Molybdenum-Catalyzed Asymmetric Allylic Alkylation Reactions Using $Mo(CO)_6$ as Precatalyst

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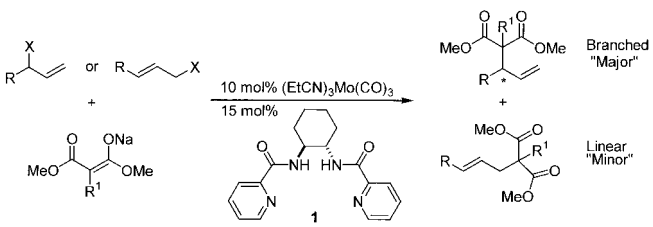
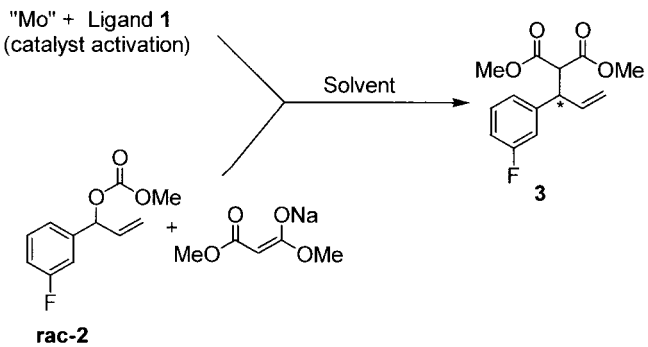
The transition metal-catalyzed asymmetric allylic alkylation of unsymmetrically substituted allyl derivatives has recently emerged as an effective method for the preparation of optically active branched regioisomers in high enantioselectivity and regioselectivity.[1] Results of these studies are in contrast to the traditional palladium-catalyzed reactions that predominantly afford the linear regioisomeric product.[2,3] Particularly interesting is the molybdenum-catalyzed asymmetric allylic alkylation method developed by Trost, which has emerged as one of the most promising methods for obtaining optically active branched regioisomeric products, Scheme 1.[1c,4] Indeed, high enantio- and regioselectivities have been achieved for a range of allylic substrates with various malonate nucleophiles.



Scheme 1. Trost's asymmetric allylic alkylation reaction

Our primary interest in the described reaction arose from our desire to utilize the chiral unsymmetrically substituted "branched" allylic derivative **3** as a key intermediate in the synthesis of a lead drug candidate (Scheme 2). The results published by Trost suggest that the molybdenum-catalyzed asymmetric allylic alkylation methodology would provide the desired product **3** in good enantio- and regioselectivities. However, it became clear that direct implementation of the reaction to large-scale production would not be straightforward due to the limited availability of the precatalyst $(EtCN)_3Mo(CO)_3$ and ligand **1**, both of which are not commercially available.[5,6] The synthesis of $(EtCN)_3Mo(CO)_3$ requires refluxing a solution of $Mo(CO)_6$ in a large excess of propionitrile.[7] This procedure represents a potential hazard since propionitrile decomposes upon heating to hydrogen cyanide and ethylene.[8]



Scheme 2. Synthesis of the desired optically active branched regioisomeric product

The effectiveness of $(EtCN)_3Mo(CO)_3$ as precatalyst presumably derives from the lability of the propionitrile ligand, thus allowing for facile substitution with the chiral ligand. In addition to $(EtCN)_3Mo(CO)_3$, Trost has recently disclosed that $(C_7H_8)Mo(CO)_3$ can be used in place of $(EtCN)_3Mo(CO)_3$ with comparable results.[9,10] Both $(EtCN)_3Mo(CO)_3$ and $(C_7H_8)Mo(CO)_3$ are air-sensitive and are made from the commercially available $Mo(CO)_6$. We reasoned that, since both molybdenum-precatalysts are derived from $Mo(CO)_6$, perhaps the air stable, readily available $Mo(CO)_6$ could be directly used as a molybdenum-

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precatalyst. In this communication we describe our efforts which have led to the successful and general use of $Mo(CO)_6$ in asymmetric allylic alkylations.[11]

