Solvent-Dependent Dynamic Kinetic Asymmetric Transformation/ Kinetic Resolution in Molybdenum-catalyzed Asymmetric Allylic Alkylations

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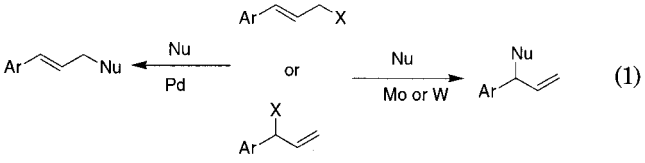
Catalytic asymmetric alkylation reactions of branched racemic carbonates **1a** and **1b** with sodium dimethyl malonate, promoted by molybdenum and ligand **5**, proceed by a kinetic resolution in toluene, THF, tetrahydropyran, *i*-PrOAc, 1,2-dichloroethane, and MeCN with k_{rel} of 7−16. In THF, MeCN, tetrahydropyran, and *i*-PrOAc using the (*S*,*S*)-**5** ligand, the fast reacting (*S*)-carbonate enantiomer provides the branched product with high ee (97−99.5%) and branched/linear selectivity, but the ee erodes as the reaction of the slow-reacting (*R*)-enantiomer takes place. This implies that the rate of equilibration of the oxidative addition complexes in these solvents is competitive with the subsequent malonate displacement step. In toluene and dichloroethane, the ee and branched/linear ratios diminish during the reaction of the slow-reacting (*R*)-isomer, but not nearly as much as in the other solvents. This is most likely due to either an increase in the rate of equilibration of the oxidative addition complexes relative to the malonate displacement step, or vice versa. Because of the minimal stereochemical memory effect in toluene and 1,2-dichloroethane, the reactions in these solvents can be carried to completion (dynamic kinetic asymmetric transformation) and still provide product with excellent ee (>95%). The anion of dimethyl methylmalonate also reacts via a kinetic resolution, although the ee's, rates, and k_{rel} values differ from those of the reactions with dimethyl malonate.

Introduction

Nucleophilic substitution reactions of allylic carboxylates and carbonates, catalyzed by transition metals, have enjoyed widespread application in organic synthesis over the past 2 decades.[1] While palladium has been the most widely employed metal, a few studies have been aimed at identifying other transition metals that could provide a benefit relative to palladium. During the 1980s Trost and co-workers pioneered the use of group VI transition metals (molybdenum and tungsten) in allylic alkylations, finding these metals often provided regiochemistry complementary to that of palladium.[2] Thus, while palladium-catalyzed reactions generally provided the linear product, W and Mo gave predominately the branched product (eq 1). Introduction of a chiral center



(1)

via the Mo- or W-catalyzed reactions made these potentially high-value products if an asymmetric variant of the reaction could be realized. Toward this end, stoichiometric asymmetric alkylations were described by Faller et al. for allylmolybdenum complexes during the 1980s.[3] The first catalytic asymmetric alkylation reaction, promoted by tungsten, was reported by Pfaltz in 1995 for the reactions of allylic phosphates with malonate nucleophiles using chiral *P*,*N*-ligands.[4] These reactions, while giving high enantioselectivity, generally provided poor regioselectivity (4/1 branched/linear ratio for most substrates) and required long reaction times (1 week). A truly practical variant was reported by Trost in 1998 using molybdenum as the metal source and the bispicolinamide ligand **5**.[5] High yields, ee's, and regioselectivities were obtained with a variety of substrates and nucleophiles. More recently, Pfaltz[6] and Kočovský[7] have designed ligands that also gave excellent results with molybdenum.

The source of molybdenum in all of these reports was $Mo(CO)_3$(cycloheptatriene) or $Mo(CO)_3$(propionitrile)$_3$, neither of which is ideal for larger scale applications due to instability and relative unavailability. We recently com-

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(2) Molybdenum: (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1982**, *104*, 5543. (b) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1983**, *105*, 3344. (c) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469. (d) *Tetrahedron* **1987**, *43*, 4817. (e) Trost, B. M.; Merlic, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9590. Tungsten: Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757; **1984**, *106*, 6837. Trost, B. M.; Tometzki, G. B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176.

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(7) Malkov, A. V.; Spoor, P.; Vinader, V.; Kočovský, P. *Tetrahedron Lett.* **2001**, *42*, 509−512. Kočovský, P.; Malkov, A. V.; Vyskocil, S.; Lloyd-Jones, G. C. *Pure Appl. Chem.* **1999**, *71*, 1425−1433.

