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Molybdenum-Catalyzed Asymmetric Allylic Alkylations

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ABSTRACT

The highly regio- and enantioselective molybdenum-catalyzed allylic alkylation reaction has become a powerful synthetic tool during the past few years. This Account describes the achievements gained so far in the area, with special attention directed to the different chiral ligands that have been used for inducing chirality in the products, the range of allylic substrates and nucleophiles employed, mechanistic studies, and applications of the reaction in asymmetric syntheses.

Introduction

The Pd-catalyzed asymmetric allylic alkylation reaction has been the subject of numerous studies and a large variety of ligands have been developed, allowing for the highly enantioselective formation of carbon−carbon and carbon−heteroatom bonds.[1] The analogous Mo-catalyzed reaction has been less studied, but it has already developed into a powerful synthetic procedure complementary to the Pd-catalyzed process in that, in contrast to the situation with Pd, allylic alkylation takes place mostly at the more substituted carbon atom when unsymmetrical substrates are used (Scheme 1).[2]

Other metals that have been shown to catalyze asymmetric allylic alkylation reactions are W,[3] Rh,[4] Ir,[5] Ni,[6] Pt,[7] and Cu.[8] The differences between the diverse metals employed in the allylation reaction involve their regioselectivity, their reactivity toward different types of nucleophiles (stabilized or nonstabilized carbon nucleophiles or other heteroatomic nucleophiles), types of substrates undergoing reaction (aliphatic or aromatic substituents), different reactivity (required amount of catalyst and reaction conditions), and different practical aspects (stability and cost).

Herein we review the achievements gained so far in the area of molybdenum-catalyzed asymmetric allylic alkylations. The chiral catalysts developed and the influence of their structure on the outcome of the reaction, the types of nucleophiles and substrates used, mechanistic information, and applications in enantioselective syntheses are summarized.

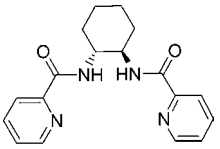

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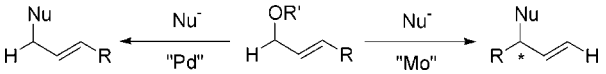
FIGURE 1. Parent ligand **1**.

Scheme 1. Attack of the Nucleophile (Nu^-) in Mo- or Pd-Catalyzed Allylations of Unsymmetrical Substrates



Ligand Classes

Molybdenum is a very versatile metal in catalysis in part because of the vast range in oxidation number (from −4 to +6) and the flexible coordination number (from 4 to 8) exhibited by the metal in the compounds that it forms.[9] Its ability to readily form π-allyl complexes made it interesting for use in the allylic alkylation reaction.[10] Nevertheless, it took more than 15 years to find a chiral catalyst that allowed for the asymmetric version of the catalytic reaction.[11] Since then, a number of ligands have been prepared and successfully employed in the Mo-catalyzed asymmetric allylic alkylation.

Pyridylamides. The first asymmetric Mo-catalyzed allylic alkylation was developed by Trost and Hachiya.[11] They used a precatalyst formed by heating bis(pyridylamide) **1** (Figure 1) and $(EtCN)_3Mo(CO)_3$ at 60 °C in tetrahydrofuran (THF) for 1 h. After addition of the allylic substrate **2**, which has become the standard substrate for comparison of ligands, and the nucleophile, sodium dimethyl malonate, the reaction mixture was further stirred at room temperature for 3 h to give **3** in 70% yield and with excellent regio- and enantioselectivity (49:1 branched-to-linear ratio and 99% enantiomeric excess (ee), Table 1). Heating the reaction at 70 °C for 3 h increased the yield to 88%, while the selectivity was almost unchanged (32:1 branched-to-linear ratio and 99% ee).

Other allylic substrates and nucleophiles were also used and the corresponding products were obtained with good to excellent regio- and enantioselectivity (vide infra). Noteworthy was the excellent selectivity shown by the catalyst even at 70 °C. This temperature stability prompted Hallberg and co-workers,[12] together with us, to develop a more convenient experimental protocol for this reaction. As shown for Pd previously,[12] microwave heating could be used instead of conventional heating to accelerate the reaction without any significant loss in selectivity. In addition, by using microwave heating, a more stable and cheaper Mo source, $Mo(CO)_6$, could be used instead of $(EtCN)_3Mo(CO)_3$. Thus, by mixing $Mo(CO)_6$, the chiral

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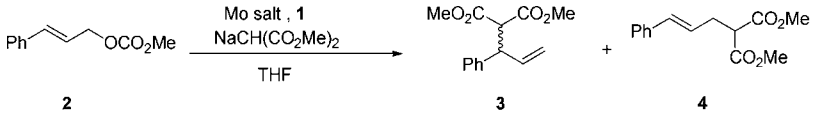
Table 1. Allylic Alkylation of 2 with Malonate, with 1 as Ligand

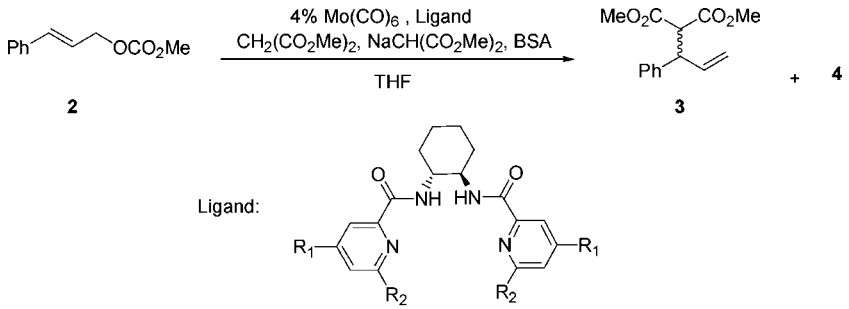


2 **3** **4**

			activation		reaction				
Mo salt	ligand	% cat. (mmol)	time (h)	*T* (°C)	time (h)	*T* (°C)	% yield	**3**:**4**	% ee
$(EtCN)_3Mo(CO)_3$	**1**	10	1	60	3	rt	70	49:1	99
$(EtCN)_3Mo(CO)_3$	**1**	10	1	60	3	70	88	32:1	99
$(C_7H_8)Mo(CO)_3$	**1**	7	0.67	60	4	70	90	28:1	99
$Mo(CO)_6$	**1**	4			0.083	165[a]	86	19:1	98
$Mo(CO)_6$	**1**	4			0.1	165	59	11:1	98
$Mo(CO)_6$	**1**	10	4	85	8	85	80	19:1	99

[a] Heating performed in a microwave cavity.