The development of a molybdenum-catalyzed asymmetric allylic alkylation method employing $Mo(CO)_6$ as precatalyst would require establishing the necessary activation time and temperature in order to ensure complete catalyst formation between the $Mo(CO)_6$ precatalyst and ligand **1**. Complete catalyst formation is necessary in order to avoid undesirable catalysis by the $Mo(CO)_6$ precatalyst as well as other possible molybdenum complexes.[12] Towards this end, *in situ* IR was used to monitor the activation process. Consumption of $Mo(CO)_6$ [assigned ν(CO) 1984 cm^{-1} in toluene] and concomitant formation of the "active catalyst" [tentatively assigned ν(CO) 2011, 1984, 1891, 1818 cm^{-1} in toluene] was followed by monitoring the CO region of the IR spectrum.[13] Thus, heating a toluene solution of $Mo(CO)_6$ (0.175 M) and 1.5 equiv of ligand **1** in the presence of an *in situ* IR probe showed that 4 h at 85–90 °C was required to reach the minimum concentration of $Mo(CO)_6$ and maximum concentration of the "active" catalyst. In THF, this steady state was reached in approximately 2–3 h at 65 °C using similar concentrations of $Mo(CO)_6$ and ligand **1**. With these results in hand, initial asymmetric allylic alkylation experiments examined the effect of varying activation time and temperature of the catalyst/ligand solution, as well as a brief survey of solvents (Table 1).

Toluene and THF were first examined as solvents since they were used in molybdenum-catalyzed asymmetric allylic alkylation reactions previously reported in the literature.[1c,1e,4] As shown in Table 1, the optimal activation times that were determined by *in situ* IR proved to be experimentally superlative. Longer or shorter activation times provided the desired product in either lower enantioselectivity, regioselectivity, or yield. Reactions carried out in toluene provided higher enantioselectivity and regioselectivity than in THF. Activation of the catalyst in THF at 65 °C followed by a room temperature alkylation reaction resulted in higher enantioselectivity, but in lower product yield (Table 1, entry 6). Similarly, alkylation reactions performed in toluene at temperatures < 65 °C were found to be extremely slow, presumably due to the poor solubility of the dimethyl sodiomalonate in toluene. Other solvents including DMF, 1,2-dimethoxyethane (DME), and 1,2-dichloroethane (DCE) were found to be less effective in either enantioselectivity or product yield (Table 1, entries 7–9).

A fundamental question which now arises is whether the same active catalyst is generated regardless of the molybdenum precatalyst. To answer this, a comparison study was performed involving three different molybdenum precatalysts ($(EtCN)_3Mo(CO)_3$, $(C_7H_8)Mo(CO)_3$, $Mo(CO)_6$) in two different solvents (THF and toluene).[14] Results of these studies, shown in Table 2, reveal that the enantioselectivity and regioselectivity are similar within each solvent system regardless of the molybdenum precatalyst. In addition, the same major product enantiomer was obtained in all cases using the same enantiomeric ligand **1**.

Other substrates were also examined using $Mo(CO)_6$ as precatalyst, with the results shown in Table 3. The enantioselectivity and regioselectivity obtained for entries 1–3 were comparable to those obtained by Trost using $(EtCN)_3Mo(CO)_3$ as precatalyst.[1c] The asymmetric allylic alkylation of the linear carbonate shown in entry 2 gave slightly better enantioselectivity and regioselectivity than the branched carbonate shown in entry 1, which also parallels the findings of Trost.[1c,15]

Table 1 Asymmetric allylic alkylation reactions of carbonate **2** with sodiodimethyl malonate using catalytic $Mo(CO)_6$/ligand **1**.[a]

Entry	Solvent	Activation Time (h)	Activation Temp(°C)[c]	% ee of **3**[b]	Branched : Linear	% Assay Yield[d]
1	toluene	0.75	85	95	95 : 5	77
2	toluene	4	85	97	95 : 5	91(84)
3	toluene	15	85	89	92 : 8	91
4[e]	THF	2	65	92	92 : 8	86
5[e]	THF	4	65	92	89 : 11	83
6	THF	4	65 to rt[f]	96	84 : 16	33
7	DMF	4	85	87	86 : 14	55
8	DME	4	80	95	85 : 15	90
9	DCE	4	80	98	96 : 4	36

