **3a**/**5**
1	none	$CHCl_3$	23	0	-
2	$Rh_2(OAc)_4$	$CHCl_3$	23	0	-
3	$Rh_2(OPiv)_4$	$CHCl_3$	23	10	1:1
4	$Rh_2(OOct)_4$	$CHCl_3$	23	38	8:1
5	$Rh_2(OAd)_4$	$CHCl_3$	23	27	1:1
6	$Rh_2(tpa)_4$	$CHCl_3$	23	12	1:1
7	$Rh_2(esp)_2$	$CHCl_3$	23	49 (41)	10:1
8	Rh_2(S-DOSP)$_4$	$CHCl_3$	23	48 (45)	5:1
9	Rh_2(S-nttl)$_4$	$CHCl_3$	23	28	3:1
10	Rh_2(S-pttl)$_4$	$CHCl_3$	23	77 (71)	13:1
11	Rh_2(S-ptad)$_2$	$CHCl_3$	23	55	9:1
13	Rh_2(S-pttl)$_4$	1,2-$C_2H_4Cl_2$	23	86 (74)	13:1
14	Rh_2(S-pttl)$_4$	PhMe	23	36	9:1
15	Rh_2(S-pttl)$_4$	PhCl	23	79 (78)	18:1
16	Rh_2(S-pttl)$_4$	2,2-DMB	23	56	13:1
17	**Rh_2(S-pttl)$_4$**	**CH_2Cl_2**	**23**	**86 (84)**	**18:1**
18	Rh_2(S-pttl)$_4$	CH_2Cl_2	40	82 (81)	17:1
19	Rh_2(S-pttl)$_4$	CH_2Cl_2	0	51	7:1

[a] Reactions were carried out with 1a (0.2 mmol) and 2 (1.0 mmol). b Conversions were determined by GC analysis; mesitylene was used as internal standard. Values in parentheses indicate isolated yields. tpa := triphenylacetate; esp := α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid; DOSP := dodecyl-phenyl-sulfonyl-pyrrolidinecarboxylate; pttl := *N*-phthaloyl-tert-leucinate; nttl := *N*-(1,8-naphthaloyl)-*tert*-leucinate; ptad := (1-adamantyl)-(*N*-phthalimido)acetato; 2,2-DMB := 2,2-dimethylbutane.

been made to the synthesis of the related α-hydroxy-β-the ketone, the synthesis of tertiary α-(hydr/alk)oxy-β-oxo-esters has been far less explored. To the best of our knowledge only two reports extend to this composition of functionality (Scheme 2). The earlier example, described by Hegedus and co-workers,[9] followed a chiral-pool approach to generate optically active quaternary carbon centres using a photo-induced addition of stoichiometric chromium-carbene complexes to valine-derived thiazolines. Three further steps were required to access the desired 2-methoxy-3-oxo-2-propanoates in moderate yields and limited substrate scope. More recently, Fernández and Lassaletta described a formal carbonyl-ene reaction of formaldehyde *tert*-butyl hydrazone with α-keto esters for the synthesis of the corresponding carbinols.[10] The unprotected α-hydroxy-β-oxo-esters proved to be unstable towards purification and only crude mixtures were obtained. Thus, with protection of the aldehyde and hydroxyl, there is lacking a straightforward and general method to generate this type of quaternary carbon centre. Towards this end, we report herein on the development of the first tandem alkoxylation/masked formylation reaction via Rh(II)-catalyzed concomitant C–O and C–C bond formation.

Experiments surveying the reaction conditions are summarized in Table 1. The simple dirhodium carboxylate complexes catalyzed insertion of the rhodium-carbenoid into a

Table 2. Reaction scope in the rhodium(II)-catalyzed alkoxylation/acetalization (masked formylation) of diazo compounds (**1**).[a,b]



[a] Reaction conditions: a solution of **1** (0.4 mmol) and **2** (1.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise (1 h) to a stirring solution of **2** (1.0 mmol) and Rh_2(*S*-pttl)$_4$ (1.0 mol %) in CH_2Cl_2 (0.3 mL) at ambient temperature; [b] isolated yields of pure product are shown; [c] reaction on 4.46 mmol scale with 0.5 mol % Rh_2(*S*-pttl)$_4$; [d] PhCl at 60 °C; [e] PhCl at 80 °C with 10 equiv. **2**; [f] 0.25 mmol scale.

