ORGANIC LETTERS

2011
Vol. 13, No. 12
3235–3237

Rhodium-Catalyzed Selective C−H Activation/Olefination of Phenol Carbamates

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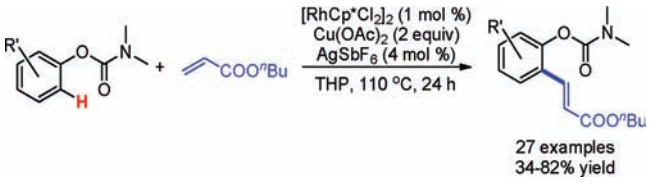
Received April 29, 2011

ABSTRACT



Rh(III)-catalyzed *ortho* C−H activation/olefination of phenol carbamates has been developed. High regioselectivity is observed with a range of phenol carbamates enabling efficient coupling with acrylates and styrenes. This reaction exhibits different reactivity as compared to the Pd-catalyzed *ortho*-arylation reaction of phenol esters and provides a new approach for the synthesis of *ortho*-substituted phenols.

The oxidative Heck reaction, as pioneered by Fujiwara and Moritani, represents an atom-economic strategy to directly functionalize arenes without prior activation of the reactants.[1] Pd is the most frequently used catalyst in this transformation, and a directing group such as an amide or carboxylic acid is usually needed to control the regioselectivity in the C−H activation process.[2] Extending this idea to other transition metals, several groups showed recently that Rh can also catalyze the oxidative Heck reaction with the assistance of several directing groups including amide, oxime, pyridyl, ketone, and carboxyl.[3−8] In comparison to the Pd-catalyzed processes, the use of Rh has been found to

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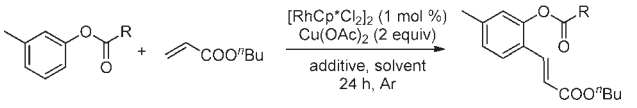
10.1021/ol201140q
Published on Web 05/23/2011

allow lower catalytic loadings, highly functional group tolerance, and a wider range of synthetic utility.

In this context, we now report that carbamate-protected phenols can be selectively olefinated in the presence of a Rh(III) catalyst. This study was a continuation of our recent work on Pd-catalyzed C−H activation/aryl−aryl coupling of phenol esters.[9] In related studies Bedford[10a] and Dong[10b] also described Pd-catalyzed *ortho*-arylation of phenol carbamates. However, after many tests we failed to use the ester or carbamate as a directing group in a Pd-catalyzed oxidative Heck reaction. Accordingly we turned our attention to the Rh catalyst systems and fortunately obtained some success. It is important to note that protected phenols (either in the ester or carbamate form) have not been examined in Rh-catalyzed C−H activation and functionalization reactions.[11]

Table 1. Rh-Catalyzed Oxidative Heck Reaction[a]

