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Asymmetric molybdenum(0)-catalyzed allylic substitution

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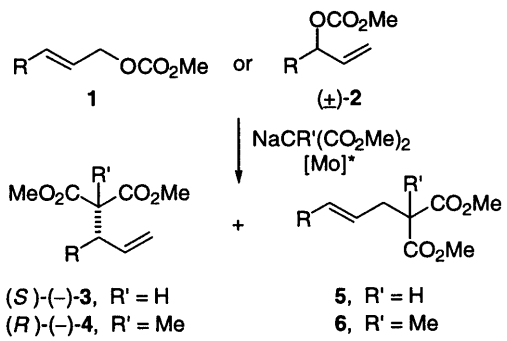
Abstract—Application of new ligands (*R*)-(−)-**8**, (*S*)-(+)-**16**, and (*S*)-(+)-**17** to the title reaction (**1** or **2** → **3**) led to excellent regio- and enantioselectivities (>30:1; ≤98% ee); although lacking the C_2-symmetry, the catalysts can be viewed as *quasi*-C_2-symmetrical since the single chiral center is sufficient to determine the sense of wrapping of the metal by the ligand. © 2001 Published by Elsevier Science Ltd.

Recently, Trost has reported on the first examples of high asymmetric induction in Mo(0)-catalyzed allylic substitution employing cinnamyl carbonates **1a** and **2a** and their aromatic, heteroaromatic, and other conjugated analogues as model substrates (Scheme 1):[1] with malonate-type nucleophiles and bis-picolinic amide **7**[2] as the chiral ligand (Fig. 1), both the regio- and enantioselectivities attained were excellent (in favor of **3**; Table 1, entries 1 and 2).[1] A similar strategy was adopted by Pfaltz,[3] who designed analogous ligands with oxazoline units in place of Trost's picolinic amide moieties.[4,5,‡] Application of microwave heating has now been reported by Moberg to further improve the reactivity of the Mo/**7** catalyst.[6]

While Trost,[1] Pfaltz,[3] and Moberg[6] have employed C_2-symmetrical ligands with *trans*-1,2-diaminocyclohexane as the chiral scaffold, we felt that one chiral center might be sufficient to determine the sense of wrapping of the metal by the ligand, thereby creating a similar chiral environment. In order to verify this hypothesis, we focused on ligand (*R*)-(−)-**8** that was readily prepared (Scheme 2) via conversion of (*R*)-(−)-methyl phenylglycinate into amide (*R*)-(−)-**12** (aq. NH_3, toluene, 70%),[7] followed by reduction ($LiAlH_4$, THF, 45%),[8] and transformation of the resulting diamine **13** into bis-amide (*R*)-(−)-**8** [α-picolinic acid, $(PhO)_3P$, pyridine, 60%].[§]



Scheme 1. **a**, R = Ph; **b**, 2-thienyl; **c**, 1-cyclohexenyl.

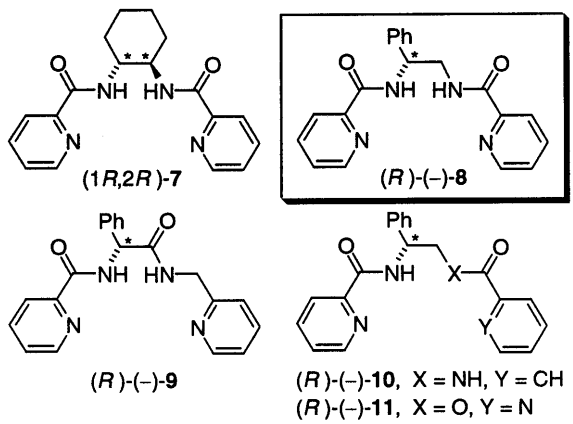


Figure 1.

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‡ For an earlier observation by us of an asymmetric induction with Mo–bis-oxazoline complexes, see Ref. 4. Since this experiment required a high catalyst loading, it was only cited in a footnote.

§ For the method, see Ref. 2b.

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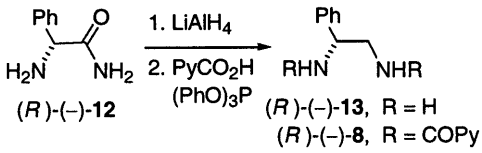
Cinnamyl-type carbonates **1a** and **2a**, in conjunction with malonate nucleophiles, were employed to probe the efficiency of ligand **8** (Scheme 1, Table 1). The catalyst was generated in situ from $(EtCN)_3Mo(CO)_3$[9] or $(C_7H_8)Mo(CO)_3$[10] and (*R*)-(−)-**8** in THF;[‖] upon addition of the ligand, the solution turned deep-red (instantaneously with the former and within 5 min with the latter complex). The reactions with $NaCH(CO_2Me)_2$, carried out in THF at 60°C, proved to be fairly regio- and enantioselective in favor of the branched product **3a** ($\geq$8:1, ~90% ee; entries 3, 4, and 6) with good yields.[¶] Little difference was observed between the regioisomeric substrates **1a** and **2a** (Table 1, entries 3, 4, and 6) and identical results were obtained with the catalyst generated from $(EtCN)_3Mo(CO)_3$ and $(C_7H_8)Mo(CO)_3$ (compare entries 3 and 4).[¶] With $NaCMe(CO_2Me)_2$, the reaction proved to be much slower and the selectivity lower (entry 5).[**]