C–O bond of trimethyl orthoformate, yielding 2-aryl-2-methoxy acetate **5** as the major side product, whilst the desired product was only formed in modest yield (entries 2-6). Gratifyingly, C–C bond formation was more pronounced when $Rh_2(esp)_2$ was employed as catalyst, yielding **3a** in 41% isolated yield at ambient temperature (entry 7). Further catalyst screening revealed an enhanced activity for masked formylation over the simple alkoxylation using Rh_2(*S*-pttl)$_4$ (entry 10) and Rh_2(*S*-ptad)$_4$ (entry 11). After other reaction parameters were explored (entries 13-19), optimal results were achieved using the air stable and easily prepared Rh_2(*S*-pttl)$_4$ catalyst in dichloromethane (entry 17) at room temperature. No improvement in the conversion was observed when running the reaction at 0 °C or 40 °C. Higher yields were recorded using an excess of the inexpensive trimethyl orthoformate, and drop-wise addition of the diazo compound was required to attenuate dimerization of the substrate. Under these optimized conditions, a pure sample of 2,3,3-trimethoxypropanoate (**3a**) was obtained in 84% isolated yield after column chromatography.

With optimized reaction conditions in hand, the scope of the tandem alkoxylation/acetalization reaction was explored

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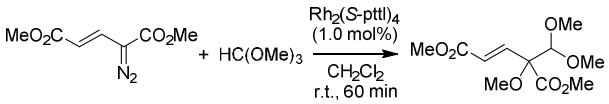
(Table 2). Both methyl and ethyl esters led to the desired product, albeit with a slight reduction in yield when using the ethyl derivatives **1b** and **1c**.[11] Halide substituted aryl substrates were all reliably accommodated, providing valuable bromo- (**3a** and **3b**), chloro- (**3c** and **3d**) and fluoro (**3e** and **3f**) bearing products in good yields. Ester, alkoxy, tosylate, mesylate and boronic ester functionalities were also tolerated and gave good yields of their corresponding products (**3g**, **3i**-**3l**). A modest yield was achieved in the unsubstituted substrate (**3h**), which was found to improve when switching the conditions from dichloromethane at 40 °C to chlorobenzene at 60 °C. Competitive dimerization was more pronounced with electron-donating substituents, nevertheless, utilizing a greater concentration of **2** successfully attenuated the side-reaction and alkoxy groups in the *meta*-position (**3i**) were well tolerated. We were discouraged into testing aryl moieties with other ortho substituents, as they have been shown to give beta lactones or undergo intramolecular cyclisation.[12] Finally, the process was found to up-scale well, as **1a** was converted to **3a** on a gram-scale and isolated in 86% yield using half the normal amount (0.5 mol%) of rhodium catalyst. To our surprise, the reaction was highly selective towards the conversion of trimethylorthoesters, as higher analogues, such as triethyl or tributyl orthoformates, did not serve as competent coupling partners.

We were pleased to find that vinyldiazo acetate **6** was an equally potent coupling partner in the alkoxylation/acetalization reaction.[13] Hence, the dimethyl glutaconoate derivative **7** was obtained in 53% isolated yield (Scheme 3).

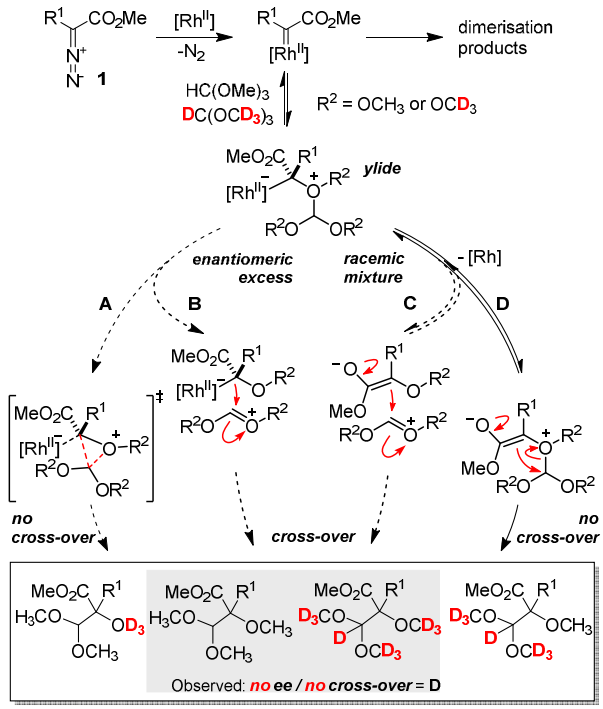
Scheme 3. Rhodium-catalyzed alkoxylation/acetalization of dimethyl diazoglutaconoate (**6**), reaction performed on 0.2 mmol scale.



