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Deacylative Oxidation Strategy for the Preparation of α-Functionalized Carbonyls

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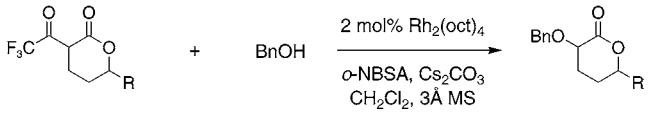
ABSTRACT



α-Alkoxylation and amination of carbonyl derivatives is made possible through a unique deacylative coupling reaction that proceeds via in situ Rh-carbene formation and subsequent heteroatom-H (X–H) insertion. Reactions perform optimally with five- and six-membered ring lactone and lactam derivatives using both alcohol and carbamate substrates as coupling partners. Substituted ethylbenzoyl acetate starting materials have also proven to be effective for this oxidative process, affording α-functionalized esters under particularly mild and operationally facile conditions.

Metal-mediated carbene insertion reactions continue to evolve as powerful tools for synthesis. Such processes can be used to fashion new C−C and C−X (X = N, O) bonds from readily available precursors under conditions that are favorable for the assembly of complex molecules. In certain instances, the preparation of α-hydroxy and α-amino acid derivatives has been achieved through metal-carbene X−H insertion.[1] Efforts to develop new protocols for the synthesis of such compounds have led us to explore 1,3-dicarbonyl derivatives as viable starting materials for tandem carbene generation and α-heteroatom functionalization (Figure 1). The successful implementation of such a strategy rests on a number of important mechanistic considerations and requires the careful coordination of many disparate chemical events. Importantly, such methodology obviates the preparation and isolation of potentially unstable α-diazo carbonyls.[2−4] Moreover, both α-oxygen and nitrogen-derived products are made available from a common starting material. In all, the process developed herein offers a simple and effective approach for exploiting the unique reactivity of carbenoid intermediates to assemble structural units found ubiquitously in natural and synthetic products.

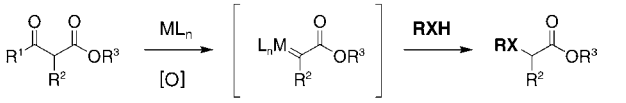


Figure 1. Oxidative reaction affords α-substituted carbonyl derivatives.

Notable advances by Doyle, Danheiser, and Taber have demonstrated the usefulness of β-dicarbonyls (e.g., **1**, Figure 2) as starting materials for α-diazoketone and -ester synthesis.[5,6] Analysis of the mechanism for such reactions suggested

(1) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley and Sons, Ltd.: New York, 1997; and references therein; (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861−2904.

(2) For recent applications of hydrazones as carbene precursors, see: (a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785−2788. (b) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426−12427. (c) Zhang, J.-L.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 8733−8737. (d) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, ASAP.

(3) For use of iodonium ylides as carbene precursors, see: (a) Müller, P.; Fernandez, D. *Helv. Chim. Acta* **1995**, *78*, 947−958. (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2002**, *4*, 4531−4533. (c) Müller, P.; Ghanem, A. *Synlett* **2003**, 1830−1833. (d) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262−1269. (e) Müller, P. *Acc. Chem. Res.* **2004**, *37*, 243−251.

(4) In situ diazotization of glycine ethyl ester with $NaNO_2$ has been described; see: Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem.* **2001**, *66*, 8260−8263.

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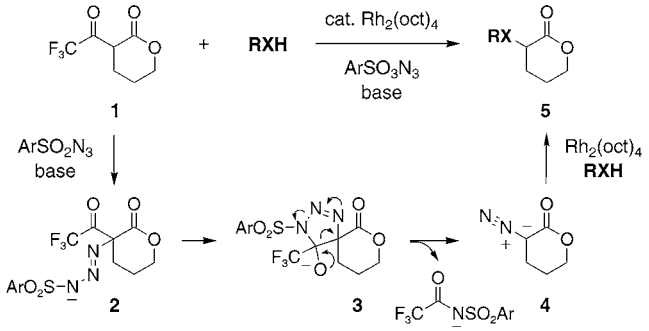


Figure 2. Tandem deacylative diazotization and X−H insertion.

that enolate diazotization and subsequent retro-Claisen could be performed in the absence of added H_2O and/or amine base, as had been employed in previous reports. Such speculation posits diazocarbonyl **4** formation to occur through intramolecular acyl transfer (**2**→**3**), extruding the sulfonamide salt as the sole byproduct (Figure 2). By avoiding water and amine reagents, the intermediate Rh-carbenoid would be free to react with a given nucleophile, RXH (**4**→**5**). Accordingly, we envisioned a protocol in which successive diazo transfer, metallocarbene generation, and carbene insertion would proceed in a single operation.

