Highly Stereo- and Regioselective Allylations Catalyzed by Mo−Pyridylamide Complexes: Electronic and Steric Effects of the Ligand

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Introduction

The asymmetric allylic substitution catalyzed by Pd(0) complexes has developed into a powerful synthetic method permitting highly stereoselective carbon−carbon and carbon-heteroatom bond formation.[1] The analogous Mo(0)-catalyzed reaction[2] has also been the subject of recent studies,[3] but is still less developed. Interestingly, the latter process exhibits complementary behavior, in that reversed regioselectivity in the nucleophilic attack as compared to Pd usually is observed.[4] Thus, with diethyl malonate as a nucleophile the Pd-catalyzed process yields the less substituted product when unsymmetrical substrates are used whereas the more substituted one is obtained employing Mo catalysts.

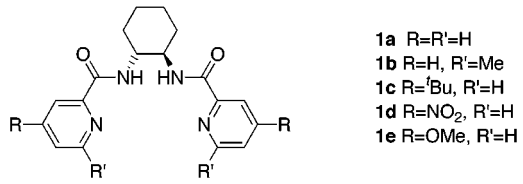
We have recently found that Pd-catalyzed allylations with a variety of *N*,*N*-, *N*,*P*-, and *P*,*P*-based ligands occur rapidly using microwave irradiation affording products in high yield and with high enantioselectivity.[5] The Mo-catalyzed process suffers from lower reactivity, usually requiring reflux in, e.g., toluene for a long time to proceed. Replacing CO ligands by more labile ligands,[6] employing, e.g., $Mo(CO)_3(EtCN)_3$ as a precatalyst, or using Mo(II)[7] or Mo(IV)[8] complexes increases the reactivity, albeit at the expense of experimental convenience. We were therefore pleased to find that the reaction of 3-phenyl-2-propenyl carbonate with dimethyl sodiomalonate occurs readily under microwave irradiation under air in the presence of (1*R*,2*R*)-1,2-bis-(2-carboxyamido]cyclohexane (**1a**)[3a] and inexpensive and easily available $Mo(CO)_6$.[9]

Having developed the Mo-catalyzed allylic substitution into a rapid and convenient process, we wanted to further improve the reaction. Facile access to substituted derivatives of **1a**,[10] prompted us to study the influence of substituents in the pyridine ring on the reactivity and selectivity of the reaction.

Results and Discussion

Our previous investigation showed that cinnamate **2** undergoes rapid substitution with dimethyl sodiomalonate in the presence of $Mo(CO)_6$ and ligand **1a** under microwave irradiation. After 5 min at 250W an 87% yield of **3a** (98% ee) and **3b** in a 19:1 ratio was obtained (Scheme 1).[9]

To study the influence of steric and electronic properties of the ligand on the catalytic properties of the molybdenum complex, ligands **1b**−**e** were prepared. The ligands were obtained through reaction of two equivalents of the appropriate pyridine carboxylic acid with (1*R*,2*R*)-1,2-diaminocyclohexane using Mukaiyama's reagent[11] (for **1b**, **1d**, and **1e**) or via the acid chloride (for **1c**).



1a R=R'=H
1b R=H, R'=Me
1c R=^{t}Bu, R'=H
1d R=NO_2, R'=H
1e R=OMe, R'=H

First the influence of alkyl groups in the 6- and 4-positions of the pyridine ring on the reaction was studied. Replacing **1a** with **1b**, carrying a methyl group in 6-position of the pyridine ring, resulted in a catalyst with considerably lower activity, affording the product in merely 30% yield after 5 min at 200W (Table 1). The enantioselectivity was also considerably lower for **1b** (79% ee) than for **1a**. In contrast, **1c**, with a *tert*-butyl substituent in 4-position, afforded the same high enantioselectivity as **1a**, but the reaction was still slow (46% yield after 5 min at 200W). It was thus concluded that the introduction of alkyl substituents on the pyridine ring resulted in catalysts with inferior properties. Electronic factors proved to be important. The 4-nitro-substituted ligand **1d** exhibited good stereoselectivity (97% ee) but

