Asymmetric Catalysis

DOI: 10.1002/anie.200601747

Rhodium-Catalyzed Enantioselective Conjugate Silyl Transfer: 1,4-Addition of Silyl Boronic Esters to Cyclic Enones and Lactones**

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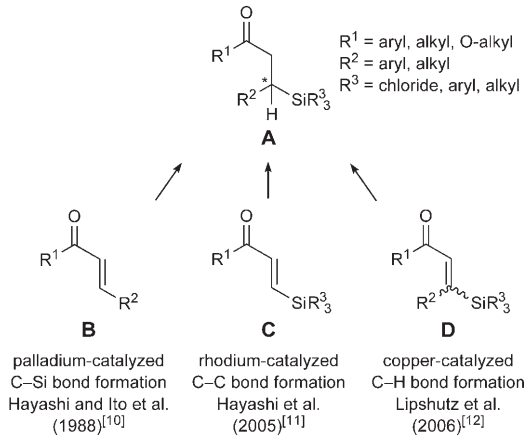
Silicon connected to a stereogenic carbon atom is an important functional group in asymmetric synthesis. The synthetic equivalence of silicon and oxygen, which is achieved by the stereospecific oxidative degradation of a C–Si bond,[1] as well as several stereoselective C–C bond-forming reactions involving α-chiral silanes[2] underscore the synthetic potential of silicon. Conversely, the number of effective methods for the direct enantioselective formation of C–Si bonds is limited[3] and, therefore, novel asymmetric transition-metal-catalyzed reactions will certainly plug a "synthetic hole".

The 1,4-addition of stoichiometric amounts of silicon-based cuprate reagents to prochiral α,β-unsaturated carbonyl compounds is one of the standard C–Si bond-forming reactions.[4] Although copper-catalyzed variants are available today,[5,6] their extension to chirally modified catalysts has so far failed.[7] Copper-catalyzed conjugate silyl transfer of disilanes has also been reported, but again only for a racemic series.[8] To date, the palladium-catalyzed enantioselective 1,4-disilylation[9] of acyclic enones using disilanes has remained the sole example (**B**→**A**, Scheme 1).[10] The importance of β-silyl carbonyl compound **A** (either as a masked aldol itself or as a functionalized precursor for the preparation of α-chiral silanes)[2b] has resulted in the development of alternative catalyst-controlled routes towards **A**. These approaches, however, rely on the more established rhodium-catalyzed enantioselective formation of C–C bonds[11] (**C**→**A**, Scheme 1) and copper-catalyzed enantioselective formation of C–H bonds[12] (**D**→**A**, Scheme 1).[13]

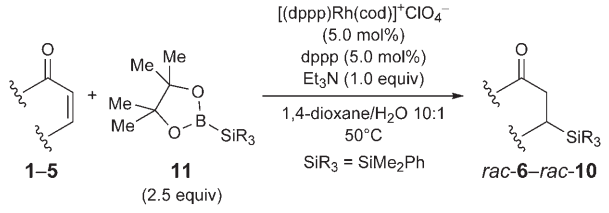
Inspired by the rhodium-catalyzed 1,4-addition of aryl boronic acids,[14] and aware of the diverse transition-metal-catalyzed chemistry of Si–B compounds,[15] we envisioned a rhodium-catalyzed (asymmetric) conjugate silyl transfer through the use of silyl boronic esters as the silyl anion source.[16] Herein we report an unprecedented conjugate C–Si bond-forming reaction, which, for the first time, enables the catalytic asymmetric 1,4-addition of nucleophilic silicon to cyclic α,β-unsaturated carbonyl compounds with excellent levels of stereoinduction.



Scheme 1. Strategies for the transition-metal-catalyzed enantioselective construction of α-chiral β-silylated carbonyl compounds.

Our search for catalysts that would facilitate silyl transfer from pinacol-derived silyl boronic ester **11**[17] to 2-cyclohexenone (**2**) commenced with a systematic screening of rhodium (pre)catalysts (Scheme 2 and Table 1). For this, typical reaction conditions for the rhodium-catalyzed 1,4-addition of aryl boronic acids served as a reasonable reference point (1,4-dioxane/H_2O solvent mixtures at elevated reaction temperatures).[14] Two crucial observations emerged from these initial investigations: Both the presence of a base and the absence of strongly coordinating counterions were critical for product formation. Replacement of chloride by weakly or noncoordinating perchlorate led to the achiral cationic catalyst [(dppp)Rh(cod)]ClO_4.[18]

