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Alkoxy- and hydroxycyclization of enynes catalyzed by Pd(II) and Pt(II) catalysts*

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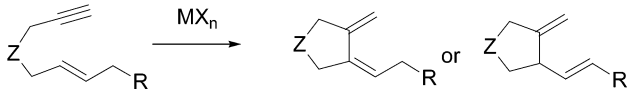
Abstract: The development of a novel reaction ideal in terms of atom economy was achieved. The scope of the reaction was evaluated in the presence of Pd and Pt catalysts. The first enantioselective Pt-promoted enyne carboalkoxycyclization was developed in up to 85 % stereoselectivity. This ideal atom-economical reaction afforded the corresponding functionalized five-membered carbo- and heterocycles in good to excellent yields. The use of silver salts combined with (*R*)-Ph-BINEPINE, a monophosphane atropisomeric ligand, was found to be the best-suited combination for moderate to high enantioselectivities on carbonated and nitrogenated substrates.

Keywords: platinum; cycloisomerization; asymmetric catalysis; palladium; atom economy.

INTRODUCTION

Over the past few years, significant research has been directed toward the development of new methodologies for synthetic efficiency and atom-economy processes [1]. Among them, tandem reactions that allow the formation of several new bonds in a single step from readily available materials are of particular interest [2]. Moreover, the potential of transition-metal-catalyzed cyclization reactions of unsaturated substrates has been steadily demonstrated, as they give a direct way toward the synthesis of highly valuable precursors of natural products or biologically active compounds [3,4]. Palladium catalysis, in particular, has been the driver of many advances, and the seminal and elegant work of Trost has placed 1,6-enynes as excellent partners for cycloisomerization reactions. These unsaturated derivatives participate in cycloisomerization reactions leading to 1,4- or 1,3-dienes (eq. 1) [1,5]. When performing the well-known cycloisomerization reaction in organoaqueous medium in the presence of the system $PdCl_2$/TPPTS (TPPTS = trisodium salt of 3,3',3"-phosphanetriylbenzenesulfonic acid [6]), we discovered a novel reaction, which allows for the simultaneous and stereoselective formation of a C–C and a C–O bond from enynes (eq. 2) [7].



(1)

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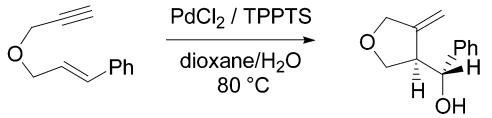

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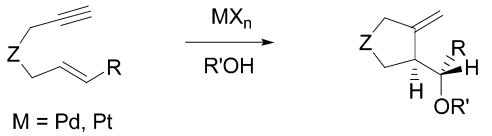


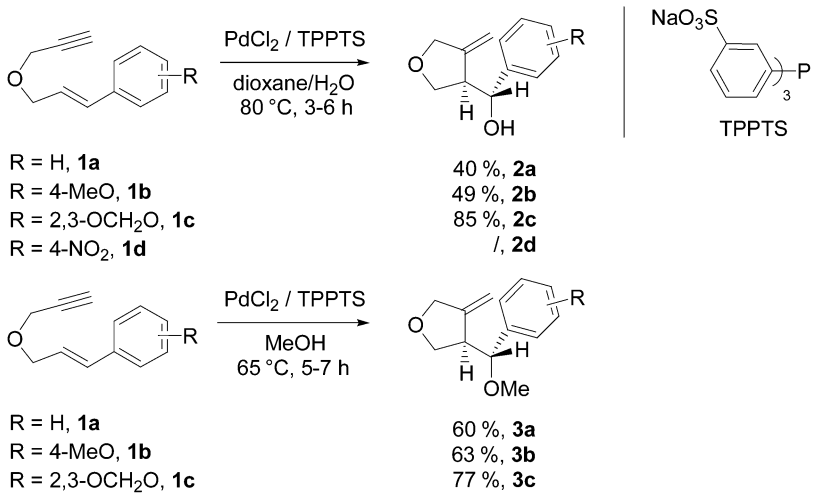
(3)

M = Pd, Pt
R' = H, Me, allyl, OAc

The hydroxyl- and alkoxycyclization reactions were then developed with various 1,6-enynes and other nucleophiles in the presence of Pd and Pt catalysts (eq. 3) [8]. The scope of this new reaction has also been assessed on some oxygenated enynes in view of its utilization in the synthesis of natural compounds of biological interest such as *Podophyllum* lignans where the accessibility of the aryltetralin fragment via this route has been already demonstrated [9]. The asymmetric version of alkoxy- or hydroxycyclization would provide a valuable synthetic tool for natural or biologically active product syntheses.