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Scheme 1

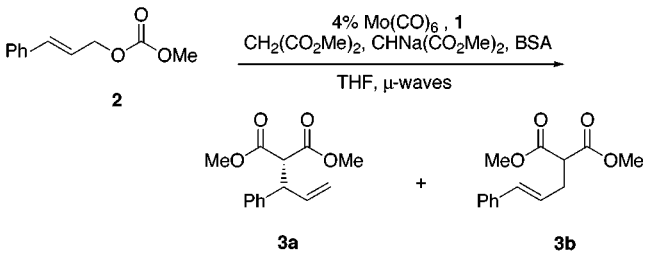

Table 1. Results of the Catalytic Reaction (Scheme 1) Using Ligands 1a−e

entry	ligand	effect (W), time (min)	yield of **3a**[a] (%)	**3a**/**3b**[a]	% ee[b]
1	**1a**	200, 6	82	19:1	98
2	**1a**	200, 5	71	19:1	98
3	**1b**	200, 5	30	13:1	79
4	**1c**	200, 5	46	13:1	98
5	**1d**	200, 5	7	16:1	97
6	**1d**	200, 8	32	16:1	97
7	**1d**	150, 15	37	16:1	97
8	**1e**	200, 4	>95 (88)[c]	41:1	>99
9	**1e**	200, 5	>95 (89)[c]	39:1	>99

[a] Determined by GC using internal standard. [b] Determined by chiral HPLC. [c] Isolated yield.

low reactivity (7% yield after 5 min and 32% yield after 8 min at 200W). Prolonged heating at lower effect did not result in considerably higher conversion (Table 1). The 4-methoxy-substituted ligand **1e** proved to have advantageous properties, however, affording the product in high yield (>95%), with high enantioselectivity (>99% ee) and with high regioselectivity (41:1).

The temperatures of the reaction mixtures were measured with an IR pyrometer, calibrated to the fluoroptic sensor used in the previous study of asymmetric molybdenum-catalyzed allylation.[9] The THF solution was easily superheated to 150−180 °C, whereafter the microwave absorption decreased to give a stable temperature. Temperature curves are shown in Figure 1.

It has been proposed that the increased Lewis acidity of the metal center enhances the reactivity of the catalytic system.[8c] The behavior of the present catalytic systems contrasts this assumption as the ligand with electron donating substituent (**1e**) exhibits higher reactivity than that carrying electron-withdrawing nitro groups (**1d**). The higher regioselectivity exhibited by ligand **1e** is in accordance with the statement by Trost[12] that σ-donating ligands enhance attack at the more substituted position.

The mechanism of molybdenum-catalyzed allylations has not yet been clearly established. Assuming a monomeric tetradentate planar complex as a reactive intermediate in the catalytic cycle, a substituent in 6-position is expected to exert severe sterical hindrance. From the results presented, it is concluded that sterical hindrance close to the coordination site is indeed deleterious for the selectivity as well as for the reactivity of the catalytic process.

Conclusion

New chiral bispyridylamido ligands were synthesized and studied in the microwave-induced Mo-catalyzed allylic substitution. The 4-methoxypyridine derivative **1e** and $Mo(CO)_6$ yielded >95% of the branched product with >99% ee and a regioisomer ratio of 41:1 within 4 min and thus proved to be superior to previously employed catalytic systems.

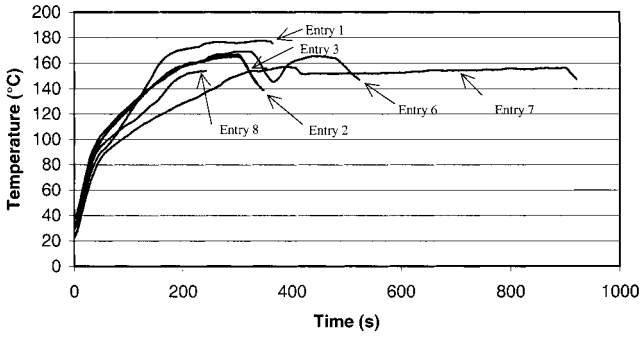

Figure 1. Temperatures measured during the reactions in Table 1 using an IR pyrometer sensor. Immediately after irradiation was completed, the reaction vessel was cooled in a water bath at room temperature. The temperature curves of entries 4, 5, and 9 are omitted for clarity, as they were quite similar to those of entries 2 and 3. The magnetron was overheated in some of the reactions, leading to a temporary shutdown, as seen in the curves of, e.g., entry 6 as a short-lasting decline in temperature.