We were pleased to find that a combination of this catalyst (5.0 mol%) and an equimolar amount of the free bidentate ligand dppp (5.0 mol%) in the presence of triethylamine as the base (1.0 equiv) promoted the desired 1,4-addition—KOH (1.0 equiv) performed equally well[19] (Scheme 2 and Table 1). The rhodium-catalyzed silyl transfer from **11** (2.5 equiv) to cyclic enones **1–3** in aqueous 1,4-dioxane at 50 °C afforded racemic products **6–8** in good yields (Table 1, entries 1–3). Acyclic enone **4** was less reactive under identical reaction conditions and required double the amount of catalyst and ligand, which then gave *rac*-**9** in good yield



Scheme 2. Rhodium-catalyzed conjugate silyl transfer (see Table 1). dppp = 1,3-bis(diphenylphosphanyl)propane, cod = 1,5-cyclooctadiene.

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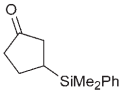
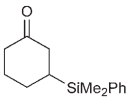
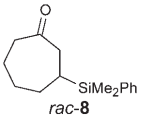
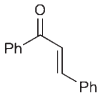
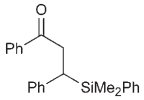
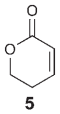
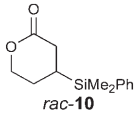
[**] Financial support for this work was provided by the Deutsche Forschungsgemeinschaft (Emmy Noether-Programm, 2001-2006), the Fonds der Chemischen Industrie, and the Aventis Foundation (Karl-Winnacker-Stipendium, 2006-2008). We thank Gerd Fehrenbach for performing the HPLC analyses.

Table 1: Rhodium-catalyzed conjugate silyl transfer (see Scheme 2).

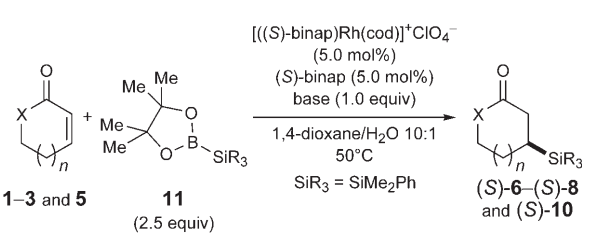
Entry	Substrate	Product	Yield [%][a]
1	 **1**	 *rac*-**6**	82
2	 **2**	 *rac*-**7**	76
3	 **3**	 *rac*-**8**	81
4[b]	 **4**	 *rac*-**9**	77
5	 **5**	 *rac*-**10**	76

[a] Yield of analytically pure product isolated by flash chromatography on silica gel. [b] $[(dppp)Rh(cod)]^{+}ClO_4^{-}$ (10 mol%) and dppp (10 mol%).

(Table 1, entry 4). Besides cyclic α,β-unsaturated ketones **1**–**3**, lactone **5** displayed similar reactivity and provided *rac*-**10** cleanly (Table 1, entry 5).

We then addressed the elusive enantioselective 1,4-addition of nucleophilic silicon to cyclic substrates by using the chiral catalyst $[((S)\text{-binap})Rh(cod)]ClO_4$[18] (5.0 mol%) with additives (*S*)-binap (5.0 mol%) and triethylamine (1 equiv)[19] (Scheme 3 and Table 2). To our delight, conjugate silylation of cyclic enones **1**–**3** proceeded with remarkably high enantioselectivities (Table 2, entries 1–3). Unfortunately, the yields of the isolated products (*S*)-**6**–(*S*)-**8** decreased with increasing ring size.[20] Thus, α,β-unsaturated lactone **5** underwent the silyl transfer with excellent enantioselectivity and in reasonable yield (Table 2, entry 4) whereas acyclic enone **4** was completely inert under these reaction conditions. The absolute configuration of (*S*)-**6**[21] and (*S*)-**7**[22] was assigned unambiguously by comparison with reported data, while those of (*S*)-**8** and (*S*)-**10** were assigned on the basis of similar HPLC characteristics on a chiral stationary phase and the sign of the optical rotation.[22]

We generally used catalyst and ligand loadings of 5.0 mol% in these reactions. We reduced the amount of $[((S)\text{-binap})Rh(cod)]ClO_4$ and (*S*)-binap to 1.0 mol% for the



Scheme 3. Catalytic asymmetric conjugate silyl transfer (see Tables 2 and 3). binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

Table 2: Catalytic asymmetric conjugate silyl transfer (see Scheme 3).