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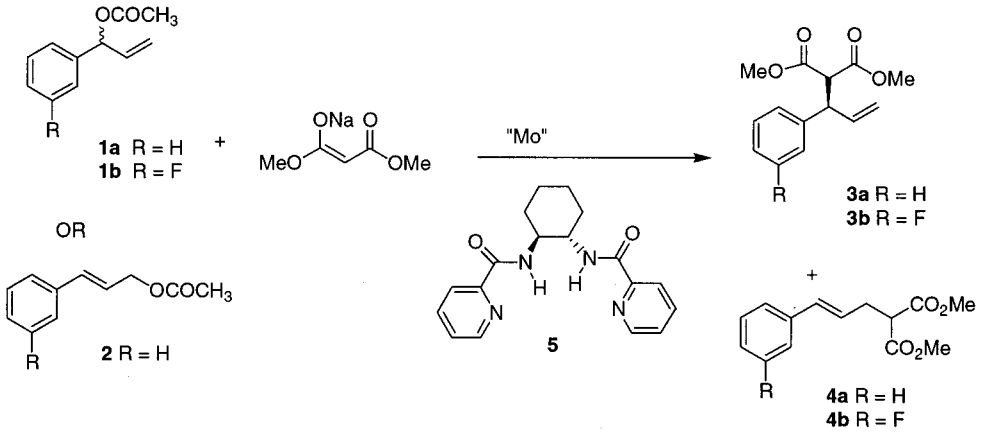
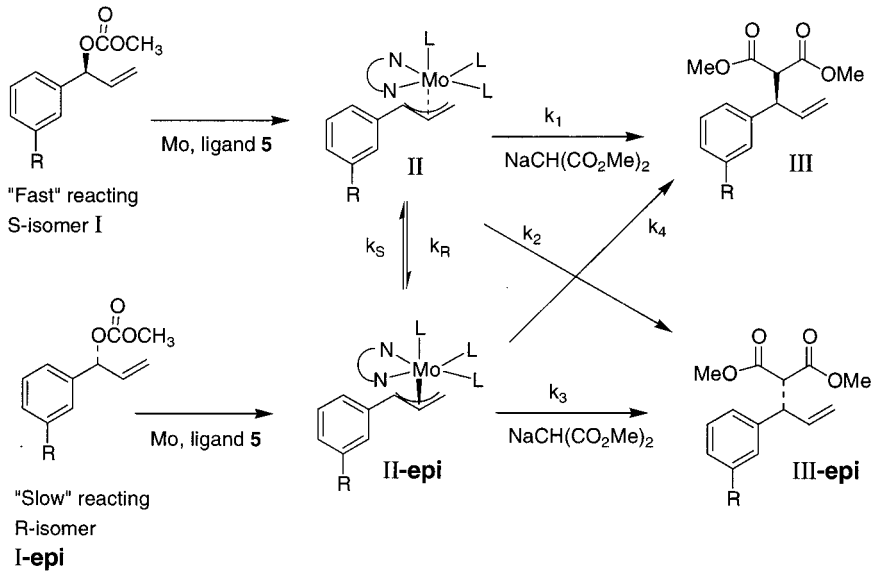
Scheme 1



Scheme 2



municated that the readily available and stable precatalyst $Mo(CO)_6$ was equally effective in the allylic alkylation if appropriately activated with the ligand.[8] Concurrently, Larhed and co-workers reported that $Mo(CO)_6$ could be used in these reactions when promoted by microwave irradiation.[9] On the basis of the similar enantio- and regioselectivities of the three precatalysts employed, we concluded they all produced the same active catalyst in the system.[8]

In recent years a handful of papers have been published regarding kinetic resolution and memory effects on Pd-catalyzed reactions of branched allylic carbonates or carboxylates. Due to the variety of ligands and conditions employed in these various studies, general mechanistic conclusions cannot be drawn except that kinetic resolutions are quite common for these types of reactions. On the other hand, Lehmann and Lloyd-Jones[10] found a complete stereochemical memory effect in tungsten-catalyzed alkylations, with chiral allylic carbonates reacting with malonate anion to give complete stereochemical retention. This result, along with crossover experiments, led the authors to conclude that catalysis by the group VI metals may involve a mechanism different from that with Pd. Given both the contrasts (complementary regiochemistry) and similarities (comparable substrates and ligands) between the Mo- and Pd-catalyzed reactions, and the potential differences in the mechanism, we have undertaken a study of the kinetic resolution and memory effects in the Mo-catalyzed asymmetric alkylation, as reported herein.

Since the racemic branched carbonates **1a** and **1b** produce the coupling products **3a** and **3b**, respectively (Scheme 1), with high enantioselectivity, the reaction must proceed via equilibration of a diastereomeric intermediate, most likely the oxidative addition products (**II** and **II-epi** in Scheme 2). Thus, the overall reaction is best described as a dynamic kinetic asymmetric transformation.[12] Trost,[5] Kočovský,[7] and Pfaltz[6] reported that the linear carbonate **2** produced higher ee's than the racemic branched carbonate **1a**. This suggested either that the two carbonate regioisomers were not reacting entirely via a common transition state or that the two enantiomers of the branched carbonate were not fully equilibrating after the oxidative addition step. We have now examined this question in more depth[11] and

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(10) Lehmann, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863−8874.

Table 1. Reactivity and Selectivity for Branched Allylic Carbonates Reacting with Sodium Dimethyl Malonate[a]