Experimental Section

General Methods. Methyl 3-phenyl-2-propenylcarbonate[13] and **1a**[14] were prepared according to previously published procedures. THF was distilled over Na/benzophenone. The microwave heating was performed with a Micro Well 10 single-mode cavity from Personal Chemistry AB, Uppsala, Sweden, producing continuous irradiation at 2450 MHz (0−500 W). The microwave-assisted reactions were performed in oven-dried, GL18 screw thread Duran glass tubes (8.5 mL, 85 mm length). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100.6 MHz, respectively.

(1*R*,2*R*)-1,2-Bis-[(6-methylpyridine)-2-carboxyamido]cyclohexane (1b). A suspension of 6-methylpyridine-2-carboxylic acid hydrochloric salt[15] (389 mg, 2.24 mmol) and 2-chloro-*N*-methylpyridinium iodide (601 mg, 2.35 mmol) in 1,2-dichloroethane (5 mL) was cooled to 0 °C before the addition of ethyldiisopropylamine (897 mg, 1.2 mL, 6.94 mmol). The resulting yellow suspension was stirred for 10 min, and a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (128 mg, 1.12 mmol) in 1,2-dichloroethane (5 mL) was added at 0 °C. The reaction mixture was then refluxed for 2 h. The solvent was removed under reduced pressure, and the crude product was purified by liquid chromatography on silica gel (eluent: EtOAc) to yield 209 mg (53%) of **1b**: $[\alpha]^{20}_D$ −129.2 (*c* 0.472, $CHCl_3$); ^{1}H NMR δ 8.27 (1H, bs), 7.80 (1H, d, J = 7.8 Hz), 7.52 (1H, dd, J = 7.8 and 7.6 Hz), 7.08 (1H, d, J = 7.6 Hz), 3.99 (1H, bs), 2.45 (3H, s), 2.17 (1H, bs), 1.75 (1H, bs), 1.39 (2H, bs); ^{13}C NMR δ 164.74, 157.12, 149.00, 137.08, 125.59, 118.98, 53.16, 32.61, 24.82, 24.14; GC−MS (*m*/*z*) 352 (M^+), 216, 120, 92, 79.

(1*R*,2*R*)-1,2-Bis[(4-*tert*-butyl)-2-carboxyamido]cyclohexane (1c). A suspension of 4-*tert*-butylpyridine-2-carboxylic acid[16] (200 mg, 1.1 mmol) in dichloromethane (10 mL) and one drop of DMF was cooled to 0 °C. Oxalyl chloride (0.24 mL, 2.75 mmol) in dichloromethane (5 mL) was added dropwise during 20 min. The reddish solution was stirred for 20 min. The reaction mixture was concentrated under reduced pressure to yield a dark solid. A solution of (1*R*,2*R*)-1,2-diaminocyclohexane (64 mg, 0.55

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mmol) in dichloromethane (10 mL) was added under nitrogen, and the solution was cooled to 0 °C. Pyridine (2 mL) was added dropwise and the reaction was stirred at room temperature for 18 h. The crude reaction mixture was washed with $NaHCO_3$ (10 mL), and the organic phase was dried ($MgSO_4$). Liquid chromatography on silica gel (eluent: EtOAc) yielded 56 mg (23%) of **1c**: $[\alpha]^{20}_D$ −21.1 (*c* 0.285, $CHCl_3$); ^{1}H NMR δ 8.41 (1H, dd, J = 5.3, 0.8 Hz), 8.24 (1H, bs), 8.10 (1H, dd, J = 2.0, 0.8 Hz), 7.32 (1H, dd, J = 5.3, 2.0 Hz), 4.05 (1H, bs), 2.21 (1H, bs), 1.82 (1H, bs), 1.46 (2H, bs), 1.28 (9H, s); ^{13}C NMR δ 165.31, 161.88, 150.12, 148.42, 123.26, 119.65, 53.58, 35.36, 33.07, 30.84, 25.20; GC−MS (*m*/*z*) 436 (M^+), 258, 162, 134, 79. Anal. Calcd for $C_{26}H_{36}N_4O_2$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.27; H, 8.34; N, 12.70.