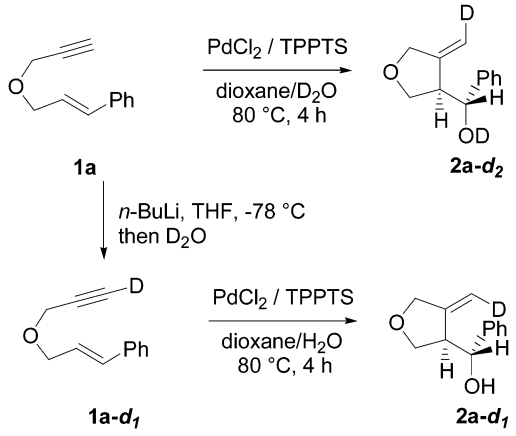
Pd- VS. Pt-CATALYZED HYDROXY- AND METHOXYCYCLIZATION REACTIONS

Aiming to examine the influence of allylic side chain, we prepared several oxygenated compounds **1a–d** via Williamson reactions of the corresponding allylic alcohols with propargyl bromide (Scheme 1). The system $PdCl_2$/TPPTS was highly efficient for the synthesis of various alcohols **2a–c**. We observed a high dependence of the electronic features as higher isolated yields were obtained for the propargylic enynes bearing electron-rich aromatic substrates. No reactivity of the nitro-substituted derivative **2d** was observed. The functionalized alcohol **2c** was a key intermediate in the synthesis of a precursor of podophyllotoxin [9]. The reactions were also conducted in MeOH at 65 °C, and the corresponding ethers were formed in 60–77 %. Once again, better results were obtained for electron-rich substituted enynes (Scheme 1).



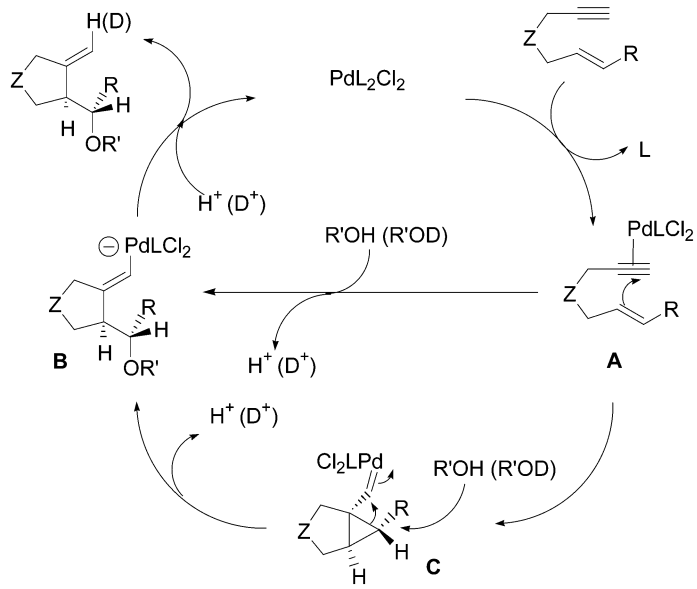
Scheme 1

The Pd-catalyzed mechanism of this highly atom-economical reaction was found to be similar to platinum catalysts [8d,e]. The reaction of propargyl cinnamyl ether **1a** with $PdCl_2$ and TPPTS as the ligand in a 1,4-dioxane/D_2O mixture at 80 °C afforded selectively deuterated **2-*d*$_2$** (Scheme 2). We have also prepared the deuterated alkyne **1-*d*$_1$** by *n*-BuLi deprotonation followed by D_2O quenching. The reaction of **1-*d*$_1$** with $PdCl_2$ and TPPTS afforded the corresponding adduct **2-*d*$_1$** [8a].