entry	substrate	solvent	temp (°C)	ligand	product ee (%)	branched/linear ratio (**3**/**4**)
1	*rac*-**1a**	THF	48	(*S*,*S*)-**5**	87 (*S*)	25
2	*rac*-**1a**	CH_3CN	48	(*S*,*S*)-**5**	83 (*S*)	23
3	*rac*-**1a**	toluene[b]	90	(*S*,*S*)-**5**	97 (*S*)	32
4	*rac*-**1a**	toluene	60	(*S*,*S*)-**5**	96 (*S*)	46
5	*rac*-**1a**	*i*-PrOAc	48	(*S*,*S*)-**5**	90 (*S*)	23
6	*rac*-**1a**	tetrahydropyran	48	(*S*,*S*)-**5**	92 (*S*)	30
7	*rac*-**1a**	tetrahydropyran	80	(*S*,*S*)-**5**	90 (*S*)	18
8	*rac*-**1a**	$ClCH_2CH_2Cl$	75	(*S*,*S*)-**5**	97 (*S*)	40
9	(*R*)-**1a**	THF	48	(*R*,*R*)-**5**	99 (*R*)	55
10	(*R*)-**1a**	THF	48	(*S*,*S*)-**5**	70 (*S*)	12
11	(*R*)-**1a**	toluene	60	(*R*,*R*)-**5**	99.5 (*R*)	65
12	(*R*)-**1a**	toluene	60	(*S*,*S*)-**5**	90 (*S*)	32
13	(*R*)-**1a**	CH_3CN	48	(*R*,*R*)-**5**	98 (*R*)	36
14	(*R*)-**1a**	CH_3CN	48	(*S*,*S*)-**5**	44 (*S*)	8
15	*rac*-**1b**	THF	48	(*S*,*S*)-**5**	88 (*S*)	15
16	*rac*-**1b**	toluene	75	(*S*,*S*)-**5**	96 (*S*)	30
17	**2**	THF	48	(*S*,*S*)-**5**	97 (*S*)	35

[a] Conditions: $Mo(CO)_3C_7H_8$ precatalyst; sodium dimethyl malonate was prepared in situ from dimethyl malonate and NaH, combined with the carbonate, and added to the preheated activated catalyst mixture. [b] $Mo(CO)_6$ precatalyst.

report that the allylic alkylation using ligand **5** proceeds via a kinetic resolution and that the rate of diastereomeric equilibration relative to the subsequent steps in the reaction is dependent on the solvent and nucleophile.

Results and Discussion

Kinetic Resolution in THF. As a baseline experiment, the reaction of linear carbonate **2** in THF at 48 °C using 10 mol % $Mo(CO)_3$(cycloheptatriene), 15 mol % (*S*,*S*)-ligand **5**, and 1.5 equiv of sodium dimethyl malonate provided product **3a** in >90% yield with 3% of the linear product **4a** (Table 1, entry 17). The ee of the branched product was 97% and did not change over the course of the reaction. On the basis of HPLC analysis, no detectable interconversion of linear carbonate **2** and branched carbonate **1a** occurred under the reaction conditions.

Under identical conditions, racemic branched carbonate **1a** was reacted with sodium dimethyl malonate in THF. Monitoring the disappearance of starting material via chiral HPLC revealed that one enantiomer reacted much faster than the other, signifying that a kinetic resolution was taking place.[12] On the basis of an independent synthesis of the enantiomerically pure isomers of **1a**, we determined that the (*S*)-isomer of **1a** was the fast-reacting enantiomer when using the (*S*,*S*)-ligand **5**. Due to convention changes, the (*R*)-product **3a** that is formed is derived from overall retention of stereochemistry (Scheme 2). Monitoring the ee and branched/linear product ratio (**3**/**4**) as the reaction proceeded revealed that a high product ee (98%) and a high branched/linear ratio (35/1) was produced during the first half of the reaction as the (*S*)-enantiomer reacted, but the ee eroded as the slower reaction of the (*R*)-isomer took place such that an overall 87% ee was obtained (Table 1, entry 1). This is shown graphically in Figure 1 as a plot of % ee vs conversion of **1a** to **3a**. Comparable results were obtained for the 3-F substrate (**1b**) (Table 1, entry 15). Using eq 2, where *c* is the conversion of starting material and ee

$$k_{rel} = \frac{\ln(1 - c)(1 - ee)}{\ln(1 - c)(1 + ee)} \qquad (2)$$

is the enantiomeric excess of starting material, to determine the relative rate constants (k_{rel}) from the ee of the starting material,[13] the k_{rel} for the reaction of the two enantiomers of **1a** was found to be 9 (Table 2, entry 1). Similarly, k_{rel} for the 3-F substrate **1b** was determined to be 9 (Table 2, entry 13).

The slow-reacting (*R*)-enantiomer of **1a** was isolated via a kinetic resolution on a preparative scale, which allowed for an independent measurement of the rate

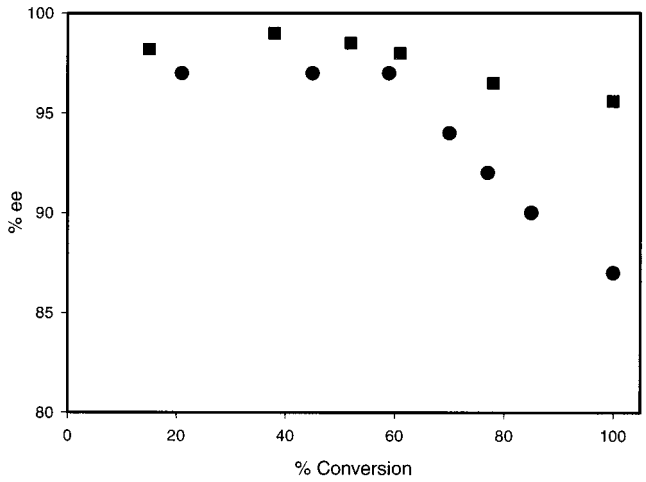

Figure 1. Percent ee vs percent conversion for reaction of **1a** in THF at 48 °C (circles) and in toluene at 60 °C (squares).