Table 2. Allylic Alkylations of 2 with Malonate, with Substituted Derivatives of 1 as Ligand



2 **3**

R_1	R_2	*T* [a] (°C)	*t* (min)	% yield	**3**:**4**	% ee
-H	-H	160	6	80	19:1	98
$-NO_2$	-H	150	15	37	16:1	97
-*t*Bu	-H	165	5	46	13:1	98
-OMe	-H	165	4	88	41:1	>99
-Cl	-H	165	6	89	74:1	96
$-NC_4H_8$	-H	170	12	91	88:1	96
-H	-Me	165	5	30	13:1	79
-H	-Br	160	6	0		
-H	-OMe	160	6	0		

[a] Heating performed in a microwave cavity.

ligand, sodium dimethyl malonate, substrate **2**, and bis-(trimethylsilyl)acetamide (BSA) under air, the reaction was completed after 4 min of heating in the microwave cavity (Table 1).[13] By comparative studies between microwave heating and conventional heating we could show that the yield and regioselectivity were somehow lower when the reaction was run in an oil bath at the same temperature for the same time (Table 1). Subsequently, Palucki et al.[14] reported that the allylation reaction could be performed in multikilo scale by using a precatalyst formed by heating a mixture of $Mo(CO)_6$ and ligand **1** in toluene at 85 °C for 4 h, followed by the addition of the nucleophile and the allylic substrate and further stirring for 8−12 h at 85 °C.

We prepared a series of derivatives of the parent ligand **1** and evaluated the substituted ligands in the allylation reaction (Table 2)[15] in order to investigate the effect of substituents with different electronic and steric properties on the outcome of the catalytic reaction. The enantioselectivity of the ligands with 4-substituents varied between 96% and >99% ee, whereas the branched-to-linear ratios and yields varied from 13:1 to 88:1 and from 0 to 91%, respectively. It was shown that π-donor groups in the 4-position of the pyridine rings favored formation of the branched product. On the other hand, substituents in the 6-position of the pyridine rings were detrimental for the reaction outcome, probably due to steric effects. Pyridylamides may act as both σ-donor and π-acceptor ligands. It looks reasonable to suppose that, for a substituent in 4-position of the pyridine ring, electronic effects are more important than steric effects. With the scarce mechanistic information available (vide infra), it is difficult to rationalize the tendency of less π-accepting ligands to favor the branched product.

Some other pyridylamides have been synthesized and used as ligands in the reaction of **2** with dimethyl malonate (Figure 2).[16] The results obtained are summarized in Table 3.

Interestingly, Trost and co-workers found that when one picolinamide group in **1** was replaced by a nicotinamide group (**5**), a higher regioselectivity (46:1 as compared to 19:1) was obtained. An even higher regioselectivity (60:1) was obtained when the picolinamide group was replaced by a benzoylamide group (**6**) (vide infra). Quinoline analogues **8** and **9**, like 6-substituted derivatives of **1**, were less efficient as ligands in the reaction. When pyridylamides having only one stereogenic center (**12**−**15**) (Figure

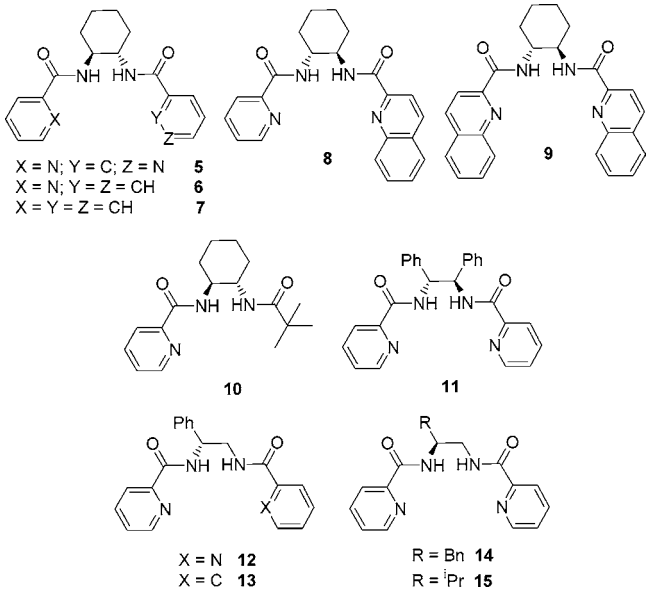
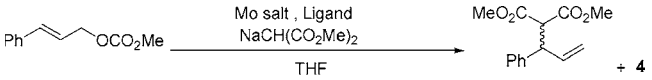


FIGURE 2. Different pyridyl- and quinolylamide ligands **5**−**15**.

Table 3. Allylic Alkylations of 2 with Malonate, with 5−15 as Ligand[a]



2 3

ligand	% yield	3:4	% ee
5	93	46:1	99
6	90	60:1	99
7	35	1:1	24
8	29	19:1	98
9	traces		
10	95	30:1	98
11	95	19:1	99
12	65	8:1	92
13	21	12:1	78
14	69	13:1	89
15	68	32:1	98

[a] Reactions were run in THF (0.1 M) with either $(C_7H_8)Mo(CO)_3$ or $(EtCN)_3Mo(CO)_3$ as Mo source.

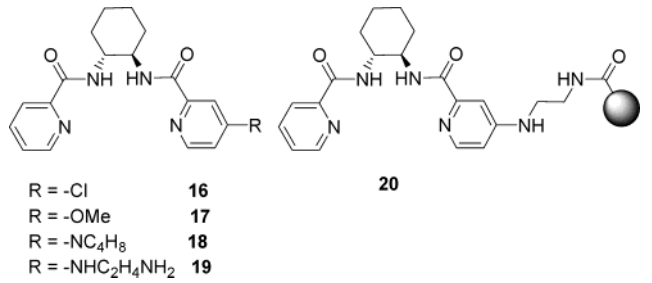


FIGURE 3. *Pseudo-C*$_2$-symmetric ligands **16**−**20**.

2) were used as ligands in the Mo-catalyzed asymmetric allylic alkylation, regioselectivities between 8:1 and 32:1 and enantioselectivities between 78% and 98% ee were obtained. These results demonstrate that C_2 symmetry of the ligand is not a requirement for obtaining high enantioselectivity in the reaction.

A number of *pseudo-C*$_2$-symmetric pyridylamides having only one substituted pyridine ring (Figure 3) has also been prepared and used as models for the development of a pyridylamide ligand attached to a TentaGel resin.[17]

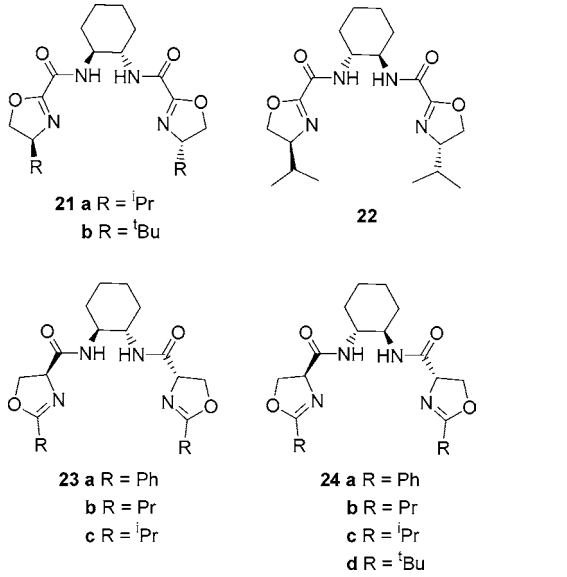
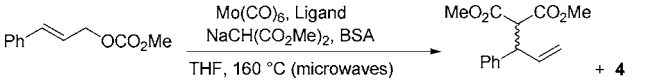


FIGURE 4. Bis(dihydrooxazole) ligands **21**−**24**.