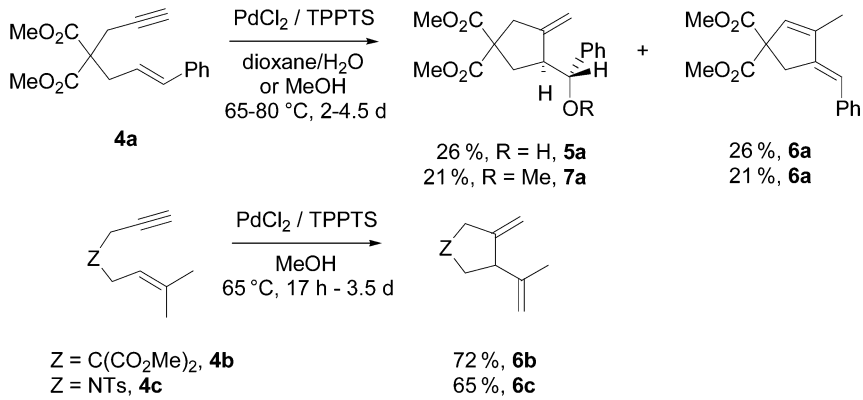
Scheme 2

A reasonable hypothesis for the mechanism is based on the Lewis acidic character of the Pd and Pt catalysts (Scheme 3). The reaction may be initiated by the formation of the π-alkynyl complex **A** through the complexation of the unsaturated triple bond to the metal catalyst. The π-alkynyl complex **A** would then evolve to give a cyclopropyl metal carbene complex **C**, which would be opened by an external nucleophile such as methanol or water and would give rise to the vinylmetallate **B**. Further protonolysis of this intermediate would form the desired cycloadduct and would regenerate the catalyst. This mechanism accounts for the deuteration pattern found in the reactions of **1** and **1-*d*$_1$**. The Pd carbene has not been isolated: therefore, the concerted addition of nucleophiles on intermediate **A** and formation of the C–C bond is possible too.



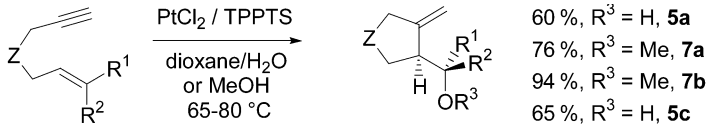
Scheme 3

The carbonated and nitrogenated 1,6-enynes behaved differently in the presence of the $PdCl_2$/TPPTS system (Scheme 4). The reaction of **4a** led to a mixture of the desired alcohol **5a** and the diene **6a**, resulting from the classic cycloisomerization reaction followed by an isomerization of the exomethylene double bond. The same trend was observed when the reaction was conducted in MeOH, despite the fact that compounds **7a** and **6a** were this time inseparable by chromatography on silica gel. This lack of selectivity for the system was also observed in the case of the dimethylated substrate **4b** or the nitrogenated derivative **4c**, which were transformed to the corresponding dienes **6b** and **6c** in 65–72 % yield.



Scheme 4

The efficiency of the system could be switched to the desired alkoxycyclization reaction in the presence of the $PtCl_2$/TPPTS system. No traces of the dienes were detected when the ligand TPPTS was added to the reaction mixture. Various alcohols and methoxyethers were, therefore, prepared in good to excellent isolated yield (Scheme 5).



Z = $C(CO_2Me)_2$, R^1 = Ph, R^2 = H, **4a**
Z = $C(CO_2Me)_2$, R^1 = R^2 = Me, **4b**
Z = NTs, R^1 = R^2 = Me, **4c**
Z = NTs, R^1 = Ph, R^2 = H, **4d**

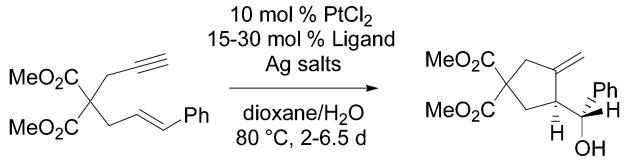
60 %, R^3 = H, **5a**
76 %, R^3 = Me, **7a**
94 %, R^3 = Me, **7b**
65 %, R^3 = H, **5c**
100 %, R^3 = Me, **7c**
81 %, R^3 = Me, **7d**

