ORGANIC
LETTERS

2007
Vol. 9, No. 21
4107−4110

Transition-Metal-Catalyzed Group Transfer Reactions for Selective C−H Bond Functionalization of Artemisinin

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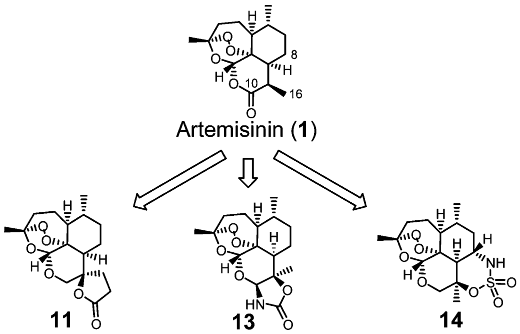
Received May 30, 2007

ABSTRACT



Three types of novel artemisinin derivatives have been synthesized through transition-metal-catalyzed intramolecular carbenoid and nitrenoid C−H bond insertion reactions. With rhodium complexes as catalysts, lactone 11 was synthesized via carbene insertion reaction at the C_{16} position in 90% yield; oxazolidinone 13 was synthesized via nitrene insertion reaction at the C_{10} position in 87% yield based on 77% conversion; and sulfamidate 14 was synthesized via nitrene insertion reaction at the C_8 position in 87% yield.

Natural products play a significant role in pharmaceutical industry as they are imperative resources for the discovery of drug leads.[1] Total synthesis allows the construction of natural products from simple and commercially available building blocks, and more importantly, it permits strategic incorporation of functionality at the desired positions.[2] Although the simplest way for natural product modification is via functional group transformations, it is restricted by the nature and position of the functional groups in natural products.

C−H bonds are generally not regarded as functional groups in organic synthesis. Yet, after decades of effort on understanding the basis of C−H bond activation,[3] the use of unactivated C−H bonds as functionality in organic synthesis has been demonstrated as a viable approach.[4] Notably, transition-metal-catalyzed C−H bond insertion reactions with carbenoids and nitrenoids[5] have been employed in the construction of complex organic molecules (Scheme 1).[6]

In line with our efforts on the development of C−H bond insertion reactions for organic synthesis,[7] we envision that

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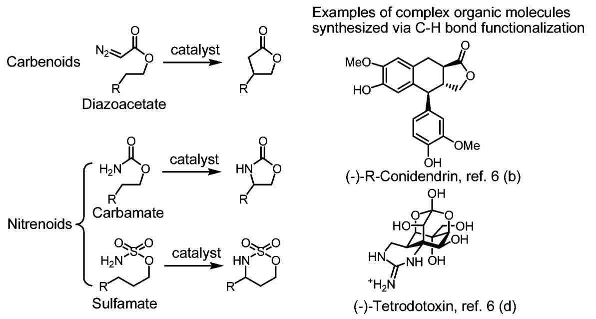
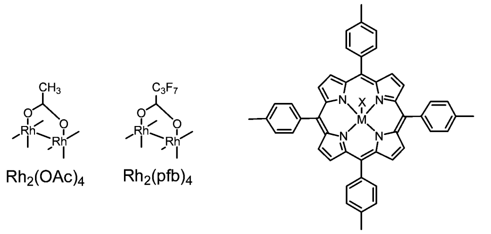
Scheme 1



C−H functionalization via carbenoid and nitrenoid insertions would be an appealing approach to achieve selective modification of natural products such as artemisinin because these reactions could be conducted under mild reaction conditions. Artemisinin (Qinghaosu, **1**)[8] is a sesquiterpene lactone endoperoxide which has been currently used for clinical treatment of malaria.[9] In addition, artemisinin and its derivatives exhibit potent in vitro cytotoxicities against cancer cells.[10] Artemisinin derivatives were mainly synthesized via chemical modifications of artemisinin at its C_{10} or C_{16} position.[11,12] Here, we report selective modification of artemisinin via transition-metal-catalyzed intramolecular C−H bond insertion reactions with carbenoids and nitrenoids. In this work, four transition metal catalysts including $Rh_2(OAc)_4$, $Rh_2(pfb)_4$, [Rh(TTP)Cl], and [Ru(TTP)CO] were used (Scheme 2). Three types of novel artemisinin derivatives have been synthesized through transition-metal-catalyzed intramolecular C−H bond functionalization at the 1° (C_{16}) and 2° (C_8 and C_{10}) C−H bonds of artemisinin. Notably, the delicate endoperoxide bridge remains intact over the course of the C−H bond functionalization reactions.