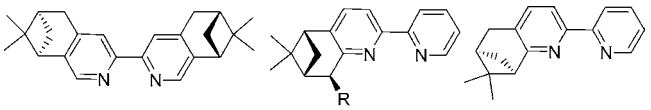
These ligands also afforded the product with high regio- and enantioselectivity (74:1−98:1 and 97−99% ee, eq 1). A trend similar to that noted for the C_2-symmetric analogues was observed for the substituent−regioselectivity relationship. Ligand **19**, with a primary amino group, afforded a catalyst with very low activity in the reaction. For the resin-supported ligand the reaction was slightly slower (30 min of microwave heating compared to 6 min for **1**), probably due to the heterogeneous nature of the catalyst, but the product obtained still presented good regio- and enantioselectivity (35:1 branched-to-linear ratio and 97% ee). Furthermore, the ligand could easily be separated from the reaction mixture by filtration and reused several times without significant deterioration of the reaction outcome.



2 3 (1)

ligand	t (min)	% yield	3:4	% ee
16	6	89	74:1	97
17	6	90	98:1	97
18	6	89	75:1	99
19	12	traces	-	-
20	30	82	35:1	97

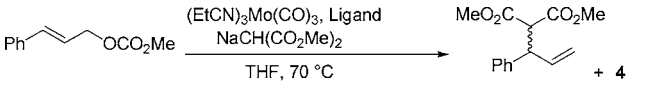
Bis(dihydrooxazoles). Another successful class of ligands for the asymmetric Mo-catalyzed allylic alkylation was developed by Glorius and Pfaltz (Figure 4).[18] These ligands are analogous to the bispyridylamide ligands in the cyclohexylamide part, but the pyridine rings were replaced by dihydrooxazole rings. In addition, these ligands incorporate additional stereogenic centers in the heterocyclic rings. The nature of the substituent in the heterocyclic ring has an influence on the outcome of the reaction, in particular on the regioselectivity. It was also observed that diastereomeric ligands catalyzed the reaction with differ-



25 R = -H **26a** R = -Me **26b** **27**

FIGURE 5. Chiral bipyridine ligands **25**−**27**.

ent rates and selectivities (vide infra).

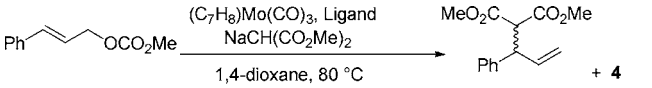


2 **3** (2)

ligand	t (h)	% yield	3:4	% ee
21a	12	86	14:1	99
23b	12	83	6:1	98

The levels of enantioselectivity induced by these ligands were excellent (98−99% ee, eq 2) when they were used in the allylation reaction of substrate **2**. On the other hand, the regioselectivity (6:1−14:1) and the catalytic activity (12−24 h reaction time at 70 °C) were somewhat lower. Furthermore, these ligands were employed for other types of allylic substrates (vide infra).

Bipyridines. It was observed early that achiral Mo(0) complexes having bipyridine as ligand were suitable catalysts for allylic substitutions.[10] Chiral bipyridines **25**, **26**, and **27** (Figure 5) were synthesized and used, after complexation to $Mo(CO)_6$, in the asymmetric version of the reaction.[19] Acetate was used as leaving group instead of carbonate as in standard substrate **2**.



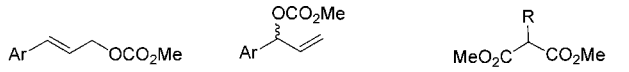
2 **3** (3)

ligand	% yield	3:4	% ee
25	42	4:1	12
26a	52	6:1	22
26b	0	-	-
27	33	7:1	8

In this case, the reactions were run in 1,4-dioxane at 80 °C from 30 min to 24 h. The results obtained with these ligands varied from 4:1 to 7:1 branched to linear product ratio and from 8% to 22% ee (eq 3). The turnover numbers were low, and catalyst decomposition was sometimes observed.

Substrates and Nucleophiles

In general, the Mo-catalyzed asymmetric allylic alkylation affords the product with high regio- and enantioselectivity for a variety of allylic substrates and nucleophiles, making it a very attractive tool in asymmetric synthesis. The more widely used leaving group is carbonate because of its high reactivity in the reaction, but acetate and phosphate have also been used successfully. Thus, different cinnamyl-like substrates have been alkylated by use of sodium dimethyl



Ar =		Ar =		R =	
Ph	**28a**	Ph	**29a**	H	**30a**
4-Cl-Ph	**28b**	4-Cl-Ph	**29b**	Me	**30b**
4-CF_3-Ph	**28c**	4-CF_3-Ph	**29c**	$CH_2CH{=}CH_2$	**30c**
4-OMe-Ph	**28d**	4-^{t}Bu-Ph	**29d**		
2-furyl	**28e**	3-F-Ph	**29e**		
		2-naphthyl	**29f**		
		2-furyl	**29g**		
		2-pyridyl	**29h**		
		2-thienyl	**29i**		

FIGURE 6. Allylic substrates **28a**−**e** and **29a**−**i** and malonates **30a**−**c**.

Table 4. Allylic Alkylations of 28a−e and 29a−i, with 1 as Ligand

allylic substrate	nucleophile	*T* (°C)	*t* (h)	% yield	b:l	% ee
28a	**30b**	60	4	67	24:1	98
28b	**30a**	165[a]	0.1	51	32:1	96
28c	**30a**	165[a]	0.1	50	11:1	99
28d	**30a**	165[a]	0.1	59	51:1	98
28e	**30b**	60	2	71	32:1	97
29a	**30a**	rt	3	61	32:1	97
29a	**30a**	165[a]	0.1	76	13:1	96
29b	**30a**	165[a]	0.1	78	26:1	96
29c	**30a**	165[a]	0.1	48	10:1	98
29d	**30a**	85	8	76	16:1	94
29e	**30a**	85	8	84	19:1	97
29f	**30a**	60	2	82	99:1	87
29g[b]	**30b**	rt	18	54	99:1	95
29g[b]	**30b**	60	2	65	32:1	87
29g[b]	**30c**	rt	12	50	99:1	98
29h	**30a**	60	2	69	8:1	96
29h	**30b**	60	2	71	5:1	94
29i	**30a**	60	2	78	19:1	88
29i	**30b**	60	2	71	13:1	75

[a] Heating performed in a microwave cavity. [b] Acetate was used as leaving group instead of carbonate.

malonate and other malonate derivatives with pyridylamide ligand **1** (Figure 6, Table 4). Noteworthy is the effect of substituents in the aromatic ring on the outcome of the reaction: the more π-donating the substituent, the higher the branched-to-linear ratio.