6 **2** **7** 53%

A plausible mechanism for this rhodium(II)-catalyzed masked-formylation of diazo compounds first involves the formation of a metal-carbenoid complex (Scheme 4), concurrent with the observed exclusion of nitrogen gas. Rather than the expected C–H bond insertion of the ortho ester it is apparent that oxygen association to the electron deficient carbenoid complex forms an oxonium ylide; a process well known in the presence of ethers.[14] We suggest this step to be reversible, as greater concentrations of the ortho ester out-competes irreversible dimerization of the carbenoid. When the ylide forms from an alcohol, a proton shift occurs to displace the metal.[15] However, the clear lack of this oxygen-bound proton in the ortho-ester opens the opportunity for subsequent ylide rearrangement[16] and C–C bond formation through four possible pathways (**A**-**D** Scheme 4). A direct 1,2-Stevens rearrangement (**A**),[17] would lead to product with some enantioselection. In addition, breakdown of the ylide and subsequent stereospecific attack of the metal bound tight ion pair (pathway **B**) would also lead to enantioselectivity. As no enantiomeric excess was observed using the chiral rhodium catalyst, pathways **A** and **B** can be disregarded.

Scheme 4. Possible mechanistic pathways for the alkoxylation/ acetalization (masked formylation) of diazo esters (**1**).



Pathways **C** and **D** involve reversible formation of a planar enolate,[18] through which any stereochemical information present in the ylide is lost. C–C bond formation can either occur through a [1,2]-Stevens rearrangement or a stepwise process involving formation of an ion pair. We initially favoured separation of the intermediate, as three component couplings involving interception of the ylide by external electrophiles are well established.[19] We reasoned that a simple cross-over experiment employing a 1:1 mixture of undeuterated ($[^2H]_0$-**2**) and fully deuterated ($[^2H]_{10}$-**2**) trimethyl ortho ester could elucidate this difference. Observation of mixed products, such as D_3-methoxy/dimethylacetal ($[^2H]_3$-**3a**) and methoxy/D_7-dimethylacetal ($[^2H]_7$-**3a**), would indicate a separation of the catalytic intermediate into the ion pair. We tested the reaction in four different solvents of varying polarity, which would affect the tightness of the ion pair and thus the degree of cross-over, and found (ESI-MS) no evidence of any mixed products. Therefore, this strongly indicates that the concerted pathway **D** is operational.[20]

There is significant potential to derivatise these functionalised building blocks, as the orthogonal reactivity of each functional group of the quaternary carbon can be exploited (Scheme 5). More specifically, we showed that (a) the acetal can be readily deprotected with I_2 and acetone from which the free aldehyde **8** serves as an excellent chemical anchor for a myriad of transformations. The ester group can be (b) saponificated to **9** or (c) selectively reduced to **10**, a halide, or related functionality, attached to the phenyl moiety can be subjected to a vast number of transformations, including (d) a C–C cross-coupling (**11**). This latter reaction was further

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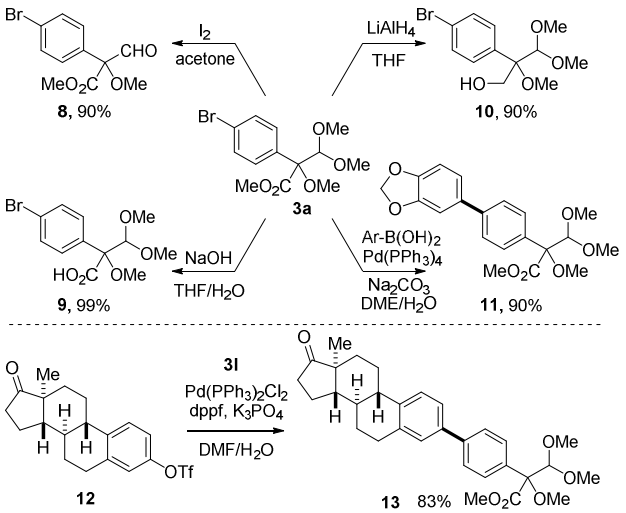
exemplified on an oestrone derivative (**12**) demonstrating the ease by which the rapid build of functionality is attainable.

Scheme 5. Upper: Useful synthetic building blocks prepared from the derivatization of 3a; lower: Cross-coupling with an oestrone derivative.[21]



In summary, we have discovered a Rh(II)-catalyzed tandem methoxylation/acetalization reaction using donor-acceptor substituted diazo compounds (**1**) and trimethyl orthoformate (**2**). The developed methodology represents a rare example of an intermolecular tandem C–O bond formation and masked-formylation, through C–C bond formation.

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