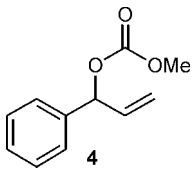
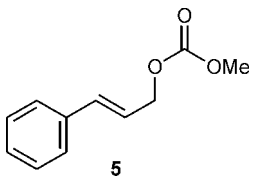
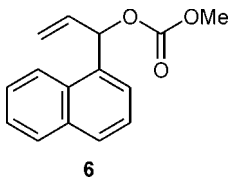
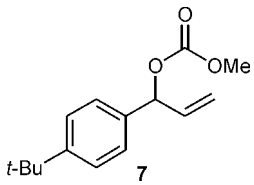
[a] Reaction conditions: 10 mol% $Mo(CO)_6$, 15 mol% ligand **1**, 2.0 equiv dimethyl sodiomalonate, 0.15 M substrate **2**, reaction time: 8–12 h.
[b] Determined by HPLC using a chiral column (CHIRALPAK AD, 25 cm × 4.6 mm, 10 μm particle diameter).
[c] The activation temperature [$Mo(CO)_6$ + ligand **1** in solvent] is also the alkylation reaction temperature.
[d] Yield in parentheses represent isolated product yield with purity > 95% as determined by HPLC and ^1H NMR.
[e] Results reported in entries 4 and 5 represent the average of two or more runs.
[f] Activation of the catalyst was performed at 65 °C, and subsequent alkylation reaction performed at room temperature.

Table 2 Comparison of different molybdenum-precatalyst for the allylic alkylation of carbonate **2** with sodiodimethyl malonate.[a]

Entry	Mo-precatalyst[b]	Solvent	Activation Time (h)	Activation Temp(°C)[c]	% ee of **3**[d]	Branched:Linear	% Assay Yield of **3**
1	$(EtCN)_3Mo(CO)_3$	toluene	0.5	85	95	93:7	84
2	$(C_7H_8)Mo(CO)_3$	toluene	0.5	85	96	96:4	87
3	$Mo(CO)_6$	toluene	4	85	97	95:5	91
4	$(EtCN)_3Mo(CO)_3$	THF	0.5	65	91	90:10	88
5	$(C_7H_8)Mo(CO)_3$	THF	0.5	65	88	88:12	81
6	$Mo(CO)_6$	THF	4	65	91	89:11	83

[a] Results represent the average of two or more runs.
[b] $(EtCN)_3Mo(CO)_3$ was prepared using a literature procedure, see reference 7.
[c] The activation temperature [$Mo(CO)_6$ + ligand **1** in solvent] is also the subsequent alkylation reaction temperature.
[d] Determined by HPLC using a chiral column (CHIRALPAK AD, 25 cm × 4.6 mm, 10 μm particle diameter).

Table 3 Asymmetric allylic alkylation of various carbonates with sodiodimethyl malonate using catalytic $Mo(CO)_6$/ligand **1**.[a]

Entry	Substrate	% ee[b]	Branched:Linear	% Isolated Yield[c]
1	 **4**	96	93:7	76
2	 **5**	99	95:5	80
3	 **6**	96	98:2	80
4	 **7**	94	94:6	76

[a] Reaction conditions: 10 mol% $Mo(CO)_6$, 15 mol% ligand **1**, 2.0 equiv dimethyl sodiomalonate, 0.15 M substrate in toluene, reaction temperature: 85 °C, reaction time: 8–12 h.
[b] Determined by HPLC using a chiral column (CHIRALPAK AD, 25 cm×4.6 mm, 10 μm particle diameter).
[c] Isolated yields represent the average of two runs with product purity >95% as determined by HPLC and ^{1}H NMR.