Scheme 5

ASYMMETRIC Pt-CATALYZED HYDROXY- AND METHOXYCYCLIZATION REACTIONS

We then turned our attention to platinum chemistry for the asymmetric version and investigated the functionalization of enyne **1a** with platinum in the presence of several chiral phosphane ligands (Table 1) [10]. Preliminary tests were performed in dioxane/water 6:1 using 10 mol % Pt catalyst and 15 mol % of bidentate or 30 mol % of mono-dentate phosphine. Even if under these conditions long reaction times are required for the alcohol **2a** to be obtained in high yield, the accelerating effect induced by the phosphorus ligand is quite evident from the fact that only traces of **2a** can be detected when the reaction is run in the absence of any phosphane (entry 1). The stereoselectivities obtained in the first batch of experiments were, however, disappointingly low [11]. The use of the well-known atropisomeric ligands (*R*)-BINAP [12] or (*R*)-MeO-BIPHEP [13] afforded the alcohol **2a** in respectively 0 and 5 % enantiomeric excess (entries 2 and 3). Other ligands such as (–)-DIOP [14], (*R*,*R*)-DIPAMP [15] or (*S*,*S*)-Et-FerroTANE [16] or (*S*,*S*)-MeDuPHOS [17] (entries 4–6) did not give better results. Interestingly, two-digit values were recorded only in three cases with (*R*)-Ph-BINEPINE [(*R*)-phenylbinaphtophosphepine] [18] (entry 7), with (*R*,*S*)-JOSIPHOS [19] (entry 8), and with (+)-BIPNOR [20], a ligand with stereogenic phosphorus centers (entry 9). The last one was the best chiral inducer of this set, but the enantiomeric excess (ee) did not exceed 25 %. Further improvements were attempted using other chiral ligands, in different cosolvents (acetone, toluene, ethylene glycol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, 1,2-dichloroethane…) at various temperature without success [11].

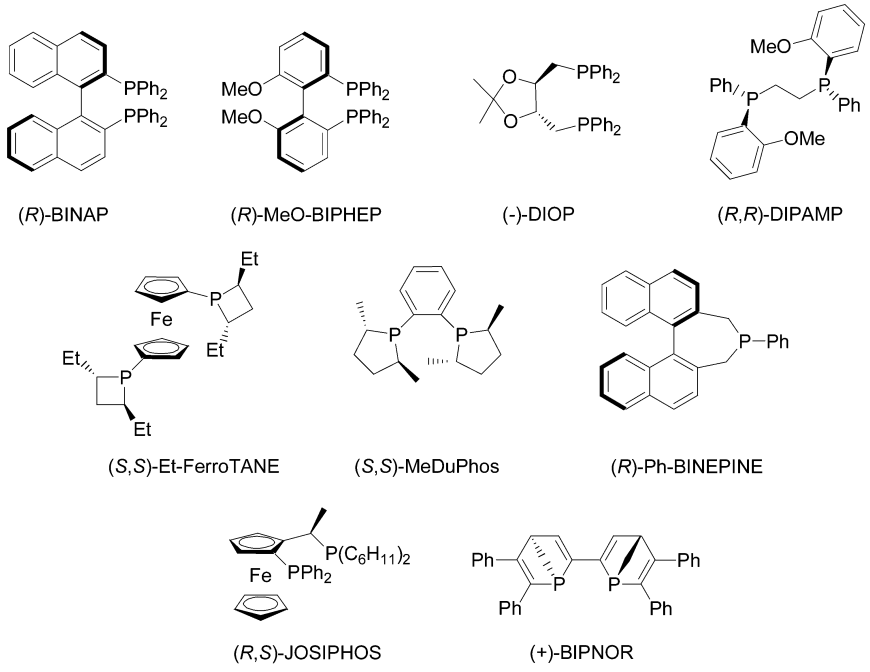
Table 1 Ligand and silver salt effect on $PtCl_2$-promoted enyne hydroxycyclization.