Entry	Substrate	*n*	X	Base	Product	Yield [%][a]	*ee* [%][b]	$[\alpha]_D$[c]
1	**1**	0	CH_2	Et_3N	(*S*)-**6**	70	97	−131
2	**2**	1	CH_2	Et_3N	(*S*)-**7**	45	96	−85.8
3	**3**	2	CH_2	Et_3N	(*S*)-**8**	22	92	−66.9
4	**5**	1	O	Et_3N	(*S*)-**10**	58	96	−38.1

[a] Yield of analytically pure product isolated by flash chromatography on silica gel. [b] HPLC analysis on Daicel columns provided baseline separation of the enantiomers: Chiralpak AD-H column (*n*-heptane/*i*PrOH 300:1 at 20°C) for **6**: t_r = 21.8 min for (*S*)-**6** and 23.7 min for (*R*)-**6**; Chiralpak AD-H column (*n*-heptane/*i*PrOH 100:1 at 20°C) for **7**: t_r = 9.48 min for (*S*)-**7** and 10.7 min for (*R*)-**7**; Chiralcel OD-H column (*n*-heptane/*i*PrOH 100:1 at 20°C) for **8**: t_r = 13.5 min for (*S*)-**8** and 14.9 min for (*R*)-**8**; Chiralpak AD-H column (*n*-heptane/*i*PrOH 100:1 at 20°C) for **10**: t_r = 19.5 min for (*S*)-**10** and 20.5 min for (*R*)-**10**. [c] *c* = 2.21 for (*S*)-**6**, 2.86 for (*S*)-**7**, 1.07 for (*S*)-**8**, and 1.77 for (*S*)-**10** in $CHCl_3$ at 20°C.

thus far best reaction **1**→(*S*)-**6** (70%, 97% *ee*), which resulted in a substantial decrease in the yield and, importantly, the enantioselectivity (47%, 85% *ee*). An excess of the free ligand, (*S*)-binap, was indispensable to ensure high enantioselectivities. The catalyst alone induced distinctly diminished enantioselection (55%, 74% *ee*).

The influence of the base on the yield and stereoinduction of related rhodium-catalyzed processes is known.[14,19] A brief survey of different organic and inorganic bases confirmed these findings for **1**→(*S*)-**6** (Table 3). Sterically hindered

Table 3: Influence of the base on enantioselectivity (see Scheme 3).

Entry	Substrate	*n*	Base	Product	Yield [%]	*ee* [%]
1	**1**	0	TMP	(*S*)-**6**	75	96
2	**1**	0	morpholine	(*S*)-**6**	0	–
3	**1**	0	K_3PO_4	(*S*)-**6**	71	98
4	**1**	0	KOH	(*S*)-**6**	68	59
5	**2**	1	KOH	(*S*)-**7**	45	78

2,2,6,6-tetramethylpiperidine (TMP) was comparable with triethylamine (Table 3, entry 1). In contrast, (*S*)-**6** was not produced when morpholine was used as the base (Table 3, entry 2). Inorganic bases such as K_3PO_4 and KOH also gave different results: stereoinduction as high as 98% *ee* was obtained with the former (Table 3, entry 3), whereas a pronounced negative effect was seen with the latter for **1** as well as **2** (Table 3, entries 4 and 5).

In summary, we have presented a novel transition-metal-catalyzed C–Si bond-forming reaction. In the presence of cationic rhodium complexes, the Si–B fragment functions as an equivalent of nucleophilic silicon, which is efficiently transferred onto acyclic as well as cyclic α,β-unsaturated carbonyl compounds. Chiral $[((S)\text{-binap})Rh(cod)]ClO_4$ has effected an unprecedented asymmetric 1,4-addition to cyclic acceptors in high enantiomeric excesses. This transformation might also pave the way for synthetically useful tandem processes. Extension of this line of research including mechanistic investigations[23] is our current focus.

Experimental Section

General procedure: A Schlenk tube equipped with a magnetic stir bar in an argon atmosphere was charged with the rhodium catalyst

(5.0 mol%) and the ligand (5.0 mol%). The compounds were then dissolved in deoxygenated 1,4-dioxane/H_2O 10:1 (ca. 0.5 M based on substrate). The α,β-unsaturated acceptor (1.0 equiv), the silyl boronic ester (2.5 equiv), and the base (1.0 equiv) were then added and the reaction mixture maintained at 50 °C for 16 h. After cooling the mixture to room temperature, silica gel was added and the solvents were evaporated under reduced pressure. The residue was subjected to flash column chromatography on silica gel using cyclohexane/ethyl acetate solvent mixtures as the eluent.

Received: May 3, 2006
Published online: July 21, 2006

Keywords: asymmetric catalysis · boron · homogeneous catalysis · rhodium · silicon

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