Table 2. Relative Enantiomeric Reactivity of Branched Carbonates Reacting with Sodium Dimethyl Malonate[a]

entry	substrate	solvent	temp (°C)	ligand	rate constant (s^{-1})	k_{rel}
1	*rac*-**1a**	THF	48	(*S*,*S*)-**5**		9[c]
2	*rac*-**1a**	CH_3CN	48	(*S*,*S*)-**5**		8[c]
3	*rac*-**1a**	toluene[b]	90	(*S*,*S*)-**5**		11[c]
4	*rac*-**1a**	toluene	60	(*S*,*S*)-**5**		13[c]
5	*rac*-**1a**	*i*-PrOAc	48	(*S*,*S*)-**5**		8[c]
6	*rac*-**1a**	tetrahydropyran	48	(*S*,*S*)-**5**		8[c]
7	*rac*-**1a**	tetrahydropyran	80	(*S*,*S*)-**5**		8[c]
8	*rac*-**1a**	$ClCH_2CH_2Cl$	75	(*S*,*S*)-**5**		10[c]
9	(*R*)-**1a**	THF	48	(*R*,*R*)-**5**	4.8×10^{-4}	9[d]
10	(*R*)-**1a**	THF	48	(*S*,*S*)-**5**	5.3×10^{-5}	
11	(*R*)-**1a**	toluene	60	(*R*,*R*)-**5**	1.8×10^{-3}	16[d]
12	(*R*)-**1a**	toluene	60	(*S*,*S*)-**5**	1.1×10^{-4}	
13	*rac*-**1b**	THF	48	(*S*,*S*)-**5**		9[c]
14	*rac*-**1b**	toluene	75	(*S*,*S*)-**5**		15[d]

[a] Conditions the same as for Table 1. [b] $Mo(CO)_6$ precatalyst. [c] From eq 2, at 50% conversion. [d] From rate constants.

(11) A very preliminary test of the possibility of differential reactivity of the two carbonate enantiomers was reported in ref 8, with the suggestion that very little kinetic resolution was occurring under one specific experimental condition.

(12) The terminology for similar transformations catalyzed by Pd is inconsistent in the literature. They are often referred to as "kinetic resolutions" since one substrate enantiomer reacts faster than the other. However, the goal of a kinetic resolution is to stop the reaction midcourse to recover enantioenriched starting material as well as product with high ee. In the current Mo-catalyzed reaction, the goal is to carry the reaction to high conversion, and this is possible since both enantiomers give the same product due to a dynamic equilibration of an intermediate. Thus, the current reaction should most properly be termed a dynamic kinetic asymmetric transformation when the reaction is carried to completion. On the other hand, the reaction can be run in a kinetic resolution mode, wherein enantioenriched substrate can be recovered after partial reaction.

(13) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Interscience: New York, 1987; Vol. 14, p 249.

constants and ee's for this enantiomer with both the (*R*,*R*)- and (*S*,*S*)-ligands **5**. Thus, instead of comparing the rates of each carbonate enantiomer in the presence of a single ligand enantiomer, the "matched" and "mismatched" rates were alternatively determined by use of one carbonate enantiomer with each of the two ligand enantiomers. These kinetic experiments verified the k_{rel} of 9 for the reactivity of (*R*)- and (*S*)-**1a** (Table 2, entries 9 and 10). In addition, these experiments confirmed that the two enantiomers of **1a** produce products with quite different ee's and branched/linear ratios (Table 1, entries 9 and 10). For the matched case, (*R*)-**1a** reacting in the presence of (*R*,*R*)-ligand **5**, the ee was >99% and the branched/linear ratio 55. For the mismatched case, (*R*)-**1a** reacting in the presence of the (*S*,*S*)-ligand **5**, the ee was only 70% and the branched/linear ratio 12/1. Thus, these reactions exhibit a modest stereochemical "memory" effect, wherein the stereochemistry of the substrate is partially maintained in the product. On the other hand, there is no regiochemical memory effect. The linear carbonate **2** provides a 97/3 ratio of branched/linear product, while the branched carbonates produce a 98/2 ratio in the matched case and a 92/8 ratio in the mismatched case. That is, the mismatched branched case gives more linear product than the linear substrate. The branched/linear ratio is thus controlled by the inherent bias of the diastereomeric transition states, not by the position of the carbonate leaving group in the starting substrate. To test whether the product had any effect, the reaction of the (*R*)-enantiomer of **1a** was carried out in the presence of the *m*-F product **3b** that had an ee of 97%. There was no effect on the product ee (67%), branched/linear ratio (11:1), or reaction rate (4.9×10^{-5} s^{-1}), which demonstrates that the product has no impact on these reactions.