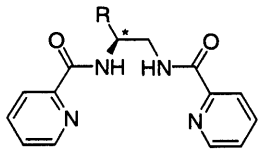
Ligand **8**, as well as its predecessor **7**,[1,3,6] can a priori offer up to four ligating atoms, namely the pyridine nitrogens and either the amidic carbonyls or nitrogen atoms. To investigate the role of the individual structural features, we have synthesized ligands **9**–**11** (Fig. 1), all of which then turned out to be inferior to **8**.



Scheme 2. Py = α-pyridyl.

Thus, ligand **9** (a positional isomer of **8**) failed to bring about the reaction, while **11** (an ester/amide) was non-selective (1:1 ratio of **3a**:**5a**) and gave low conversion rate (26%). With **10** (lacking one pyridine nitrogen atom), the enantioselectivity was high (entry 7); however, the low conversion in this instance suggests an almost stoichiometric process that can occur with a different mechanism[4,11] and/or mode of coordination. Hence, these experiments have demonstrated that (1) the original structural characteristics of the Trost–Moberg ligand **7**[1,6] and its Pfaltz analogue,[3] namely the two sp^2-type nitrogen donors and two rigid amide groups, are essential, and (2) one chiral center in the scaffold is sufficient to induce high levels of enantioselectivity. Noteworthy is the enhanced reactivity of these Mo catalysts, as compared to the previously studied bipyridine and phenanthroline complexes.[12]

Although the mode of coordination of **7** and **8** to Mo is unknown at present,[††] it can be argued that the Ph group in the *quasi*-C_2-symmetrical ligand **8** acts as an anchor, presumably occupying an 'equatorial' position in the cyclic complex, thereby mimicking the rigid scaffold of **7**. We reasoned that the ligand performance may be improved by implementing a bulkier anchor R that would ensure more rigidity of the whole framework. Therefore, we have synthesized ligands (*S*)-(+)-**16** (R = $PhCH_2$) and (*S*)-(+)-**17** (R = *i*-Pr) from (*S*)-(+)-phenylalanine and (*S*)-(+)-valine amides, respectively, in a similar fashion as in the case of (*R*)-(−)-**8**. The benzyl derivative (*S*)-(+)-**16** (note the lower A value for $PhCH_2$ than for Ph)[13] turned out to exhibit somewhat lower enantioselectivity (74–89% ee) than the parent phenyl derivative (*R*)-(−)-**8** (compare entries 3–6 with 8–10). By contrast, the isopropyl ligand (*S*)-(+)-**17** (higher A value for *i*-Pr) gave much improved results that are in the same range as those reported by Trost (98% ee, 32:1 regioselectivity; compare entries 11 and 12 with 1 and 2).



(*S*)-(+)-**16**, R = $PhCH_2$
(*S*)-(+)-**17**, R = *i*-Pr

[‖] We favor $(C_7H_8)Mo(CO)_3$ as it is more air-stable than $(EtCN)_3Mo(CO)_3$ and, according to our experience, somewhat easier to prepare in a pure and defined form. Thus, while the preparation of the former complex is straightforward (reflux for 8 h, followed by Soxhlet extraction),[10a] the latter complex is usually contaminated by $(EtCN)_2Mo(CO)_4$ so that prolonged reflux (up to 3 days) and repeated crystallization is often required to obtain the pure species. The complex generated in situ from the latter contaminant and ligand **8** is practically inert in the catalytic reaction, as revealed by control experiments. This behavior seems to suggest that a tridentate coordination of the metal by **8** is required to generate an active catalyst. Our results, cited in Table 1, were obtained with pure $(EtCN)_3Mo(CO)_3$.