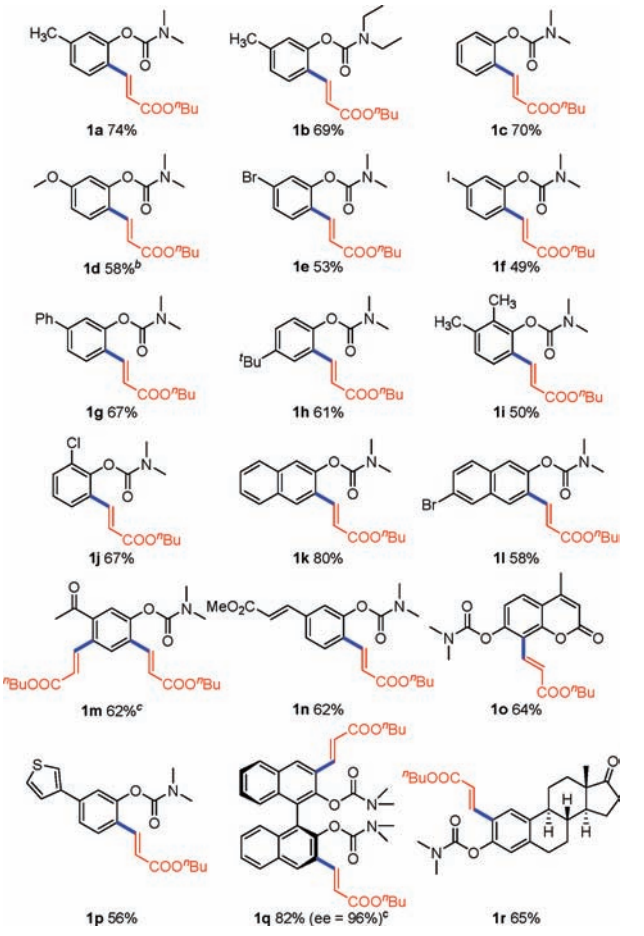


entry	R	additive (4 mol %)	solvent	temp (°C)	isolated yield (%)
1	Piv	None	*t*-AmOH	120	<5
2	Piv	$AgSbF_6$	*t*-AmOH	120	10
3	NMe_2	$AgSbF_6$	*t*-AmOH	120	70
4	NMe_2	$AgSbF_6$	DMF	120	<5
5	NMe_2	$AgSbF_6$	DMSO	120	<5
6	NMe_2	$AgSbF_6$	toluene	120	<5
7	NMe_2	$AgSbF_6$	THF	80	54
8	NMe_2	$AgSbF_6$	THP	110	74
9	NMe_2	None	THP	110	<5
10[b]	NMe_2	$AgSbF_6$	THP	110	0

[a] Reaction conditions: phenol ester or carbamate (0.25 mmol), butyl acrylate (0.50 mmol), $[RhCp^*Cl_2]_2$ (1 mol %), $Cu(OAc)_2$ (2 equiv), solvent (1 mL), 24 h, under Ar. [b] Without $[RhCp^*Cl_2]_2$.

Our work started with the oxidative Heck reaction of *m*-cresol pivalate (Table 1). We found that the desired transformation did not proceed efficiently under the reaction conditions described in the previous studies[3−7] (entries 1−2). On the basis of the previous work[10] by Bedford and Dong we then tested *m*-cresol *N*,*N*-dimethyl carbamate. We were pleased to observe that $[RhCp^*Cl_2]_2$ (1 mol %) exhibited notable catalytic activity in *t*-AmOH (*tert*-amyl alcohol) to afford the desired product in good isolated yield (70%) in the presence of $AgSbF_6$ (4 mol %) and 2 equiv of $Cu(OAc)_2$ (entry 3). This reaction is highly regioselective leading to olefination only at the C−H bond *para* to the methyl substituent presumably due to steric reasons. Change of the solvent to DMF, DMSO, and toluene inhibited the process (entries 4−6), whereas the reactions in THF and THP (tetrahydropyran) gave yields of 54% and 74% (entries 7−8). Note that the use of the $AgSbF_6$ (4 mol %) additive is crucial (entry 9). Moreover, without addition of $[RhCp^*Cl_2]_2$ the reaction did not take place (entry 10).

Scheme 1. Phenol Carbamate Scope[a]



[a] Reaction conditions: phenol carbamate (0.25 mmol), *n*-butyl acrylate (0.50 mmol), $[RhCp^*Cl_2]_2$ (1 mol %), $AgSbF_6$ (4 mol %), $Cu(OAc)_2$ (2 equiv), THP (1 mL), 110 °C, 24 h, under Ar. [b] A minor product (ca. 30% yield) was also observed for which the olefination occurred at the position *ortho* to OMe. [c] *n*-Butyl acrylate (1.25 mmol).

To explore the substrate scope, we examined different types of phenol carbamates in the reaction (Scheme 1). Electron-neutral and electron-rich phenol carbamates were found to be favored in the reaction (**1a**−**1l**), whereas some electron-poor substrates (e.g., NO_2-substituted ones) could not be efficiently converted (data not shown). A special electron-poor substrate was **1m**. This acetyl substituted phenol carbamate could participate in the reaction, but the product was bis-olefinated. This observation is consistent with the previous finding that ketone was also a good directing group in Rh-catalyzed C−H functionalization.[6a] Moreover, halide functional groups

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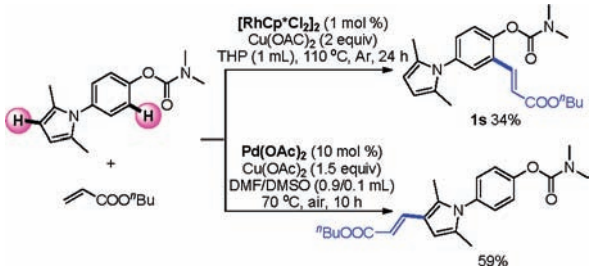
(11) During the preparation of our manuscript, we noted a related study on Rh(III)-catalyzed *ortho* C−H olefination of benzoic esters: Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372.