An interpretation of these results is outlined below and in Scheme 2. For the sake of simplicity, we assume that the major product isomer (**III**) from the fast-reacting carbonate enantiomer (**I**) (the matched case) arises from an "inversion−inversion" mechanism, for which there is literature precedence.[14] Since both enantiomers give the same major product stereochemistry (**III**), diastereomeric equilibration must occur along the reaction path. However, since the two carbonate enantiomers do not give the same ee and branched/linear ratio, the rate of equilibration ($K_{eq} = k_S/k_R$) of the diastereomeric π-allyl intermediates (**II** and **II-epi**) must be competitive with the malonate displacement steps (k_1 through k_4). If equilibration were rapid, the ratio of diastereomers would not be important since the diastereomer having the pathway with the lowest energy transition state would react preferentially (Curtin−Hammett postulate). That is, even if $k_R > k_S$, such that the equilibrium favored the (*R*)-derived oxidative addition product (**II-epi**), the major product could arise via k_1 as long as k_R and $k_S \gg [Nu]\cdot k_{1,2,3,4}$. Since different ee's and branched/linear ratios are obtained from the two carbonate enantiomers, equilibration must be slow and product arising from alkylation of the nonequilibrated isomer (**II-epi**) via k_3 is occurring to some extent.

Kinetic Resolution in Toluene. In our previous paper we had determined that reaction of **1a** and **1b** in toluene as solvent gave improved ee's (97% vs 90%) and branched/linear ratios (20/1 vs 10/1) relative to those in THF.[8] Due to the insolubility of sodium dimethyl malonate in toluene, these reactions were carried out at 90 °C vs the 65 °C temperature used for THF.[8] Examination of the reaction of **1a** in toluene at 90 °C using $Mo(CO)_6$ as precatalyst revealed that a kinetic resolution was again occurring with a k_{rel} of 11 (Table 2, entry 3). Likewise, a kinetic resolution was operable with the *m*-F substrate with a k_{rel} of 15 (Table 2, entry 14). Most interestingly, however, for both substrates the ee and branched/linear ratio eroded only modestly as the reaction continued past the 50% conversion point, with an ee of 99% during the early phase of the reaction and a final ee of 96−97% (Table 1, entries 3 and 16). Similar results were obtained with $Mo(CO)_3$(cycloheptatriene) as precatalyst at a temperature of 60 °C, and is shown graphically in comparison to the reaction in THF in Figure 1.

To compare the reactivity of each enantiomer, the (*R*)-enantiomer of carbonate **1a** was reacted in the presence of the individual (*S*,*S*)-**5** and (*R*,*R*)-**5** ligands. These experiments confirmed that the matched case gave very high ee (>99%) (Table 1, entry 11), similar to the reaction in THF, but the mismatched case still gave reasonably high ee (90%) (Table 1, entry 12), which is in contrast to that in THF. In addition, the rate constants measured for the matched and mismatched systems in toluene gave a k_{rel} of 16 vs the value of 13 determined from eq 2 for the reaction with the racemate (Table 2, entries 11 and 12).

In toluene, the equilibration of the two diastereomeric complexes **II** and **II-epi** relative to alkylation must be faster than in THF, thus giving improved selectivity. A possible explanation for the difference between the two solvents may be the poor solubility of sodium dimethyl malonate in toluene, which would cause the malonate displacement reaction to be slower and allow for the diastereomeric complexes to equilibrate before malonate displacement. To test this hypothesis, the reaction in THF was run with slow addition of sodium dimethyl malonate, thus keeping the concentration of malonate low such that the displacement reaction is retarded. In this case the ee for the mismatched case ((*R*)-carbonate reacting in the presence of (*S*,*S*)-**5** ligand) in THF at 48 °C provided the product with 91% ee vs 70% observed when the malonate was added at the beginning. Thus, poor solubility of the malonate salt in toluene may account for the improved selectivity in this solvent.

Kinetic Resolution in Other Solvents. The allylic alkylation of **1a** with malonate in 1,2-dichloroethane, tetrahydropyran (THP), MeCN, and *i*-PrOAc occurred with kinetic resolution with k_{rel} in the 8−13 range (Table 2). The reactions in MeCN, *i*-PrOAc, and THP were similar to those in THF, with the matched case giving an ee of 99% or better and the mismatched case giving a substantially lower ee, such that the overall ee for the reaction of the racemic substrate was in the 83−92% range (Table 1). In THP the reactions were studied at both 48 and 80 °C (entries 6 and 7 of Tables 1 and 2),

(14) The alternative "retention−retention" argument would lead to the same conclusions. Another possibility is that each enantiomer reacts by different mechanisms, for example, the (*S*)-isomer by "retention−retention" and the (*R*)-isomer by "inversion−retention." Kočovský has demonstrated a retention−retention pathway for Mo-catalyzed allylic alkylations. Dvorak, D.; Stary, I.; Kočovský, P. *J. Am. Chem. Soc.* **1995**, *117*, 6130−6131. Liebeskind has demonstrated that a change in experimental conditions can cause a change in oxidative addition from retention to inversion, so he cautions that either retention−retention or inversion−inversion pathways may be viable in many cases. Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 897−898.