(1*R*,2*R*)-1,2-Bis[(4-nitropyridine)-2-carboxyamido]cyclohexane (1d). A mixture of 4-nitropyridine-2-carboxylic acid[17] (100 mg, 0.59 mmol) and 2-chloro-*N*-methylpyridinium iodide (150 mg, 0.59 mmol) in dichloromethane (5 mL) was reacted with ethyldiisopropylamine (76 mg, 103 μL, 0.59 mmol) and (1*R*,2*R*)-1,2-diaminocyclohexane (34 mg, 0.30 mmol) in dichloromethane (3 mL) as described for **1b** (reflux for 18 h). Purification by liquid chromatography on silica gel (eluent: EtOAc) yielded 55 mg (45%) of **1d**: $[\alpha]^{20}_D$ −14.5 (*c* 0.117, $CHCl_3$); ^{1}H NMR δ 8.87 (1H, d, J = 5.3 Hz), 8.73 (1H, d, J = 2.3), 8.20 (1H, bs), 8.10 (1H, dd, J = 5.3, 2.3 Hz), 4.10 (1H, bs), 2.22 (1H, bs), 1.88 (1H, bs), 1.50 (2H, bs); ^{13}C NMR δ 162.82, 155.43, 153.27, 150.97, 118.88, 115.56, 54.14, 32.86, 25.10; GC−MS (*m*/*z*) 414 (M^+), 247, 151, 123, 77. Anal. Calcd for $C_{18}H_{18}N_6O_6$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.42; H, 4.55; N, 20.11.

(1*R*,2*R*)-1,2-Bis-[(4-methoxypyridine)-2-carboxyamido]-cyclohexane (1e). 4-Methoxypyridine-2-carboxylic acid[17] (132 mg, 0.86 mmol), 2-chloro-*N*-methylpyridinium iodide (230 mg, 0.9 mmol), ethyldiisopropylamine (465 mg, 0.63 mL, 3.6 mmol), and (1*R*,2*R*)-1,2-diaminocyclohexane (49 mg, 0.43 mmol) were reacted in 1,2-dichloroethane (2 + 1 mL) as described for **1b** (reflux 3 h). Liquid chromatography on silica gel (eluent: EtOAc) yielded 103 mg (62%) of **1e**: $[\alpha]^{20}_D$ −19.4 (*c* 0.525, $CHCl_3$); ^{1}H NMR δ 8.28 (1H, d, J = 5.9 Hz), 8.23 (1H, bs), 7.58 (1H, d, J = 2.6 Hz), 6.80 (1H, dd, J = 5.9, 2.6 Hz), 4.02 (1H, bs), 3.81 (3H, s), 2.18 (1H, bs), 1.80 (1H, bs), 1.43 (2H, bs); ^{13}C NMR δ 167.12, 164.82, 152.22, 149.65, 113.05, 107.72, 55.84, 53.64, 32.99, 25.20; GC−MS (*m*/*z*) 384 (M^+), 232, 136, 108, 79. Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.30; H, 6.19; N, 14.40.

General Procedure for Microwave-Assisted Allylic Alkylations. Two different stock solutions were prepared: "*Solution-N*", containing the nucleophile dimethyl sodiomalonate in THF, was made by adding dimethyl malonate (660 μL, 5.78 mmol) over a suspension of 60% NaH (20 mg, 0.50 mmol) in THF (10 mL). "*Solution-S*", containing the allylic substrate, was prepared by dissolving the internal standard 2,3-dimethylnaphthalene (401 mg, 2.6 mmol) and substrate **2** (4.01 g, 21 mmol) in THF (20 mL). The appropriate ligand (0.025 mmol) and $Mo(CO)_6$ (5 mg, 0.02 mmol) were transferred to a heavy-walled Pyrex tube. *Solution-N* (1 mL, 0.58 mmol of the nucleophile), *Solution-S* (0.5 mL, 0.53 mmol of the substrate **2**), and BSA (156 μL, 0.63 mmol) were added in this order and the sample was irradiated with the appropriate power and time (as indicated in Table 1). Directly after reaction, the reaction mixture (very dark colored) was cooled in a water-bath at room temperature and diluted with diethyl ether to a total volume of 10 mL (a precipitated appears). The yellow-orange solution was filtrated and analyzed by GC−MS. The GC−MS yields were calculated using the internal standard.

General Procedure for ee Determination. A sample from the diethyl ether phase (20 μL) was diluted to 1 mL with a mixture of hexanes and 2-propanol (9:1), filtered and injected into a chiral DAICEL CHIRALCEL OD-H (0.46 cm ∅ × 25 cm) HPLC column (eluent: degassed hexanes/2-propanol (99.5:0.5), flow rate: 0.5 mL/min, UV detection at 220 nm, $t_R(R)$ = 18.7 min, $t_R(S)$ = 20.2 min). Reported ee values are mean values of three to six injections.

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