Another interesting fact is that linear allylic substrates afford the product with higher regioselectivity than the corresponding branched substrates (vide infra). Bulkier, 2-substituted dimethyl malonates (**30b**,**c**) also afford products with good regio- and enantioselectivity (Table 4) despite the large steric hindrance in these systems. Polyallylic substrates (Figure 7)[20] have also been alkylated successfully and, in this case, substitution took place mostly at the 4-position. No attack on the benzylic position was observed (Table 5). The selectivities were in the range of 6.1:1 to 49:1 for the branched-to-linear ratio and 80% to >99% for the enantiomeric excess.

When the allylic carbonate is conjugated with an alkyne (**35a**,**b**), the attack also leaves the triple bond intact and the products were obtained with good selectivity (5.3:1 branched-to-linear ratio and 99% ee for **35a** and 7.3:1 branched-to-linear ratio and 99% ee for **35b**).

The alkylation can also be performed on aliphatic substrates (Table 6) and an extensive study was made by

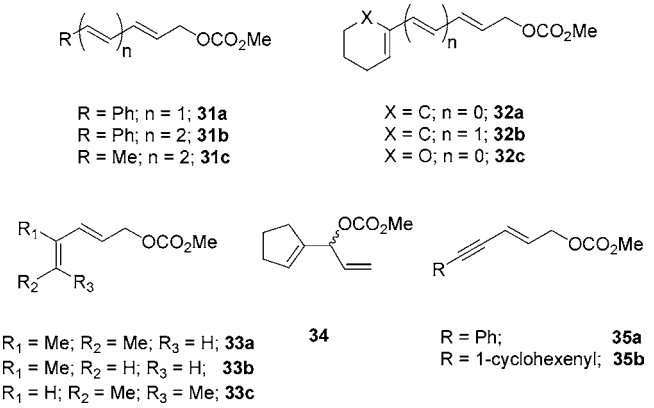


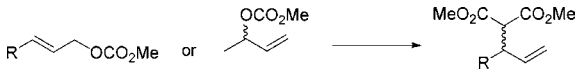
FIGURE 7. Conjugated substrates **31**−**35**.

Table 5. Allylic Alkylations of Conjugated Allylic Carbonates with Malonate, with 1 as Ligand[a]

allylic substrate	*t* (h)	% yield	b:l	% ee
31a	3	95[b]	6.1:1	98
31b	3.5	68[b]	6.1:1	>99
31c	3	81	10.1:1	98
32a	3	91	11.5:1	94
32b	2	70	11.5:1	97
32c	1.5	93	13.3:1	96
33a	3	89	49:1	98
33b	3	81	8.1:1	80
33c	2	96	15.7:1	86
34	2	94	11.5:1	87

[a] Reactions run with ligand **1** and $(EtCN)_3Mo(CO)_3$ in THF/$PhCH_3$ (1:1) at 80−90 °C. [b] Ligand **11** was employed in this run.

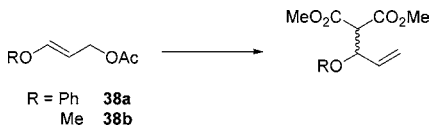
Table 6. Allylic Alkylations of 36a,b and 37 with Malonate



allylic substrate	ligand	% yield	b:l	% ee
36a	**1**	85	5:1	94 (*R*)
36a	**21a**	88	1.5:1	94 (*R*)
36a	**21b**	79	2.2:1	80 (*R*)
36a	**22**	53	0.6:1	26 (*S*)
36a	**23a**	73	5:1	74 (*R*)
36a	**23b**	81	9:1	97 (*R*)
36a	**23c**	81	9:1	95 (*R*)
36a	**24a**	76	7:1	85 (*S*)
36a	**24b**	80	11:1	96 (*S*)
36a	**24c**	86	7:1	92 (*S*)
36a	**24d**	85	1.5:1	0
37	**23b**	83	5:1	80 (*R*)
36b	**1**	80	8:1	98 (+)
36b	**23b**	69	2:1	96 (+)
36b	**23c**	54	2:1	86 (+)
36b	**24b**	84	8:1	98 (−)
36b	**24c**	83	8:1	97 (−)

Pfaltz and co-workers employing bis(dihydrooxazole) ligands **21**−**24** for the allylic alkylation of substrates **36** and **37** with sodium dimethyl malonate.[18] The yields and regio- and enantioselectivities of the products obtained were dependent on the structure of the substituent on the oxazoline rings (Table 6). Thus, better results were obtained for 2-alkyloxazolines bearing a Pr or *iso*-Pr group (**23b,c** and **24b,c**). Increasing the steric bulk from *iso*-Pr to *tert*-Bu (**24d**) afforded the racemic product, and changing the substituent from alkyl to phenyl gave a less selective catalyst. Diastereomeric forms of these ligands (**23** vs **24**) afforded products with different branched-to-linear ratios and enantiomeric excesses. The absolute configuration of the product was different for the diastereomeric ligands, implying that the enantioselectivity is controlled mainly by the diaminocyclohexane unit. The 5-alkyloxazolines (**21** and **22**) afforded products with lower regio- and/or enantioselectivity.

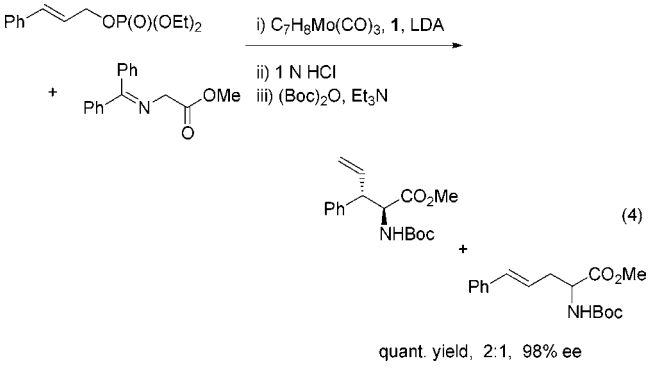
Table 7. Allylic Alkylations of 38a,b with Malonate



allylic substrate	ligand	% yield	b:l	% ee
38a	**1**	79	>20:1	93 (−)
38a	**23b**	79	>20:1	98 (−)
38a	**23c**	78	>20:1	95 (−)
38a	**24b**	81	>20:1	93 (+)
38a	**24c**	75	>20:1	96 (+)
38b	**1**	60	>20:1	74 (+)
38b	**23b**	52	6:1	62 (+)
38b	**23c**	72	5:1	66 (+)
38b	**24b**	38	5:1	63 (−)
38b	**24c**	54	13:1	76 (−)
38b	**24d**	35	3:1	21 (−)

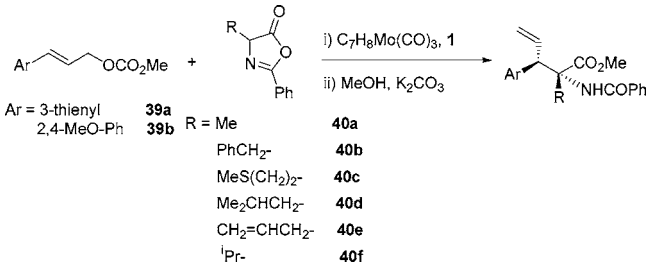
These ligands were also employed in the allylation of **38a**,**b** (Table 7). In this case ligand **23b** proved to afford the most efficient catalyst.