Table 3. Reactivity and Selectivity for Allylic Carbonates 1a and 2 Reacting with Sodium Dimethyl Methylmalonate[a]

entry	substrate	solvent	temp (°C)	ligand	product ee (%)	branched/linear ratio (**3**/**4**)	k_{rel}
1	*rac*-**1a**	THF	48	(*S*,*S*)-**5**	80 (*S*)	9	18[b]
2	*rac*-**1a**	toluene	60	(*S*,*S*)-**5**	89 (*S*)	9	4[b]
3	(*R*)-**1a**	THF	48	(*R*,*R*)-**5**	99 (*R*)	36	19[c]
4	(*R*)-**1a**	THF	48	(*S*,*S*)-**5**	40 (*S*)	5	
5	(*R*)-**1a**	toluene	60	(*R*,*R*)-**5**	99 (*R*)	21	
6	(*R*)-**1a**	toluene	60	(*S*,*S*)-**5**	62 (*S*)	6	
7	**2**	THF	48	(*S*,*S*)-**5**	95 (*S*)	20	

[a] Conditions: $Mo(CO)_3C_7H_8$ precatalyst; sodium dimethyl malonate was prepared in situ from dimethyl malonate and NaH, combined with the carbonate, and added to the preheated activated catalyst mixture. [b] From eq 2. [c] From rate constants.

with minimal differences in the ee and k_{rel} at the two temperatures. The reaction in dichloroethane mirrored that in toluene, with the overall ee for the racemic carbonate being 97% (Table 1, entry 8), indicating the mismatched case was still giving a high ee in the reaction. Like toluene, the low solubility of sodium dimethyl malonate anion in this solvent may be responsible for the increased ee.

Kinetic Resolution with Dimethyl Methylmalonate. The anion of dimethyl methylmalonate reacts with branched carbonate **1a** to provide the corresponding branched and linear products, as summarized in Table 3. Reaction with racemic carbonate in THF and toluene (entries 1 and 2) reveals that the ee's are lower vs those with dimethyl malonate (80% vs 87% in THF and 89% vs 96% in toluene). The lower ee's result from a greater memory effect with dimethyl methylmalonate, as shown in entries 3−6 in Table 3. In both solvents, the matched case of the (*R*)-carbonate catalyzed by the (*R*,*R*)-**5** ligand provides product with 99% ee, but the mismatched case gives ee's of only 40% in THF and 62% in toluene. Using Scheme 2 as a model for the reaction pathway, the results with dimethyl methylmalonate indicate that the equilibration of **II-epi** to **II** (k_S) has been slowed relative to the reaction to form product (k_3). Two of the factors which control k_3 are the basicity and steric effects of the anion. Comparing dimethyl methylmalonate vs dimethyl malonate, addition of the methyl group adds steric hindrance, which should reduce the nucleophilicity, yet previous work indicates displacement reactions with carbon nucleophiles are relatively insensitive to small steric effects.[15] On the other hand, addition of a methyl group increases the basicity of the anion by 1.5−2 pK_a units,[16a] and this in turn will increase the nucleophilicity (k_3), leading to the increased rate of k_3 vs the equilibration rate. Previous work has shown the more substituted enolate is more reactive in alkylations.[16b]

Regarding the branched/linear ratio, the dimethyl methylmalonate anion gives an increase in the amount of linear product vs dimethyl malonate for both the branched carbonate **1a** (11% vs 3%) and the linear carbonate **2** (5% vs 3%). This is likely due to a steric effect, with the more sterically demanding dimethyl methylmalonate reacting toward the least hindered unsubstituted end of the π-allyl complex to form more of the linear product.

As with dimethyl malonate, a kinetic resolution is operative, with the (*S*)-carbonate reacting faster than the (*R*)-carbonate when catalyzed by the (*S*,*S*)-**5** ligand. In THF the k_{rel} is higher for dimethyl methylmalonate vs dimethyl malonate (18 vs 9), while in toluene it is reduced (4 vs 11). An interpretation of these results is difficult, but it is important to note that the nucleophile is involved in some way in the rate-determining step. This is also true for the reaction with the linear carbonate **2**, where the dimethyl methylmalonate anion reacts about twice as fast as dimethyl malonate in THF. These results suggest that the malonate anion may ligate to Mo and be a part of the catalytic species, or that the basicity of the malonate may be important in activating the Mo−ligand catalytic complex. Relevant to this, Trost[2c] has studied the relative reactivity of unsubstituted vs substituted malonates in achiral molybdenum-catalyzed allylic alkylations. In the most dramatic case, the unsubstituted malonate was unreactive while methylmalonate gave the expected alkylated product. When both the unsubstituted and substituted malonates were present together, no reaction occurred. Trost proposed that the unsubstituted malonate was binding to molybdenum, greatly attenuating its catalytic abilities, where as the more hindered, substituted malonate could not bind and therefore reacted as expected.

Comparison of Mo- and Pd-Catalyzed Reactions. The molybdenum-catalyzed allylic alkylations described in this paper occur with kinetic resolution and show modest stereochemical memory effects. These features are common in a number of Pd-catalyzed reactions that have been reported in the past few years. In this section, we summarize the literature on Pd-catalyzed reactions to compare and contrast those with molybdenum.

The first kinetic resolution involving Pd catalysis was with unsymmetrical acyclic allylic acetates using ferrocencylphosphine ligands, reported by Hayashi and Ito in 1986.[17] These reactions had k_{rel} values in the 1−14 range, depending on the substrate. Since the substrates were unsymmetrical and produced two regioisomeric products, it was not clear whether these reactions proceeded via a dynamic equilibration of the π-allyl intermediate, and the authors did not invoke equilibration to explain the outcome. A more straightforward example of a kinetic resolution/dynamic kinetic asymmetric transformation was reported by Osborn in 1998.[18] In this case, using a chiral bisphosphine ligand, cyclohexenyl acetate as substrate, malonate as nucleophile, and THF and dichloromethane as solvents, k_{rel} values in the 2.4−8.1 range were measured. This was the first unambiguous case that demonstrated a selective activation of a racemic allylic substrate could occur with Pd catalysis. In these reactions, the product ee remained unchanged throughout the course of the reactions, indicating that rapid dynamic equilibration of the diastereomeric π-allyl complexes was occurring prior to reaction with the nucleophile. Therefore, these reactions exhibited no memory effects. Osborn found similar results with the acyclic substrate 4-acetoxy-2-pentene.[18]

(15) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737−2769.