In summary, the molybdenum-catalyzed asymmetric allylic alkylation reaction originally developed by Trost has been modified by using the readily available $Mo(CO)_6$ in place of $(EtCN)_3Mo(CO)_3$. Using *in situ* IR, the proper activation time required to maximize catalyst formation was determined. The new protocol has been shown to be effective for various substrates. Results from comparison studies are consistent with the notion that the same active catalyst is generated regardless of the molybdenum-precatalyst. Current work is focused on determining the structure of the active catalyst and on developing a better understanding of the mechanistic aspects controlling the enantio- and regioselectivity.

Experimental Section

Representative Procedure for the Asymmetric Allylic Alkylation Reaction

A 12-L, 3-necked round-bottomed flask was charged with $Mo(CO)_6$ (219 g, 0.828 mol), ligand **1** (402 g, 1.24 mol), and evacuated/back filled with argon (3 cycles). To this was added anhydrous toluene (4.36 L). The flask was evacuated/back filled with argon (3 cycles) and the resulting mixture heated to 85–88 °C for 4 hours. Separately, a 100-L flask was charged with dimethyl sodiomalonate (2.36 kg, 12.42 mol), a toluene solution of carbonate **2** (2.0 kg, 8.28 mol, 3 L of anhydrous toluene), and toluene (30.6 L). The flask was evacuated/back filled with argon and the resulting solution heated to 70 °C followed by the addition of the catalyst solution via cannula. The resulting mixture was heated to 85 °C for 15 h and subsequently cooled to room temperature. Water (36 L) was added and the organic layer separated and filtered through a small pad of silica gel. Product assay yield was 91%, with a 97% ee and a 95 : 5 regioselectivity (branched:linear ratio). R_f = 0.35 (hexane: EtOAc = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.52 (m, 2H), 7.01 (d, J = 7.7 Hz, 1H), 6.90–6.95 (m, 2H), 5.96 (ddd, J = 17.0, 10.2, 8.2 Hz, 1H), 5.11–5.16 (m, 2H), 4.09–4.14 (m, 1H), 3.84 (d, J = 10.9 Hz, 1H), 3.75 (s, 3H), 3.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 167.6, 162.8 (d, J_{CF} = 241 Hz), 142.6 (d, J_{CF} = 10 Hz), 137.1, 131.0 (d, J_{CF} = 10 Hz), 123.6 (d, J_{CF} = 10 Hz), 117.2, 114.9 (d, J_{CF} = 20 Hz), 114.1 (d, J = 10 Hz), 57.1, 52.6, 52.5, 49.3; IR (neat, cm^{-1}): 2955, 1732, 1614, 1590, 1489, 1435, 1268, 1177, 1140, 1026; anal. calcd. for $C_{14}H_{15}O_4F$: C, 63.15; H, 5.68%; found C, 62.94; H, 5.63%; HPLC (ChiralPak AD, 4.6×250 mm, flow rate = 0.8 mL/min, detection at 210 nm, 2% MeOH in hexane), t_R = 9.1 min (minor), t_R = 10.4 min (major).

Reference

[1] (a) G. C. Lloyd-Jones, A. Pflatz, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 462–464; (b) J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025–8026; (c) B. M. Trost, I. Hachiya, *J. Am. Chem. Soc.* **1998**, *120*, 1104–1105; (d) P. A. Evans, J. D. Nelson, *J. Am. Chem. Soc.* **1998**, *120*, 5581–5582; (e) F. Glorius, A. Pfaltz, *Organic Lett.* **1999**, *1*, 141–144.

[2] For reviews on asymmetric transition metal-catalyzed allylic alkylations, see (a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422; (b) T. Hayashi, in: *Catalytic Asymmetic Synthesis*, (Ed.: I. Ojima), VCH, New York, **1993**, pp 325–365.

[3] For notable exceptions wherein chiral branched products are obtained as the major isomer using palladium-catalyzed systems, see: (a) T. Hayashi, M. Kawatsura, Y. Uozumi, *J. Chem. Soc., Chem. Commun.* **1997**, 561–562; (b) R. Prétôt, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 323–325.

[4] B. M. Trost, S. Hildbrand, K. Dogra, *J. Am. Chem. Soc.* **1999**, *121*, 10416–10417.