The reaction has been performed with other types of stabilized carbon nucleophiles. Thus, the lithium enolate of glycine ester reacted with cinnamyl phosphate in the presence of a precatalyst prepared from $(C_7H_8)Mo(CO)_3$ and ligand **1** at 0 °C to give, after hydrolysis and protection, a 2:1 ratio of the branched and linear amino acids in quantitative yield (eq 4).[21] The dr and ee of the branched product were excellent (20:1 and 98%). The reactivity of this system is the highest that has been observed so far for any other nucleophiles than malonates. Analogously, lithium salts of azlactones (**40a**−**f**) reacted in the presence of the same precatalyst at 65 °C in THF with a variety of allylic substrates (Table 8) to give the branched quaternary amino acids, after basic methanol solvolysis, in excellent yield, dr, and ee.



No example of Mo-catalyzed asymmetric allylic alkylation using nonstabilized nucleophiles has been reported so far.

Table 8. Allylic Alkylations of 39a,b with Azlactones 40a−f



allylic substrate	nucleophile	% yield	b:l	% ee	dr
2	**40a**	92	>99:1	99	97:3
39a	**40a**	84	>99:1	91	96:4
28e	**40a**	84	21:1	92	>98:2
39b	**40a**	89	>99:1	90	>98:2
2	**40b**	92	>99:1	96	>98:2
39a	**40b**	86	>99:1	94	>98:2
39b	**40b**	90	>99:1	94	>98:2
2	**40c**	86	14:1	92	>98:2
2	**40d**	85	17:1	96	>98:2
2	**40e**	82	14:1	97	>98:2
2	**40f**	76	7:1	96	>98:2

Mechanistic Studies

The operating mechanism for the molybdenum-catalyzed asymmetric allylic alkylation has been less studied than that for the palladium-catalyzed process. It was realized early that when branched allylic substrates were used in the reaction, the product was obtained with lower regio- and enantioselectivity than when the linear isomers were employed. This phenomenon was studied in depth by Hughes et al.,[22] who found that even though the different enantiomers of the branched carbonate **29a** gave the same enantiomer of **3**, they reacted with different rates. Thus, it was shown that the allylic alkylation of these substrates, using ligand **1**, proceeds via a kinetic resolution. When the reaction is conducted to full conversion, the process should be referred as a dynamic kinetic asymmetric transformation (DYKAT),[1a] as distinguished from a kinetic resolution, in which the reaction is stopped at less than 50% conversion and enantioenriched starting material and product are obtained. Furthermore, the rate of diastereomeric equilibration of the π-allyl intermediates relative to the subsequent steps in the reaction was shown to be dependent on the solvent and the nucleophile (Scheme 2). Thus, in solvents such as THF, tetrahydropyran, *iso*-PrOAc, and MeCN, a significant stereochemical memory effect is operative, with the slow-reacting enantiomer providing the product in much lower ee than the fast-reacting one. Therefore, when the reaction was run to completion in these solvents, the branched carbonate afforded the product with lower ee than the linear carbonate. In toluene and 1,2-dichloroethane, the product was obtained with similar ee from the two enantiomers of the branched carbonate, probably due to the lower solubility of sodium dimethyl malonate, allowing for a faster equilibration of the π-allyl intermediates before nucleophilic attack and thus a minimized memory effect.

A complex formed upon reaction of $(EtCN)_3Mo(CO)_3$ and ligand **24a** was crystallized and its structure was elucidated by X-ray crystallography.[18a] The ligand binds to the metal with the oxazoline nitrogen atoms, which are cis to each other, and one of the amide carbonyl oxygen atoms (Figure 8).

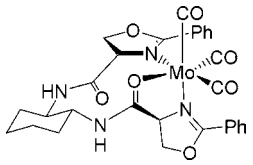
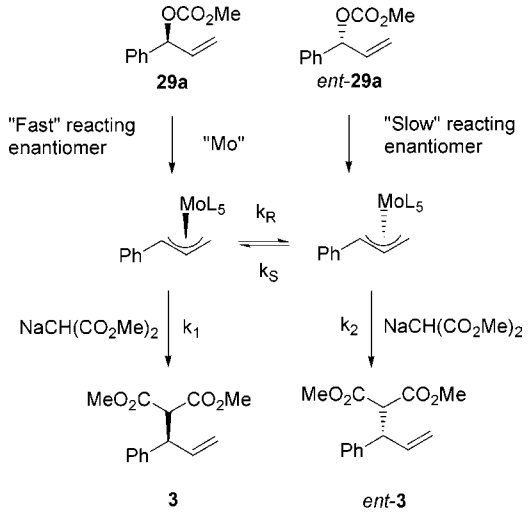


FIGURE 8. Structure of the Mo complex with ligand **24a**.

Scheme 2. Memory Effect in Mo-Catalyzed Asymmetric Allylic Alkylations[a]



Fast equilibrium: k_R and k_S >> k_1 and k_2

substrate	solvent	% ee	ligand
rac-**29a**	THF	87 (*S*)	(*S*,*S*)-**1**
rac-**29a**	MeCN	83 (*S*)	(*S*,*S*)-**1**
rac-**29a**	toluene	97 (*S*)	(*S*,*S*)-**1**
(*R*)-**29a**	THF	99 (*R*)	(*R*,*R*)-**1**
(*R*)-**29a**	THF	70 (*S*)	(*S*,*S*)-**1**
(*R*)-**29a**	toluene	99.5 (*R*)	(*R*,*R*)-**1**
(*R*)-**29a**	toluene	90 (*S*)	(*S*,*S*)-**1**

[a] The original scheme[22] has been modified for a retention−retention mechanism.[25]

On the basis of the results obtained with ligands **1**, **6**, **7**, and **10**, it was concluded that coordination of the two pyridine rings was not involved or was at least not necessary to obtain good selectivities.[16a] In the same study, it was shown that one of the amide groups in ligand **6** was deprotonated upon oxidative addition of the allylic substrate **2** to complex **41** to give π-allyl complex **42**. A definitive proof for this coordination mode was the characterization of complex **42** by X-ray crystallography and NMR spectroscopy (Scheme 3).[23]

The allyl moiety binds in a η^3 fashion to Mo, and ligand **6** binds to the metal via one pyridine nitrogen atom, the nitrogen atom of one deprotonated amide, and the carbonyl oxygen of the neutral amide. The complex contains two CO ligands in a syn orientation with respect to the allyl moiety. The stoichiometry of the reaction involves two molecules of **41** and one molecule of **2** to give **42**, $Mo(CO)_6$, MeOH, CO_2, and **6**. There is one additional example of a molybdenum π-allyl complex with