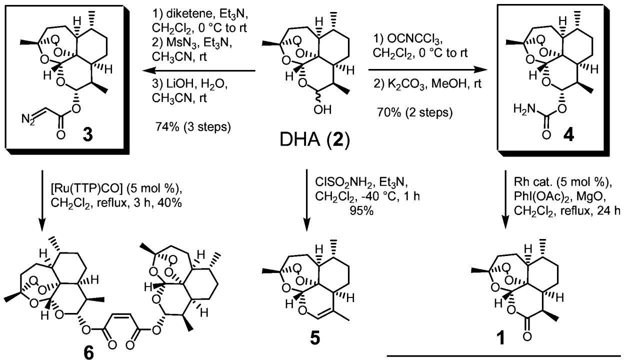
Scheme 2



M = Rh, X = Cl [Rh(TTP)Cl]
M = Ru, X = CO [Ru(TTP)CO]
H_2TPP = *meso*-tetrakis(*p*-tolyl)porphyrin

At the outset, diazoester **3** and carbamate **4** were prepared from readily available 10-dihydroartemisinin (DHA, **2**) in 74% and 70% yields, respectively (Scheme 3, see Supporting Information). Several attempts to synthesize the sulfamate ester derivative of **2** failed, and only the dehydrated product **5** was obtained.

Scheme 3



	convn (%)	yield (%)
$Rh_2(OAc)_4$	15	94
$Rh_2(pfb)_4$	19	96

Treatment of diazoester **3** with 5 mol % of $Rh_2(OAc)_4$, $Rh_2(pfb)_4$, or [Rh(TTP)Cl] at room temperature in 3 h gave

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mixtures of intractable products without a C−H insertion product being identified. This could be due to the formation of oxonium ylide, which would lead to the decomposition of the endoperoxide bridge. A *cis*-dimer **6** arising from intermolecular diazo coupling was obtained in 40% yield based on complete substrate conversion when [Ru(TTP)CO] was used as the catalyst (Scheme 3). The dimerization catalyzed by the Ru catalyst suggested that the reactivity of the Ru carbene reactive intermediate was much lower than that of the Rh carbenes. In addition, the exclusive formation of the *cis*-dimer is consistent with our previous work that ruthenium porphyrin catalysts selectively gave *cis*-dimers in intermolecular coupling reactions of diazoacetates.[13]

Carbamate **4** was converted into artemisinin (**1**) in 94% yield based on 15% conversion when $Rh_2(OAc)_4$ was used as the catalyst (Scheme 3), and a similar result was obtained for $Rh_2(pfb)_4$. Yet, no reaction was observed when **4** was treated with a catalytic amount of [Rh(TTP)Cl] or [Ru(TTP)-CO].

Apart from 10-dihydroartemisinin (DHA, **2**), 9-hydroxy-deoxoartemisinin (**7**)[14] derived from **5** was used as an intermediate to prepare diazoester **8**, carbamate **9**, and sulfamate **10** (Scheme 4). Diazoester **8** and carbamate **9** were synthesized in good yields from **7** in two to three steps (see Supporting Information). Owing to the steric bulkiness of the tertiary C−OH functionality of **7**, the conversion of **7** to **10** was found to proceed with 20% substrate conversion and 90% product yield. Because of the instability of the tertiary sulfamate ester moiety, a mixture of **10** and **7** (**10**/**7** = 1:4) was used for the subsequent C−H insertion reactions without further purification by flash column chromatography.