For initial studies, trifluoroketone **1** (Figure 2) was chosen as a model substrate and tested in combination with inorganic bases, sulfonyl azide oxidants, and Rh catalysts. The nature of and interactions between the diverse number of reaction components are critical to the success of this coupling process. Unlike amine bases commonly employed in diazo transfer reactions (Et_3N, DBU), the insolublity of Cs_2CO_3 in CH_2Cl_2 establishes a phase partition between the solid base and the solution containing dissolved catalyst. We hypothesized that such conditions would minimize axial coordination of carbonate ion and/or the Cs^+ enolate to the Rh dimer, thus freeing the catalyst to decompose the α-diazo carbonyl substrate rapidly as it was generated.[7] Viable oxidants were considered on the basis of their activity with the weakly nucleophilic enolate derived from **1**. Readily prepared *o*-nitrobenzenesulfonyl azide (*o*-NBSA) was found to outperform considerably other sulfonyl azide reagents and does not decompose in the presence of the Rh-catalyst.[8] The optimized reaction thus employs trifluoroketone **1**, 2 mol % $Rh_2(oct)_4$, 1 equiv of *o*-NBSA, Cs_2CO_3, and BnOH to afford 68% of the corresponding α-benzyloxy lactone **5** (RX = OBn).[9]

(5) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663−1666.

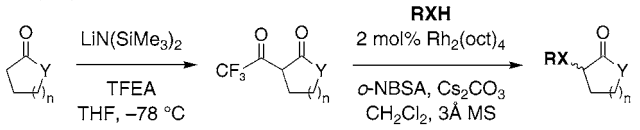
(6) (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959−1964. (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth.* **1996**, *73*, 134−143. (c) Detrifluoroacetylative diazo transfer to form α-diazo-γ-lactones has been described. See: Brown, R. C. D.; Bataille, C. J. R.; Bruton, G.; Hinks, J. D.; Swain, N. A. *J. Org. Chem.* **2001**, *66*, 6719−6728.

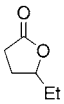
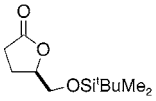
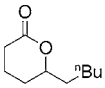
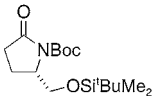
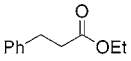
(7) Axial coordination of dirhodium catalysts by Lewis basic ligands is known to inhibit catalytic activity; see: Nagashima, T.; Davies, H. M. L. *Org. Lett.* **2002**, *4*, 1989−1992.

(8) For a discussion of the unique electronic properties of *o*-NBSA, see: Besenyei, G.; Párkányi, L.; Foch, I.; Simándi, L. I.; Kálmán, A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1798−1802.

Deacylative oxidation has proven to be general for five- and six-membered rings lactones and lactams (Table 1).

Table 1. Detrifluoroacetylative X−H Insertion with Catalytic $Rh_2(oct)_4$



entry	starting material	RXH[a]	yield[b]
1		BnOH	68
2			74
3		EtOH	79
4		MeOH	66
5			74
6			75
7		BnOH	78[c]
8		H_2NCO_2Me	76[c]
9		EtOH	61
11			72
10		^tBuOH	64
12		BnOH	73
13		BnOH	65[d]

[a] Standard reaction conditions employed 1 equiv of *o*-NBSA, 1 equiv of Cs_2CO_3, and 4 equiv of RXH. [b] Isolated yield of product over two steps. Chiral products are formed with diastereomeric ratios ranging from 1 to 3:1; see Supporting Information for details. [c] Optimum results were obtained with LiN^iPr_2 in place of $LiN(SiMe_3)_2$. [d] Optimum results were obtained with $LiN(^cHx)^iPr$ in place of $LiN(SiMe_3)_2$.