Scheme 3. Preparation of Mo−Allyl Complex 42

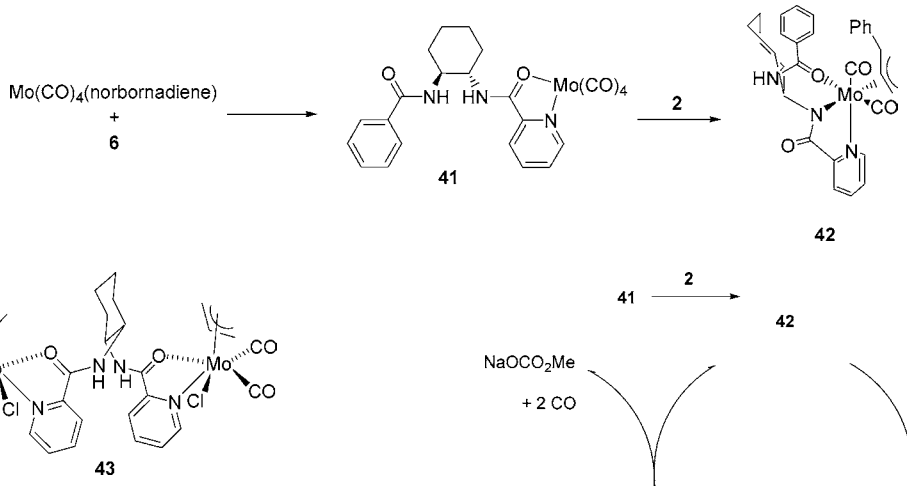


FIGURE 9. Structure of the Mo−allyl complex with ligand **1**.

bispyridylamide ligand **1**.[24] This complex was generated by reaction of [MoCl(η^3-C_3H_5)$(CO)_2(NCMe)_2$] with ligand **1**. The resulting complex, **43** (Figure 9), had a 2:1 Mo-to-ligand ratio where the ligand was binding via the pyridine nitrogen atoms and the carbonyl oxygen atoms of the amide groups and Mo kept two CO ligands, the Cl and the allyl group. The stereocenter in the ligand is situated far from the metal atoms, and therefore it seems probable that a different complex, resembling **42**, operates in the allylation reaction when deprotonation of the amides is possible.

Complex **42** reacted with dimethyl malonate to afford **3** in >95% ee. However, when isolated **42** was reacted with dimethyl malonate, no reaction occurred. It was found that the presence of CO was necessary for the reaction with malonate to form **44** and the product **2**. Tetracarbonyl−Mo complex **44** could be prepared independently by reaction of **41** with NaH, and it reacted with allylic carbonate **2** to afford the π-allyl complex **42**. With this information in hand, a mechanism was proposed (Figure 10), where precatalyst **41** reacts with carbonate **2** to generate the π-allyl complex **42**, which reacts with sodium dimethyl malonate in the presence of CO to give the product and complex **44**. Further reaction with carbonate **2** regenerates **42** and CO.

Although the stereochemistry of the Mo-catalyzed allylic alkylation was known to proceed with overall retention, the stereochemistry of each step, the oxidative addition and the nucleophilic attack, was unknown until recently. Conclusive evidence has now been provided by Lloyd-Jones et al.[25] for a retention−retention pathway.

The different regioselectivity exhibited by Pd and Mo was previously attributed to the different bonding mode of the allyl moiety.[26] Thus it was stated that, in the case of Mo, the reactive species adopts an enyl coordination mode where electronic control of the selectivity predominates. Characterization of complex **42** favors the presence of π-allyl species as reactive intermediates also in the Mo-catalyzed processes. However, some fundamental questions, such as how the transfer of chirality, the high

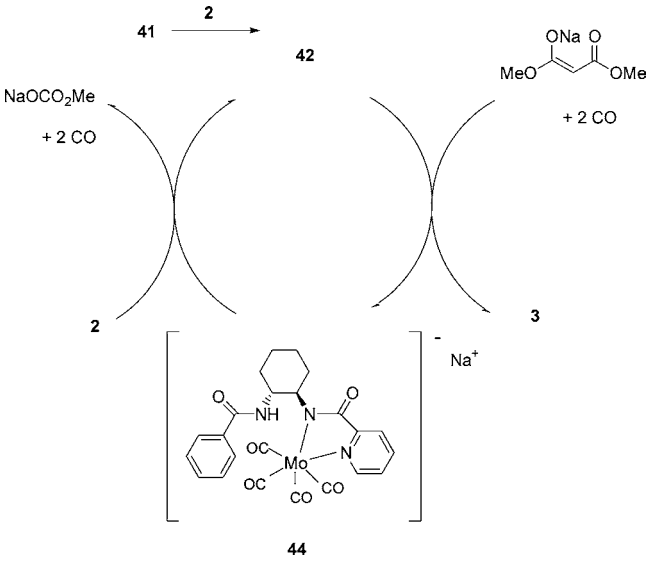


FIGURE 10. Proposed mechanism.

regioselectivity, and the kinetic resolution and memory effects observed occur, remain to be explained.

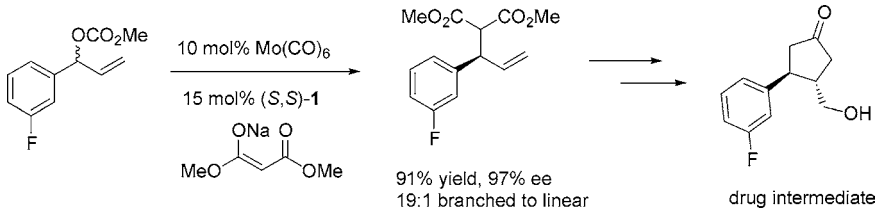
Applications in Enantioselective Synthesis

Metal-catalyzed asymmetric allylic alkylations are very useful synthetic tools since they allow for the enantioselective formation of a new C−C or C−X bond to form a product containing a double bond, which can be further elaborated via a variety of processes in a diastereoselective manner.[11] The utility of the Mo-catalyzed asymmetric allylic alkylation reaction in asymmetric synthesis is not limited to the preparation of amino acids (vide supra). Since branched allylic substrates are readily prepared by condensation of an aldehyde and vinylmagnesium chloride and subsequent formation of the carbonate with methyl chloroformate, these have been so far the kind of allylic substrates used in practical applications.

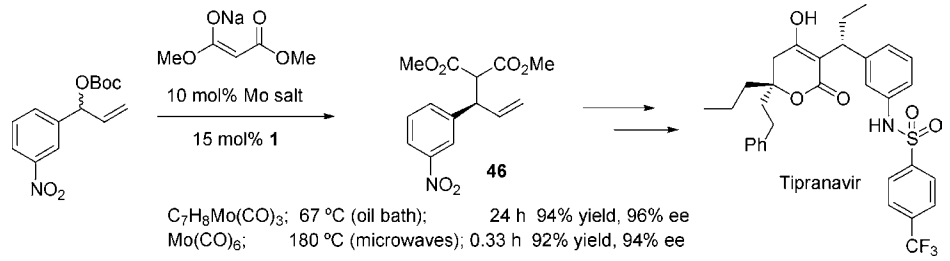
Palucki et al.[27] used a Mo-catalyzed dynamic kinetic asymmetric transformation (DYKAT) together with an intramolecular cyclopropanation to form a new chiral 3,4-disubstituted cyclopentanone, a key intermediate in the synthesis of a new drug candidate at Merck & Co (Scheme 4). The DYKAT proceeded with high regio- and enantioselectivity (19:1 branched-to-linear ratio and 96−97% ee) in a multikilo scale.