Scheme 4

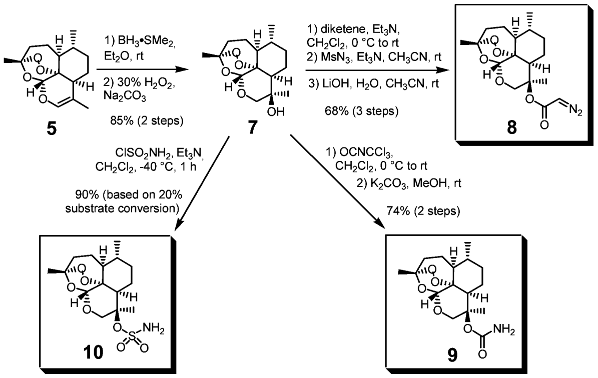
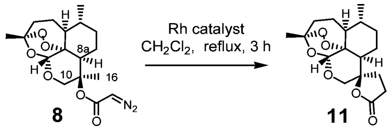


Table 1. C−H Insertion Reactions Catalyzed by Rh Complexes[a]



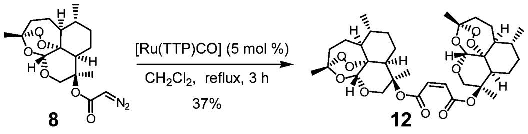
entry	catalyst	(mol %)	convn (%)[b]	yield (%)[c]
1	$Rh_2(OAc)_4$	5	100	89
2	$Rh_2(pfb)_4$	5	100	90
3	[Rh(TTP)Cl]	5	26	84
4	[Rh(TTP)Cl]	10	100	87

[a] Reaction conditions: unless otherwise indicated, all reactions were carried out by dropwise addition of 0.1 mmol of diazoester **8** in 3 mL of anhydrous CH_2Cl_2 to a solution of Rh complexes (5 mol %) in 2 mL of anhydrous CH_2Cl_2 via a syringe pump for 2 h under reflux. The reaction mixture was stirred for an additional 1 h. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield based on conversion.

Upon treatment of diazoester **8** with 5 mol % of $Rh_2(OAc)_4$, an exclusive carbenoid insertion to the unactivated 1° C−H bond of the methyl group (C_{16}) was achieved, and lactone **11** was obtained in 89% yield with 100% conversion (Table 1, entry 1). $Rh_2(pfb)_4$ exhibited catalytic activity comparable to that of $Rh_2(OAc)_4$ (entry 2). With 5 mol % of [Rh(TTP)Cl], only 26% conversion was found (entry 3). When the loading of [Rh(TTP)Cl] was increased to 10 mol %, complete conversion of diazoester **8** was observed, and the product lactone **11** was obtained in 87% yield (entry 4). In all the reactions, no C−H insertion at the adjacent C_{8a} or C_{10} position was observed.[15]

Using [Ru(TTP)CO] (5 mol %) as the catalyst, a *cis*-dimer **12** was obtained in 37% yield based on complete conversion from diazoester **8** (Scheme 5).

Scheme 5



When carbamate **9** was treated with $Rh_2(OAc)_4$ using $PhI(OAc)_2$ as an oxidant and MgO as a base, oxazolidinone **13** was exclusively obtained in 85% yield, and the substrate conversion was 27% (Scheme 6). $Rh_2(pfb)_4$ afforded a higher substrate conversion (77%) and gave oxazolidinone **13** in 87% yield. No reaction was obtained when [Rh(TTP)Cl] or [Ru(TTP)CO] was used as the catalyst.

For sulfamate **10**, an exclusive C−H bond amidation at the unactivated secondary C−H bond of the C_8 position was achieved to give sulfamidate **14** in 85% yield with 100% conversion using a catalytic amount of $Rh_2(OAc)_4$ (Scheme 6). A comparable result was obtained when $Rh_2(pfb)_4$ was used. The stereochemistry of the newly generated tertiary carbon center (C_8) of **14** was established by $^1H-^1H$ NOESY analysis. NOE signals between H_8 and H_6 and between H_8 and H_{12} were observed, indicating that the H_8 is at the *syn*-position to H_6 and H_{12}. To our knowledge, this is the first

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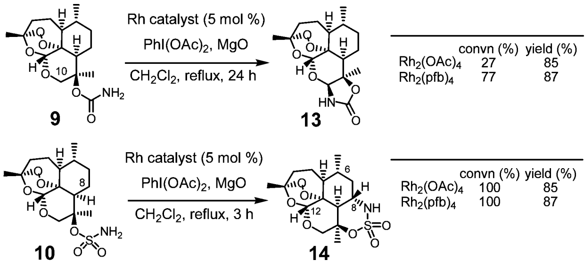
Scheme 6