[¶] *Typical experiment*: A mixture of $(EtCN)_3Mo(CO)_3(EtCN)_3$ (34 mg, 0.1 mmol) and a ligand (0.15 mmol) was dissolved in THF (3 mL). The solution, which instantaneously turned deep red, was heated with stirring at 60°C for 40 min. The solution was cooled to room temperature and then a solution of the corresponding sodiomalonate (2.0 mmol) in THF (2 mL), generated from dimethyl malonate (or dimethyl methylmalonate) and NaH, and a solution of allylic carbonate (1.0–1.3 mmol) in THF (1 mL) were successively added. Usually, the addition of the reactants was accompanied by a change of color to orange or yellow-brown. The mixture was stirred at 60°C until the reaction was complete (as evidenced by TLC), then diluted with ether (20 mL), and washed successively with 5% aqueous $NaHCO_3$ and water. The organic phase was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (15×2 cm) with a 9:1 hexane–ethyl acetate mixture as an eluent. Enantiomeric purity of the products **3a** and **4a**, respectively, was determined by chiral HPLC using Chiralcel OD-H (**3a**) or Chiralpak AD (**4a**) columns (equipped with a guarding silica gel column) and a mixture of hexane and 2-propanol (99.5:0.5) as eluent; UV detection at 220 nm. For compound **3a**, retention times were as follows: (*S*)-enantiomer 17.4 min, (*R*)-enantiomer 18.7 min. For compound **4a**, retention times were: (*R*)-isomer 6.4 min, (*S*)-isomer 10.7 min.

[**] Note the pseudo-inversion of configuration of the product due to the change in the substituent priorities.

[††] Trost has hypothesized on a bidentate mode in the complex of **7** with *trans*-configuration of the ligating nitrogens about the metal center.[1]

Table 1. Mo(0)-catalyzed allylic substitution (Scheme 1)[a]

Entry	Substrate	R′	Ligand	Time (h)	Ratio **3**/**4**:**5**/**6**[b]	Yield (%)	ee of **3**/**4** (%)[c]
1	**1a**	H	**7**[d]	3	32:1	88	99 (*S*)[f]
2	**2a**	H	**7**[d]	3	13:1	70	92 (*S*)[f]
3	**1a**	H	**8**[d]	4	8:1	63	92 (*S*)
4	**1a**	H	**8**[e]	4	8:1	65	92 (*S*)
5	**1a**	Me	**8**[d]	12	4:1	37	73 (*R*)[g]
6	**2a**	H	**8**[d]	4	12:1	72	88 (*S*)
7	**1a**	H	**10**[d]	24	12:1	21	78 (*S*)
8	**1a**	H	**16**[d]	4	13:1	69	89 (*R*)[h]
9	**1a**	Me	**16**[d]	10	10:1	32	57 (*S*)[g,h]
10	**2a**	H	**16**[d]	4	13:1	68	74 (*R*)[h]
11	**1a**	H	**17**[d]	12	32:1	68	98 (*R*)[h]
12	**2a**	H	**17**[d]	12	38:1	59	97 (*R*)[h]
13	**1b**	H	**8**[e]	5	10:1	68	90 (*S*)
14	**1b**	H	**17**[e]	5	18:1	87	92 (*R*)[h]
15	**2b**	H	**7**[d]	2	19:1	78	88 (*S*)[f]
16	**1c**	H	**8**[e]	24	5.5:1	59	86 (*S*)
17	**1c**	H	**17**[e]	24	6.2:1	61	87 (*R*)[h]
18	**1c**	H	**7**[d]	3[i]	11.5:1	91	94 (*S*)[j]

[a] Conditions: THF, 60°C, cat. 7–10 mol%.
[b] Determined from the ^{1}H NMR spectra of the product mixture.
[c] Determined by chiral HPLC.
[d] The catalyst was generated from $(EtCN)_3Mo(CO)_3$.
[e] The catalyst was generated from $(C_7H_8)Mo(CO)_3$.
[f] Ref. 1a.
[g] The pseudo-inversion of configuration of the product is due to the change in the substituent priorities.
[h] Note that the ligand has the opposite absolute configuration to **8**.
[i] In a toluene–THF mixture at 90°C.
[j] Ref. 1b.

Similarly high selectivities were observed for the 2-thienyl and 1-cyclohexenyl substrates **1b** and **1c** (entries 13, 14, 16, and 17), demonstrating that the success of our new ligands (especially **8** and **17**) is not confined to one substrate. Note that our results are comparable with those reported by Trost[1] (entries 15 and 18).

In conclusion, we have synthesized a set of ligands **8**, **16**, and **17** to develop asymmetric, molybdenum(0)-catalyzed allylic substitution. Optimization of the ligands along the working hypothesis resulted in identifying the isopropyl-substituted ligand **17** as that with highest enantio- and regioselectivity in most cases (e.g. entry 11). For this champion ligand we propose the acronym 'VALDY' (**val**ine+**d**i**py**ridine). This study has demonstrated that, in this instance, *one chiral center in the scaffold is sufficient to determine the sense of the chiral environment at the metal*, which may have further interesting implications in asymmetric catalysis.

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