(16) (a) The pK_a in Me_2SO of α-methylacetylacetone is 15.07 vs 13.33 for acetylacetone. The pK_a of ethyl α-methyacetoacetate is 15.75 vs 14.26 for ethyl acetoacetate. (Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299−3305.) (b) Caine, D.; Huff, R. *Tetrahedron Lett.* **1967**, 3399.

(17) Hayashi, T.; Yamamoto, A.; Ito, Y. *Chem. Commun.* **1986**, 1090−1092.

(18) Ramedeehul, S.; Dierkes, P.; Aguado, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3118−3121.

The first suggestion of a memory effect in Pd-catalyzed alkylations came from the Fiaud laboratories, where racemic and optically active cyclohexenyl acetate gave different ee's, although the overall ee's were quite low (<20%).[19] The authors invoked an (*o*-allyl)palladium complex to account for the results. A careful study by Trost and Bunt in 1996 conclusively demonstrated a memory effect was operative in the reactions of cyclopentenyl acetates and carbonates. These authors suggested intimate ion pairs could be the factor behind the memory effects.[20] More recently, the cyclopentenyl system has been studied in depth by Lloyd-Jones and Stephen. They reported that chloride ion has a large effect on the kinetic resolution of Pd-catalyzed reactions of cyclopentenyl pivalate in THF with sodium dimethyl malonate as nucleophile.[21] In the presence of chloride, the mismatched rate is enhanced, leading to a diminution of the k_{rel} for this system. They concluded that chloride coordination to Pd^0 resulted in a more reactive and less selective catalyst.[21] Incisive studies by Lloyd-Jones and co-workers of memory effects in Pd-catalyzed reactions using labeled substrates demonstrated that memory effects were dependent on the nature of the ligand, steric effects in the allylic substrate, and the counterion.[22] The effect of counterions on memory effects and kinetic resolution has also been noted by Togni[26] and Trost,[27] which led them to conclude ion pairs play a key role in controlling the outcome of these reactions. Finally, Zhang[23] and Gilbertson[24] have recently reported kinetic resolutions and significant memory effects in Pd-catalyzed allylic alkylations, while Trost and co-workers have demonstrated a near perfect kinetic resolution/kinetic asymmetric transformation with a cyclohexenyl substrate.[25]

It is clear from these examples that kinetic resolution is a common and perhaps the preferred pathway for Pd-catalyzed reactions of branched allylic acetates, and that memory effects are also common and variable. Kinetic resolution and memory effects are governed by a variety of factors, including ligand structure, solvent, counterion effects, nucleophile, and substrate structure. In the single study in which memory effects were studied in a non-Pd-catalyzed reaction, a complete memory effect was observed for the alkylation of allylic carbonates using malonate anion catalyzed by tungsten.[10] This result, combined with crossover experiments, led the authors to speculate that these reactions may not be occurring by the widely accepted π-allyl mechanism that is invoked in Pd catalysis.[10] Our results with the Mo-catalyzed reactions reported in this paper, wherein modest memory effects are observed, mirror those of Pd and can be explained using the conventional π-allyl mechanism.

Conclusion

The molybdenum-catalyzed allylic alkylation of branched carbonates **1a** and **1b** with sodium dimethyl malonate in the presence of ligand **5** can be carried out either as a dynamic kinetic asymmetric transformation (100% conversion of starting material) or as a kinetic resolution (partial reaction and isolation of enantioenriched starting material). In all solvents investigated, the reaction proceeds via a kinetic resolution with k_{rel} values in the 7−16 range. While not extremely large, these k_{rel} values are of a magnitude to effectively carry out these reactions in the resolution mode to obtain recovered starting material in high ee (<95%) at 60−65% conversions, as well as produce product with an excellent ee. The effectiveness of the dynamic kinetic asymmetric transformation is dependent on the solvent. In THF, THP, *i*-PrOAc, and MeCN, a significant stereochemical memory effect is operative, with the slow-reacting enantiomer providing product in much lower ee than the fast-reacting enantiomer. Thus, a lower product ee for reactions of the racemic branched carbonate (80−90%) vs the linear carbonate (>97%) results when the reactions are carried to completion. In toluene and 1,2-dichloroethane, even though the two enantiomers of the carbonate differ in reactivity by an order of magnitude, the memory effect is minimal, and therefore the product ee's in these solvents are excellent (95%) for reactions carried to completion. Spectroscopic and kinetic experiments, along with studies using designed ligand probes, are in progress to further elucidate the mechanism. These studies will be disclosed shortly.