[5] The only reported synthesis of ligand **1** yields the desired product in 47% yield from picolinic acid and 1,2-diaminocyclohexane, via activation with triphenyl phosphite. See: D. J. Barnes, R. L. Chapman, R. S. Vagg, E. C. Walton, *J. Chem. Eng. Data.*, **1978**, *23*, 348–359. We have found that activation of picolinic acid with 1,1-carbodiimidazole is remarkably effective and provides crystalline ligand **1** in 86% isolated yield, D. A. Conlon, N. Yasuda, *Adv. Synth. Catal.*, **2001**, *343*, 137–138.

[6] During the course of manuscript review, ligand **1** became commerically available from Strem Chemical Company.

[7] G. J. Kubas, L. S. Van Der Sluys, *Inorg. Syntheses*, **1990**, *28*, 29–33.

[8] *The Merck Index*, 11th ed, Merck & Co., Inc. Rahway N. J. 1989 item 7839, pp 1244.

[9] B. M. Trost, personal communication.

[10] $(C_7H_8)Mo(CO)_3$ is commercially available in limited quantities from Strem Chemical Co. For the synthesis of $(C_7H_8)Mo(CO)_3$ see: F. A. Cotton, J. A. McCleverty, J. E. White, *Inorg. Syntheses*, **1990**, *28*, 45–47.

[11] Subsequent to manuscript review, a report describing the asymmetric alkylation of allyl carbonates with sodiodimethyl malonate using $Mo(CO)_6$ as precatalyst with ligand **1** appeared. The reaction employs the use of microwave irradiation resulting in internal reaction temperatures of 140–180 °C. See: O. Belda, N.-F. Kaiser, U. Bremberg, M. Larhed, A. Hallberg, C. Moberg, *J. Org. Chem.* **2000**, *65*, 5868–5870.

[12] The $Mo(CO)_6$-catalyzed alkylation reaction of carbonate **2** performed in the absence of ligand **1** gave, after 15 h at 90 °C, a 42% assay yield of a mixture of regioisomeric products in a 1.4 : 1 ratio of branched to linear products. By comparison, alkylations performed using the chiral catalyst are complete within 8–12 h. No alkylation product was observed in the absence of any molybdenum-precatalyst.

[13] A waterfall plot of the CO region of the IR spectra from our *in situ* IR studies is included in the supporting information.

[14] Preliminary *in situ* IR data show that activation of $(C_7H_8)Mo(CO)_3$ with ligand **1** was achieved in < 30 min. Similarly, Trost and Pfaltz used a 30 min activation time at 60–65 °C using $(EtCN)_3Mo(CO)_3$ as precatalyst in THF.

[15] Trost has suggested that π-allylmolybdenum complexes **A** and **B** are in dynamic equilibrium and that the enantiodifferentiating step is preferential nucleophilic attack of the malonate on either π-allylmolybdenum complex **A** or **B** (ref. [1c]). The small differences observed in using the prochiral linear carbonate versus the racemic branched carbonate may arise from the ability of the prochiral linear carbonate to preferentially produce one π-allylmolybdenum complex over the other, whereas, ionization/complexation of the racemic branched carbonate produces a 50:50 mixture of diastereomeric π-allylmolybdenum complexes. This would then suggest that equilibration of the π-allylmolybdenum complexes **A** and **B**, although rapid, is not fully under Curtin-Hammett conditions. Our preliminary results show that a kinetic resolution of the racemic carbonate **4** afforded a 5% ee of starting material at 52% conversion at 90 °C in toluene, giving a k_{rel} of 1.12. Using the opposite enantiomer ligand, a ~10% ee at 88% conversion was observed, giving a k_{rel} of 1.10. k_{rel} was calculated using the equa-

tion k_{rel} = ln[(1 – c)(1 – ee)]/ln[(1 – c)(1 + ee)], where ee is the enantiomeric excess of the starting material and c the conversion of the starting material. See: H. B. Kagan, J. C. Fiaud, in: *Topics in Stereochemistry Vol 5* (Eds.: N. L. Allinger, E. L. Eliel), Interscience; New York **1987**, vol 14, pp 249.