(I, Br, Cl) were well tolerated (**1e**, **1f**, **1j**, **1l**), with no Heck-type coupling or proto-dehalogenation products being detected. This particular feature shows one important advantage of the Rh-catalyzed transformation in comparison to many Pd-catalyzed ones, because the halogenated products may allow further functionalization via cross-coupling reactions.

High regioselectivity was observed for most of the substrates favoring the C−H functionalization at a sterically less hindered position. However, it is interesting to note that, in the substrate **1o**, the olefination occurred at the 8-position of the coumarin ring. This observation might be explained by the participation of the coumarin 1-oxygen in the C−H activation process, but at the same time we must note that **1d** was still mainly olefinated at the position *para* to the methoxyl group.

Furthermore, the present reaction provides a means to achieve 3,3′-bisolefination of BINOL (**1q**). HPLC analysis indicated that the chirality of BINOL was maintained during the transformation. The reaction was also applicable to the olefination of biologically relevant compounds (**1r**). Interestingly, for a pyrrole-containing substrate (Scheme 2), the Rh catalyst caused C−H olefination on the phenyl ring (**1s**), whereas the Pd catalyst caused C−H olefination on the pyrrole ring. Thus, the use of Rh can lead to new selectivity in the C−H functionalization.

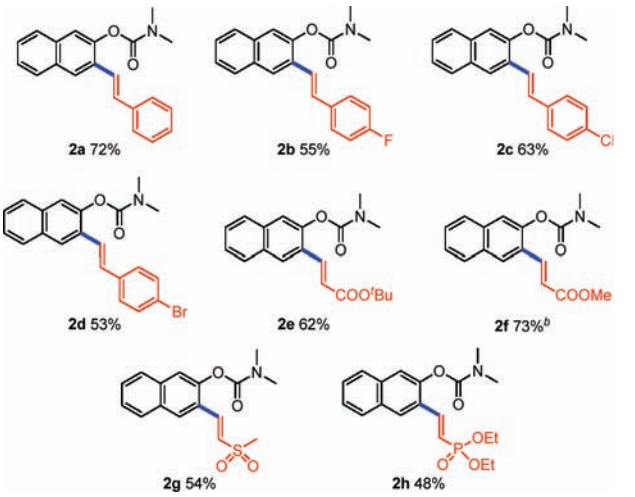
Scheme 2. Selective C−H Activation



The scope of the reaction with respect to the alkene reactant is shown in Scheme 3. Both substituted styrenes and acrylates of various alcohols were smoothly incorporated to afford the corresponding products in good yields. The halide functional groups were again tolerated (**2b-2d**) showing no proto-dehalogenation or Heck-type coupling. In addition, (methylsulfonyl)ethene (**2g**) and diethyl vinylphosphonate (**2h**) could be used as the substrates. Nonetheless, our current method does not allow for the coupling of unactivated, aliphatic alkenes.[4c]

A significant kinetic isotope effect ($k_{H/D}$ = 3.1) was observed (Scheme 4). This observation indicated that the C−H bond cleavage is most likely involved in the rate-limiting step of the transformation. Fagnou et al. reported a similar kinetic isotope effect in a related Rh-catalyzed

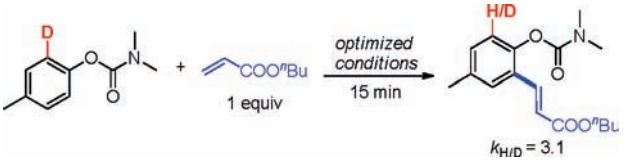
Scheme 3. Alkene Scope[a]



[a] Reaction conditions: phenol carbamate (0.25 mmol), olefin (0.50 mmol), $[RhCp^*Cl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), $Cu(OAc)_2$ (2 equiv), THP (1 mL), 24 h, 110 °C, under Ar. [b] 80 °C.

C−H functionalization reaction.[3e] According to their study, the mechanism of the transformation should involve a cyclometalation step through the concerted metalation−deprotonation mechanism. This step is presumably followed by olefin insertion and β-hydride elimination to provide the target product. Rh(III) is reduced to Rh(I) in the process, which is reoxidized by Cu(II) to generate the catalytically active Rh(III) species.

Scheme 4. Kinetic Isotope Effect



In summary, we report a practical protocol for the Rh(III)-catalyzed *ortho* C−H activation/olefination of phenol carbamates. This reaction complements the recently developed Pd-catalyzed processes for the *ortho*-arylation of phenol esters and carbamates. Because substituted phenols are important organic intermediates, the present reaction is likely to find synthetic utility.

Acknowledgment. We thank the NSFC (Nos. 20932006 and 91013007).

Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.