Tipranavir is a nonpeptidic human immunodeficiency virus (HIV) protease inhibitor. By combined use of Mo- and Pd-catalyzed DYKAT, an efficient enantioselective synthesis of tipranavir was recently developed (Scheme

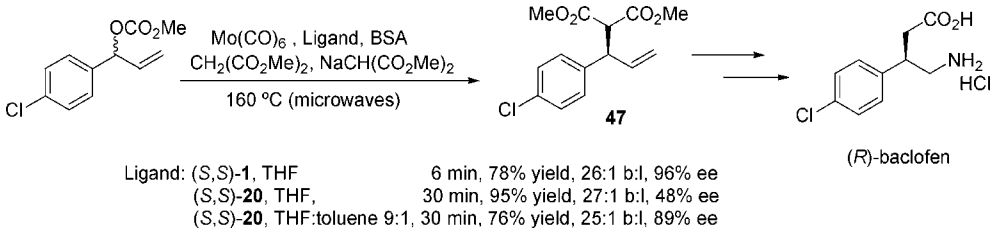
Scheme 4. Application of Mo-Catalyzed Asymmetric Allylic Alkylation in the Synthesis of a Drug Intermediate



Scheme 5. Application of Mo-Catalyzed Asymmetric Allylic Alkylation in the Synthesis of Tipranavir



Scheme 6. Application of Mo-Catalyzed Asymmetric Allylic Alkylation in the Synthesis of (*R*)-Baclofen



5).[28] The key intermediate **46** reacted slowly (24 h) in THF at reflux. However, the reaction time could be reduced drastically, to 20 min, by use of microwave heating, with only a small loss in enantioselectivity (from 96% to 94% ee).

In a recent example, we used a Mo-catalyzed DYKAT as the key step in the synthesis of (*R*)-baclofen.[18] Intermediate **47** was formed with high regio- and enantioselectivity by use of ligand **1** (Scheme 6). Solid-phase-supported ligand **20** afforded the product with decreased enantioselectivity (48% ee), probably due to a memory effect. When the reaction was run in a 1:9 THF/toluene mixture, the ee was increased to 89%, in accordance with previous findings by Hughes et al.[22] (vide supra).

Conclusions and Outlook

Asymmetric allylic alkylations are catalyzed by several metals, each particular metal exhibiting its own reactivity and preference for products with different regio- and stereochemistry. The Mo-catalyzed reaction is characterized by its high tendency to form the more substituted products from unsymmetrical substrates. Recent developments allow these products to be obtained in high yields with extremely high enantioselectivity. Along with accumulating mechanistic information, conditions permitting a wider range of substrates to yield products with high control of their regio- and stereochemistry are expected to be found. This is important, since the reaction tolerates robust reaction conditions and $Mo(CO)_6$, used as Mo source, is cheap, rendering the process suitable not only for laboratory applications but also for large-scale synthesis.

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Note Added after ASAP Posting

This article was released ASAP on 12/20/2003. Changes were subsequently made to ref 21, and the article was reposted on 1/15/2004.

References

(1) (a) Trost, B. M. Pd Asymmetric Allylic Alkylation (AAA). A Powerful Synthetic Tool. *Chem. Pharm. Bull.* **2002**, *50*, 1−14. (b) Trost, B. M.; Lee, C. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 593−650. (c) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 833−884.

(2) There are few examples where this regioselectivity is also observed for Pd. See (a) You, S.-L.; Zhu, X.-Z; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. Highly Regio- and Enantioselective Pd-Catalyzed Allylic Alkylation and Amination of Monosubstituted Allylic Acetates with Novel Ferrocene P,N-Ligands. *J. Am. Chem. Soc.* **2001**, *123*, 7471−7472, and references therein. (b) Prétôt, R.; Pfaltz, A. New Ligands for Regio- and Enantiocontrol in Pd-Catalyzed Allylic Alkylations. *Angew. Chem., Int. Ed.* **1998**, *37*, 323−325. (c) For a reversed regioselectivity with Mo, see Co, T. T.; Paek, S. W.; Shim, S. C.; Cho, C. S.; Kim, T.-J.; Choi, D. W.; Kang, S. O.; Jeong, J. H. 1,2-Ferrocenediylazaphosphinines: An Unusual Coordination Behavior and Application to Allylic Alkylation. *Organometallics* **2003**, *22*, 1475−1482.

(3) Lloyd-Jones, G. C.; Pfaltz, A. Chiral Phosphanodihydrooxazoles in Asymmetric Catalysis: Tungsten-Catalyzed Allylic Substitution. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462−464.