Experimental Section

General Procedures. The molybdenum-catalyzed reactions were carried out under an atmosphere of argon after thorough degassing of the solvent. NMR spectra were recorded on Bruker 300, 400, and 500 MHz instruments. All solvents were dried with molecular sieves prior to use. The molybdenum precatalysts were obtained from Aldrich and Strem. The synthesis and characterization of the allylic carbonates and reaction products have been described previously.[8]

HPLC Assays. Reversed-Phase Assay. To determine conversion, the reactions were monitored by reversed-phase HPLC using a Zorbax SB-phenyl column with the following conditions: eluent, 28/72 MeCN/0.1% aqueous H_3PO_4 isocratic for 40 min and then gradient to 70/30 over 5 min, column temperature 45 °C, flow rate 1.5 mL/min, detection at 220 nm. Elution times: branched phenyl carbonate (**1a**), 27 min; branched *m*-fluorophenyl carbonate (**1b**), 32.5 min; linear phenyl carbonate (**2**), 28 min; branched phenyl product (**3a**), 34.5 min; branched *m*-fluorophenyl product (**3b**), 42.5 min; linear phenyl product (**4a**), 45 min; linear *m*-fluorophenyl product (**4b**), 46 min.

Chiral Assay. A chiral assay was developed which separated both enantiomers of the branched phenyl and *m*-fluorophenyl carbonates as well as the corresponding malonate products. Either an (*R*,*R*)- or (*S*,*S*)-Whelko column could be used; the enantiomer elution order was reversed on the two columns and provided a check that the correct enantiomer peaks were being observed and that there were no interfering peaks. The eluent was 99% hexanes/1% *i*-PrOH isocratic, 220 nm detection, 1.5 mL/min flow rate , 25 °C. Reaction samples for assay were quenched into 10% *i*-PrOH/90% hexanes and an equal volume of 0.5 N HCl, and the organic layer was assayed. Elution times for the (*S*,*S*)-Whelko column: branched

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(26) Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155−159.
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phenyl carbonate (**1a**), (*R*)-isomer at 4.4 min, (*S*)-isomer at 6.5 min; branched *m*-fluorophenyl carbonate (**1b**), (*R*)-isomer at 3.9 min, (*S*)-isomer at 5.5 min; linear phenyl carbonate (**2**), 7.5 min; branched phenyl product (**3a**), (*S*)-isomer at 8.1 min, (*R*)-isomer at 8.9 min; branched *m*-fluorophenyl product (**3b**), (*S*)-isomer at 7.3 min, (*R*)-isomer at 8.1 min; linear phenyl product (**4a**), 14 min; linear *m*-fluorophenyl product (**4b**), 13 min.

Typical Reaction. To a 25 mL Schlenk tube were added (*S*,*S*)-ligand **5** (65.4 mg, 0.20 mmol) and 3.0 mL of THF. While being stirred, the solution was degassed by three vacuum/argon backfill cycles. Tricarbonylmolybdenum cycloheptatriene (55.7 mg, 0.20 mmol) was added, and three additional vacuum/argon backfill cycles were carried out. The mixture was then warmed to 48 °C for 30 min. The catalyst solution turned dark purple with some solids precipitating. To another 25 mL Schlenk tube were added dimethyl malonate (459 mg, 3.48 mmol) and THF (7.5 mL). With stirring, NaH (60%, 122 mg, 3.05 mmol) was added in one portion, resulting in vigorous hydrogen evolution. After 5 min when most hydrogen evolution had ceased, the solution was degassed by two vacuum/argon backfill cycles, and then the linear phenyl carbonate **2** (391 mg, 2.04 mmol) was added and degassed twice. The mixture remained homogeneous. The solution was warmed to 48 °C for 5 min and then transferred to the activated catalyst mixture via gastight syringe to initiate the reaction. Samples were taken via syringe to monitor the reaction and assayed as outlined above. In kinetic runs with carbonate **2** and the individual enantiomers of **1a**, the disappearance of the carbonate followed good first-order kinetics for >3 half-lives. The details of the kinetics will be described in a future paper.

Preparative-Scale Kinetic Resolution of 1a. To a 25-mL Schlenk tube were added (*S*,*S*)-ligand **5** (528 mg, 1.62 mmol) and THF (14 mL). While being stirred, the solution was degassed by two vacuum/argon backfill cycles. Tricarbonylmolybdenum cycloheptatriene (406 mg, 1.49 mmol) was added, and two additional vacuum/argon backfill cycles were carried out. The mixture was then warmed to 48 °C for 30 min. To a 250 mL flask were added dimethyl malonate (6.24 g, 47.3 mmol) and THF (85 mL). To the stirring solution was added 60% NaH (1.57 g, 39.3 mmol) portionwise over 5 min (vigorous hydrogen evolution). The homogeneous solution was degassed by three vacuum/argon backfill cycles and then warmed to 48 °C. The catalyst mixture was added to the sodium dimethyl malonate solution at 48 °C, the resulting mixture was stirred for 5 min, and then the branched phenyl carbonate **1a** (4.89 g, 25.5 mmol) was added. After 30 min the reaction was quenched by addition of water (40 mL) and hexanes (30 mL). Assay at this point indicated 63% conversion. The layers were separated, and the organic layer was washed with brine, filtered through a pad of sodium sulfate, and concentrated to a red oil. The carbonate was separated from product by flash chromatography, eluting with 7% EtOAc/hexanes. The (*R*)-carbonate **1a** (1.81 g, 93% purity) was recovered as a colorless oil, with an ee of 94%. The recovered malonate product, which eluted after the carbonate, had an ee of 97%.

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