Preparation of the requisite trifluoroketone is facilitated using $LiN(SiMe_3)_2$ and commercial trifluoroethyl trifluoroacetate (TFEA). Enolate acylation is efficient under these conditions, and purification of the product is unnecessary prior to conducting the subsequent step. The method extends to medium-sized ring systems as well as aliphatic esters (entries 9, 13); reaction efficiencies are slightly more variable, however, for such substrates. To highlight the versatility of this process, a number of structurally diverse alcohols were screened as nucleophilic partners for the coupling reaction. Primary and secondary alcohols, including benzylic and allylic derivatives, all perform effectively. With allyl alcohol

(9) In the absence of BnOH, several decomposition products are observed, none of which appear to correspond, however, to the α,β-unsaturated lactone or dimerized material.

as the trapping agent, olefin cyclopropanation and allylic C−H insertion were not observed.[10] Somewhat diminished product yields were obtained when *t*-BuOH and, inexplicably, MeOH were employed (entries 4, 10). In addition to alkanol nucleophiles, 1° carbamate esters can also act as suitable partners in the X−H insertion step (entry 8).[11] Thus, access to either α-alkoxy or α-amino adducts is achieved from a common precursor.

In an effort to advance further strategies for deacylative oxidation, we have investigated alternative 1,3-dicarbonyl starting materials (Figure 3). Inspired by the work of Taber,[12]

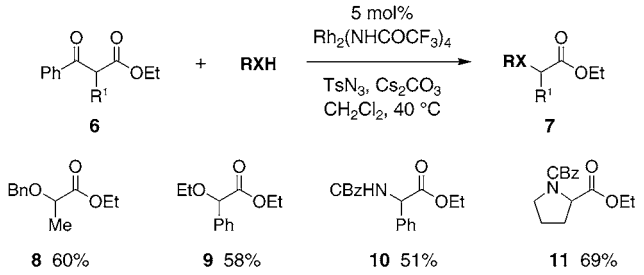


Figure 3. Debenzoylative α-functionalization of acyclic esters.

a small set of benzoylated esters was evaluated. Reactions of these compounds proceed efficiently with TsN_3 as the diazo transfer agent and $Rh_2(HNCOCF_3)_4$ as the catalyst (5 mol %).[13] The increased reactivity of the Cs^+ enolate makes possible use of the less reactive toluenesulfonyl azide. α-Functionalized ester products are isolated in moderate yields by employing this reagent combination. Importantly, ethylbenzoyl acetate **6** (R^1 = H) may be easily converted into substituted derivatives and thus offers particularly convenient access to numerous α-alkoxy and amine products. As an example, alkylation of **6** with *N*-CBz-3-bromopropylamine (NaH, KI, DMF, 50 °C) and subsequent deacylative oxidation affords proline ester **11**.[14,15] The synthesis of more advanced heterocyclic structures should follow through a similar route.

A two-step method for the preparation of α-functionalized carboxylic acid derivatives has been developed. This process capitalizes on the unique activity of Rh-carbene intermediates to insert into heteroatom-H bonds. A tandem sequence of events leading to product formation is made possible with the ability to modulate the production of reactive diazo and carbenoid species. As such, new opportunities to exploit Rh-carbene reactions for complex molecule synthesis are afforded that circumvent the assembly of potentially unstable diazo compounds. The effectiveness of *β*-dicarbonyls as carbene precursors should thus expand the general utility of carbenoid chemistry for C−C and C−X bond formation.

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Supporting Information Available: Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468−4484.

(11) Aller, E.; Buck, R. T.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2879−2884.

(12) Taber, D. F.; You, K.; Song, Y. *J. Org. Chem.* **1995**, *60*, 1093−1094.

(13) (a) $Rh_2(HNCOCF_3)_4$ has been employed previously for X−H insertion reaction. See: Cox, G. G.; Miller, D. J.; Moody, C. J.; Sie, E.-R. H. B. *Tetrahedron* **1994**, *50*, 3195−3212. (b) A detailed preparation of $Rh_2(HNCOCF_3)_4$ is available in Supporting Information.

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