4a **5a**

Entry	Ligand	Ag salts (0.25 equiv)	Time [d]	Yield [%]	ee [%][a] (config.)
1	(*R*)-BINAP	/	5	100	0
2	(*R*)-MeO-BIPHEP	/	4.5	100	5 (+)
3	(–)-DIOP	/	5	72	8 (+)
4	(*R*,*R*)-DIPAMP	/	5	70	5 (–)
5	(*S*,*S*)-Et-FerroTANE	/	5	97	6 (+)
6	(*S*,*S*)-MeDuPHOS	/	5	98	0
7	(*R*)-Ph-BINEPINE	/	6.5	91	20 (–)
8	(*R*,*S*)-JOSIPHOS	/	4	91	13 (–)
9	(+)-BIPNOR	/	3	79	25 (–)
10	(*R*,*S*)-JOSIPHOS	$AgPF_6$	4	58	35 (–)
11	(*R*,*S*)-JOSIPHOS	$AgBF_4$	2	65	38 (–)
12	(*R*,*S*)-JOSIPHOS	$AgSbF_6$	2.5	62	41 (–)
13	(+)-BIPNOR	$AgSbF_6$	3	53	33 (–)
14[b]	(*R*)-Ph-BINEPINE	$AgSbF_6$	4	94	85 (+)
15[c]	(*R*)-Ph-BINEPINE	$AgSbF_6$	4	60[d]	85 (+)

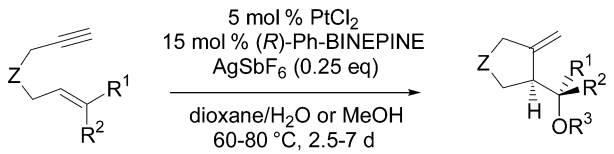
[a] The ee value was determined by HPLC [Chiralcel OD-H, hexane/propan-2-ol (95:5)].
[b] 5 mol % $PtCl_2$, 60 °C.
[c] 5 mol % $PtCl_2$, aqueous acetone, 60 °C.
[d] Conversion.



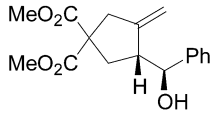
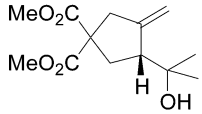
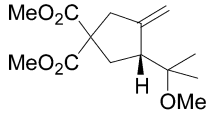
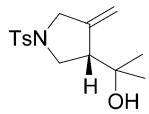
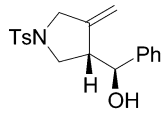
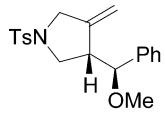
As it was our feeling that the catalytic performance of our Pt-derivative should have gained from an increased electrophilicity at the metal center (Scheme 3), we undertook to remove the chloride ligands from the coordination sphere of the Pt-phosphane complexes. The activation of Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt/(*R*,*S*)-JOSIPHOS system (entries 10–12), the silver additives had a moderately positive influence on yields and ee and the use of $^{-}BF_4$ and $^{-}SbF_6$ salts led consistently to a fair increase of both values. For instance, the hydroxycyclization of enyne **1a** gave the corresponding alcohol **2a** in 62 % isolated yield in 2.5 days in up to 41 % ee (entry 12). A similar trend was observed also with the (+)-BIPNOR-based complex (entry 13). These ee's, however, could not be improved further upon changing cosolvents, temperatures, and reagent ratios. On the contrary, addition of silver salts to the (*R*)-Ph-BINEPINE-based catalyst had a pronounced positive effect on the rate and allowed the reaction to be run at lower temperature (60 °C) even at halved catalyst loading (5 mol %). These conditions were found to be the best suited for a high yield (94 % in 4 days) to be matched by a substantial enantioselectivity (up 85 %) (entry 12). Once again, various modifications of the reaction conditions did not give better results [11]. For example, when the reaction is conducted in aqueous acetone (entry 13), a similar ee is obtained but the conversion does not increase upon 60 %.