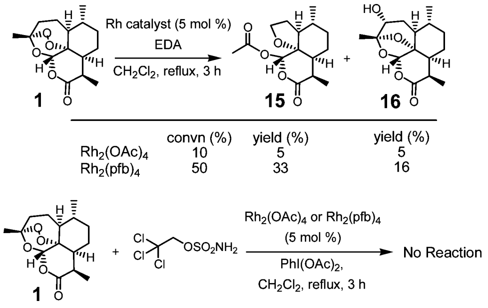
	convn (%)	yield (%)
$Rh_2(OAc)_4$	27	85
$Rh_2(pfb)_4$	77	87

	convn (%)	yield (%)
$Rh_2(OAc)_4$	100	85
$Rh_2(pfb)_4$	100	87

example of an artemisinin derivative bearing a non-hydrogen atom at the C_8 position; no chemical or biotransformation at this position has been reported. Sulfamate **10** was decomposed to **5** when [Rh(TTP)Cl] and [Ru(TTP)CO] were used as the catalyst.

As control experiments, treatment of artemisinin (**1**) with ethyl diazoacetate (EDA) and 5 mol % of $Rh_2(OAc)_4$ or $Rh_2(pfb)_4$ as the catalyst afforded decomposed products **15** and **16** (Scheme 7) with no C−H insertion product identified.[16]

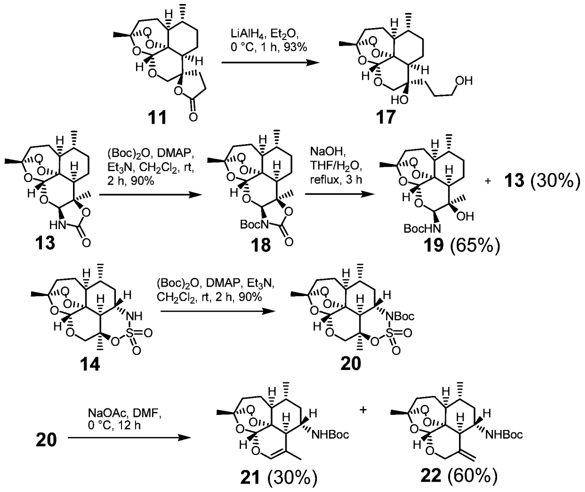
Scheme 7



	convn (%)	yield (%)	yield (%)
$Rh_2(OAc)_4$	10	5	5
$Rh_2(pfb)_4$	50	33	16

No substrate conversion was observed when artemisinin (**1**) was treated with trichloroethyl sulfamate using 5 mol % of $Rh_2(OAc)_4$ or $Rh_2(pfb)_4$ as the catalyst. These experiments indicated that intramolecular reactions are the key to success in the C−H bond functionalization of artemisinin.

Scheme 8



We have further elaborated the C−H bond functionalized artemisinin derivatives by ring-opening reactions. As shown in Scheme 8, lactone **11** was reduced to diol **17** by $LiAlH_4$ in 93% yield. Upon heating under alkaline reaction conditions, Boc-oxazolidinone **18** was converted into amino alcohol **19** and **13** in 65% and 30% yields, respectively. Boc-sulfamidate **20** was converted into alkenes **21** and **22** (in a ratio of 1:2) in 90% yields by treatment with NaOAc at 70 °C.

In conclusion, new methods have been developed to modify artemisinin at the C_8, C_9, C_{10}, and C_{16} positions by selective functionalization of C−H bonds. These new methods provide a convenient access to new artemisinin derivatives. Preliminary studies revealed that compounds **11** (IC_{50} = 37.5 μM) and **21** (IC_{50} = 79.9 μM) exhibited moderate cytotoxic activity, whereas compounds **13**, **14**, **17**, **19**, and **22** are nontoxic (IC_{50} > 100 μM) toward the HepG2 cell line.

Acknowledgment. This work was supported by The University of Hong Kong (University Development Fund), SRT on Drug Discovery and Synthesis (HKU), and Hong Kong Research Grants Council (HKU 7011/04P and 7012/05P).

Supporting Information Available: Experimental procedures, compound characterization data, and cytotoxicity studies of some selected artemisinin derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071269R

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