(4) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. High Enantioselectivity in Rhodium-Catalyzed Allylic Alkylation of 1-Substituted 2-Propenyl Acetates. *Org. Lett.* **2003**, *5*, 1713−1715.
(5) (a) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. Enantio- and Diastereoselective Ir-Catalyzed Allylic Substitutions for Asymmetric Synthesis of Amino Acid Derivatives. *Angew. Chem., Int. Ed.* **2003**, *42*, 2054−2056. (b) Takeuchi, R.; Kashio, M. Iridium Complex-Catalyzed Allylic Alkylation of Allylic Esters and Allylic Alcohols: Unique Regio- and Stereoselectivity. *J. Am. Chem. Soc.* **1998**, *120*, 8647−8655. (c) Janssen, J. P.; Helmchen, G. First Enantioselective Alkylations of Monosubstituted Allylic Acetates Catalyzed by Chiral Iridium Complexes. *Tetrahedron Lett.* **1997**, *38*, 8025−8026.
(6) Bricout, H.; Carpentier, J.-F.; Mortreux, A. Bis(aminophosphine)−Nickel Complexes as Efficient Catalysts for Alkylation of Allylic Acetates with Stabilized Nucleophiles. *Tetrahedron Lett.* **1996**, *37*, 6105−6108.
(7) Brown, J. M.; MacIntyre, J. E. Allylic Alkylation Catalyzed by Platinum Complexes: Structure and Reactivity of Intermediates, and the Overall Stereoselectivity. *J. Chem. Soc., Perkin Trans. 2* **1985**, 961−970.
(8) van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. Chiral Arenethiolatocopper(I) Catalyzed Substitution Reactions of Acyclic Allylic Substrates with Grignard Reagents. *Tetrahedron Lett.* **1995**, *36*, 3059−3062.
(9) Curtis, M. D. In *Encyclopedia of Inorganic Chemistry*; King, R. B., Ed.; John Wiley & Sons Ltd.: New York, 1994; pp 2346−2361.
(10) Trost, B. M.; Lautens, M. Molybdenum catalysts for allylic alkylation. *J. Am. Chem. Soc.* **1982**, *104*, 5543−5545.
(11) Trost, B. M.; Hachiya, I. Asymmetric Molybdenum-Catalyzed Allylic Alkylations. *J. Am. Chem. Soc.* **1998**, *120*, 1104−1105.
(12) (a) Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. Microwave-mediated palladium-catalyzed asymmetric allylic alkylation; an example of highly selective fast chemistry. *J. Organomet. Chem.* **2000**, *603* (1), 2−5. (b) Bremberg, U.; Lutsenko, S.; Kaiser, N.-F.; Larhed, M.; Hallberg, A.; Moberg, C. Rapid and Stereoselective C−C, C−O, C−N and C−S Couplings via Microwave-Accelerated Palladium-Catalyzed Allylic Substitutions. *Synthesis* **2000**, *7*, 1004−1008. (c) Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. Rapid Microwave-Induced Palladium Catalyzed Asymmetric Allylic Alkylation. *J. Org. Chem.* **1999**, *64*, 1082−1083.
(13) Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. Fast, Convenient, and Efficient Molybdenum-Catalyzed Asymmetric Allylic Alkylation under Noninert Conditions: An Example of Microwave-Promoted Fast Chemistry. *Angew. Chem., Int. Ed.* **2000**, *39*, 3596−3598.
(14) Palucki, M.; Um, J. M.; Conlon, D. A.; Yasuda, N.; Hughes, D. L.; Mao, B.; Wang, J.; Reider, P. J. Molybdenum-Catalyzed Asymmetric Allylic Alkylation Reactions Using $Mo(CO)_6$ as Precatalyst. *Adv. Synth. Catal.* **2001**, *343*, 46−50.
(15) (a) Belda, O.; Moberg, C. Substituted Pyridylamide Ligands in Microwave Accelerated Mo(0) Catalyzed Allylic Alkylations. *Synthesis* **2002**, 1601−1606. (b) Belda, O. Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Hallberg, A.; Moberg, C. Highly Stereo- and Regioselective Allylations Catalyzed by Mo−Pyridylamide Complexes: Electronic and Steric Effects of the Ligand. *J. Org. Chem.* **2000**, *65*, 5868−5870.
(16) (a) Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S.; Reamer, R. A.; Palucki, M.; Yasuda, N.; Reider, P. J. Designed Ligands as Probes for the Catalytic Binding Mode in Mo-Catalyzed Asymmetric Allylic Alkylation. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929−1932. (b) Malkov, A. V.; Spoor, P.; Vinader, V.; Kočovský, P. Asymmetric molybdenum(0)-catalyzed allylic substitution. *Tetrahedron Lett.* **2001**, *42*, 509−512. (c) Kočovský, P.; Malkov, A. V.; Vyskočil, Š.; Lloyd-Jones, G. C. Transition metal catalysis in organic synthesis: reflections, chirality and new vistas. *Pure Appl. Chem.* **1999**, *71*, 1425−1433.
(17) Belda, O.; Lundgren, S.; Moberg, C. Recoverable Resin-Supported Pyridylamide Ligand for Microwave-Accelerated Molybdenum-Catalyzed Asymmetric Allylic Alkylations: Enantioselective Synthesis of Baclofen. *Org. Lett.* **2003**, *5*, 2275−2278.
(18) (a) Glorius, F.; Neuburger, M.; Pfaltz, A. Highly Enantio- and Regioselective Allylic Alkylations Catalyzed by Chiral [Bis(dihydrooxazole)]molybdenum Complexes. *Helv. Chim. Acta* **2001**, *84*, 3178−3196. (b) Glorius, F.; Pfaltz, A. Enantioselective Molybdenum-Catalyzed Allylic Alkylation Using Chiral Bisoxazoline Ligands. *Org. Lett.* **1999**, *1*, 141−144.
(19) Malkov, A. V.; Baxendale, I. R.; Bella, M.; Langer, V.; Fawcett, J.; Russell, D. R.; Mansfield, D. J.; Valko, M.; Kočovský, P. Synthesis of New Chiral 2,2′-Bipyridyl-Type Ligands, Their Coordination to Molybdenum(0), Copper(II), and Palladium(II), and Application in Asymmetric Allylic Substitution, Allylic Oxidation, and Cyclopropanation. *Organometallics* **2001**, *20*, 673−690.
(20) Trost, B. M.; Hildbrand, S.; Dogra, K. Regio- and Enantioselective Molybdenum-Catalyzed Alkylations of Polyenyl Esters. *J. Am. Chem. Soc.* **1999**, *121*, 10416−10417.
(21) Trost, B. M.; Bouix-Peter, C. Unpublished work, described in Trost, B. M.; Dogra, K. Synthesis of Novel Quaternary Amino Acids Using Molybdenum-Catalyzed Asymmetric Allylic Alkylation. *J. Am. Chem. Soc.* **2002**, *124*, 7256−7257.
(22) Hughes, D. L.; Palucki, M.; Yasuda, N.; Reamer, R. A.; Reider, P. J. Solvent-Dependent Dynamic Kinetic Asymmetric Transformation/Kinetic Resolution in Molybdenum-Catalyzed Asymmetric Allylic Alkylations. *J. Org. Chem.* **2002**, *67*, 2762−2768.
(23) Krska, S. W.; Hughes, D. L.; Reamer, R. A.; Mathre, D. J.; Sun, Y.; Trost, B. M. The Unusual Role of CO Transfer in Molybdenum-Catalyzed Asymmetric Alkylations. *J. Am. Chem. Soc.* **2002**, *124*, 12656−12657.
(24) Morales, D.; Pérez, J.; Riera, L.; Riera, V.; Corzo-Suárez, R.; García-Granda, S.; Miguel, D. An Easily Accessed Molybdenum Lewis Acid as a Catalyst for Imine Aziridination. *Organometallics* **2002**, *21*, 1540−1545.
(25) Lloyd-Jones, G. C.; Krska, S.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Reamer, R. A. Conclusive Evidence for a Retention−Retention Pathway for Molybdenum-catalyzed Asymmetric Alkylation. *J. Am. Chem. Soc.*, in press.
(26) Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Sathya Shanker, P. Hydrogen Bond Directed Highly Regioselective Palladium-Catalyzed Allylic Substitution. *J. Am. Chem. Soc.* **2003**, *125*, 5115−5120.
(27) Palucki, M.; Um, J. M.; Nobuyoshi, Y.; Conlon, D. A.; Tsay, F.-R.; Hartner, F. W.; Hsiao, Y.; Marcune, B.; Karady, S.; Hughes, D. L.; Dormer, P. G.; Reider, P. J. Development of a New and Practical Route Chiral 3,4-Disubstituted Cyclopentanones: Asymmetric Alkylation and Intramolecular Cyclopropanation as Key C−C Bond-Forming Steps. *J. Org. Chem.* **2002**, *67*, 5508−5516.
(28) Trost, B. M.; Andersen, N. G. Utilization of Molybdenum- and Palladium-Catalyzed Dynamic Kinetic Asymmetric Transformations for the Preparation of Tertiary and Quaternary Stereogenic Centers: a Concise Synthesis of Tipranavir. *J. Am. Chem. Soc.* **2002**, *124*, 14320−14321.

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