The scope of this new asymmetric reaction has been assessed on various enynes. While allyl propargyl ethers were found to be poorly suited substrates for this reaction and led to unpractical mixtures of compounds, carbo- and azo-type enynes **4** reacted smoothly under mild conditions giving the cyclic product in high selectivity (Table 2). The malonate-derived enyne **4a**, the N-tosylated substrate **4d** and the *gem*-dimethyl-substituted enynes **4b** and **4c** all performed well in the hydroxycyclization with Ph-BINEPINE. The chemical yields ranged from good to excellent while the ee's were comprised in between 56 and 85 % (entries 1–6). The asymmetric reaction did work also when methanol was used as the solvent, and this allowed us to introduce a methoxy group in the place of the hydroxyl. Thus, from the substrates **4d** and **4b**, the relevant methyl ethers were obtained in 78 and 50 % ee, respectively (entries 6 and 3). The absolute configurations of the alcohols obtained from hydroxycyclizations have been determined by empirical methods from the ^{1}H NMR spectra of the *O*-methylmandelate esters derived from **5d** [22,10].

Table 2 $PtCl_2$-promoted enyne hydroxy- and alkoxycyclizations.



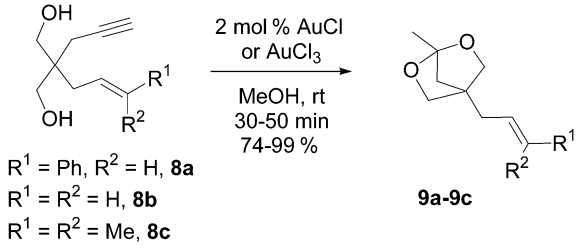
Z = $C(CO_2Me)_2$, R^1 = Ph, R^2 = H, **4a**
Z = $C(CO_2Me)_2$, R^1 = R^2 = Me, **4b**
Z = NTs, R^1 = R^2 = Me, **4c**
Z = NTs, R^1 = Ph, R^2 = H, **4d**

Entry	Enyne	Time [d]	Yield [%]	Product	ee [%][a]
1	**4a**	4	94		85 (+)-**5a**
2	**4b**	3.5	87		66 (+)-**5b**
3	**4b**	5.5	100		50 (+)-**7b**
4	**4c**	6.5	57		56 (+)-**5c**
5	**4d**	7	86		84 (+)-**5d**
6[b]	**4d**	2.5	49		78 (+)-**7d**

[a]The ee value was determined by HPLC (Chiralcel OD-H or Chiralpak AS-H).
[b]Reaction at 80 °C in screw-capped tube.

This asymmetric reaction is still highly challenging as no general metal/chiral ligand association is available. The group of Echavarren showed that Au catalysts may also be suitable for an asymmetric induction at room temperature or 60 °C [23a] and observed that $AgSbF_6$ salts, as in the platinum case, were highly beneficial in the AuCl/(*R*)-TolBINAP system to induce promising ee's. A unique example based on the methoxycylization of a substituted sulfonated substrate was described so far in an excellent 94 % ee. Our ongoing studies on the Au-catalyzed hydroxy- and alkoxycyclization reactions are quite promising too, as the alcohol **2a** was prepared at room temperature in the presence of $AuCl_3/AgSbF_6$ associated with an analog of (*R*)-MeO-BIPHEP ligand in 78 % ee [24]. Moreover, recent years witnessed tremendous growth in the number of Au-catalyzed reactions for carbon–carbon and carbon-heteroatom bond formations [23,25]. In pursuit of investigation on atom-economical metal-catalyzed cycloisomerization reactions [8a,10,26], we recently showed that 1,6-enynes bearing alcohols **8a–c** might undergo clean Au-catalyzed cyclization under extremely mild conditions [27]. No alkoxy-

cyclization or reactivity of the allylic side chain was observed (Scheme 6), as the bicyclic ketals **9a–c** were isolated in high yields. This demonstrates the opened reactivity of all 1,6-enynes and, therefore, the difficulty to discover a general and universal system.



Scheme 6

In conclusion, we have developed the first enantioselective Pt-promoted enyne alkoxycyclization in up to 85 % stereoselectivity. This ideal atom-economical reaction leads to the corresponding functionalized five-membered carbo- and heterocycles in good to excellent yields. The use of silver salts combined with (*R*)-Ph-BINEPINE, a monophosphane atropisomeric ligand, is by now the best-suited combination for moderate to high enantioselectivities on carbonated and nitrogenated substrates, and the first C–C application with this ligand. Further improvements are still needed for this reaction. The higher catalyst activity of Au catalysts would probably allow further applications toward the synthesis of a broader range of substrates and other structurally original polycyclic derivatives.

ACKNOWLEDGMENTS

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