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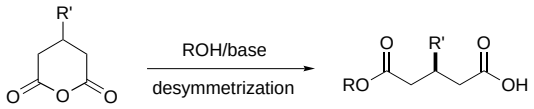
[57] Although the lead inhibitor **1** was assembled by *Electrophorus electricus* AChE, it has a similarly high affinity for the *Torpedo californica* enzyme. This observation suggests a high degree of functional similarity with respect to binding in the active center gorge for these two enzymes (see: S. Simon, J. Massoulié, *J. Biol. Chem.* **1997**, *272*, 33045 – 33055), and justifies our use of the crystallographically well-characterized (2.8 Å resolution) *Torpedo* enzyme for modeling studies. At the present time *Electrophorus* AChE has only been characterized to 4.2 Å resolution (Y. Bourne, J. Grassi, P. E. Bourgis, P. Marchot, *J. Biol Chem.* **1999**, *274*, 30370 – 30376).

Highly Enantioselective Desymmetrization of Anhydrides by Carbon Nucleophiles: Reactions of Grignard Reagents in the Presence of (−)-Sparteine**

Ryo Shintani and Gregory C. Fu*

The desymmetrization of *meso* and other prochiral compounds represents a powerful approach to asymmetric synthesis,[1] and a number of enantioselective total syntheses have been based on this strategy.[2] The desymmetrization of anhydrides has been a particular focus of interest. Most investigations of this family of substrates have employed an alcohol as the nucleophile[3] [for example, a chiral alcohol[4] or an achiral alcohol in combination with a chiral catalyst;[5] Eq. (1)]. In addition, success has been reported for reactions with a stoichiometric quantity of an enantiopure reducing agent[6] or amine.[7]

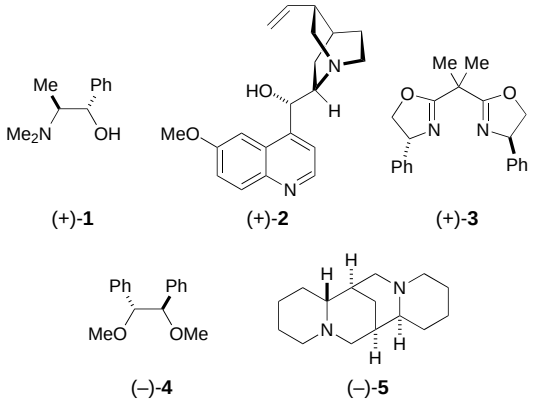


(1)

ROH and/or the base is chiral

On the other hand, very little progress has been described for the desymmetrization of anhydrides with carbon-based nucleophiles. In fact, to the best of our knowledge, only one report has begun to successfully address this challenge, a study by Real and co-workers that focused on the reaction of a single substrate, a bicyclic anhydride, with Grignard reagents bearing chiral oxazolidine auxiliaries.[8] In an attempt to remedy this methodological deficiency, we have recently initiated an investigation of the desymmetrization of anhydrides by carbon nucleophiles. Rather than covalently attaching a chiral auxiliary to the nucleophile and then releasing it, we chose to concentrate our efforts on the use of chiral ligands as the source of asymmetry. Here we report that (−)-sparteine-bound Grignard reagents effectively desymmetrize an array of cyclic anhydrides to furnish ketoacids in very good enantiomeric excess.

In our initial work, we decided to explore the ring-opening of 3-phenylglutaric anhydride by phenylmagnesium chloride. We examined a structurally diverse set of chiral ligands (Scheme 1) that have proved useful in a number of other

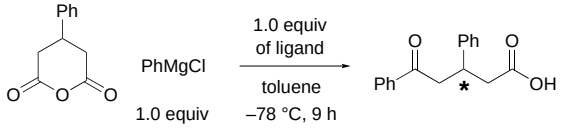


Scheme 1. Ligands used in preliminary experiments.

enantioselective processes, including a simple aminoalcohol (Table 1, entry 1), a cinchona alkaloid (entry 2), a bisoxazoline (entry 3), and a dimethyl ether (entry 4). Disappointingly, all were rather ineffective at desymmetrizing the anhydride (<40% *ee*). Fortunately, however, we discovered that readily available (−)-sparteine accomplishes the ring opening with high enantioselectivity (88% *ee*; entry 5).

Of course, we are not the first to document the remarkable capacity of (−)-sparteine to control enantioselection. Pioneering observations by Nozaki et al. in the 1960's[9] have been followed by fascinating studies by a number of groups, including those of Hoppe and Beak.[10, 11] The large majority

Table 1. Desymmetrization of 3-phenylglutaric anhydride by PhMgCl: a survey of chiral ligands.[a]



Entry	Ligand	*ee* [%]	Yield [%]
1[b]	(+)-**1**	1	76
2[b]	(+)-**2**	12	76
3	(+)-**3**	32	66
4	(−)-**4**	39	77
5	(−)-**5**	88	63

[a] All data are the average of two runs. [b] 2.0 equiv of PhMgCl was used.

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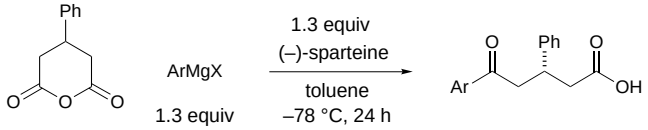
of these investigations have focused on the use of (−)-sparteine to achieve asymmetric reactions of organolithium reagents. The result described in Table 1, entry 5, represents a rare example in which (−)-sparteine furnishes very good enantiocontrol for a reaction of a Grignard reagent.[12, 13]

For the desymmetrization of 3-phenylglutaric anhydride by PhMgCl, we subsequently determined that the use of a slight excess of Grignard reagent/(−)-sparteine leads to an enhancement in stereoselectivity (88% *ee* →92% *ee*) and an improvement in yield (63% →91%; entry 5 of Table 1 vs. entry 1 of Table 2). Under these conditions, a change in the electronic nature of the Grignard reagent has a relatively moderate influence on enantioselection (Table 2, entries 1–3), whereas an increase in the steric demand has a very substantial impact (entry 1 vs. entry 4).

Table 2. Desymmetrization of 3-phenylglutaric anhydride: a survey of Grignard reagents.[a]

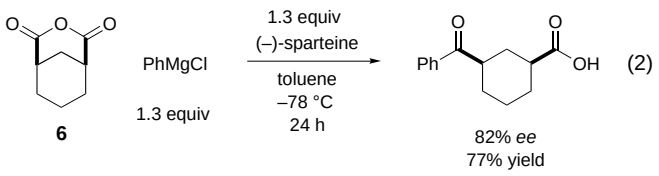


Entry	ArMgX	*ee* [%]	Yield [%]
1[b]	PhMgCl	92	91
2	*p*-$MeOC_6H_4MgBr$	89	88
3	*p*-FC_6H_4MgBr	78	82
4	*o*-TolMgCl	37	66

[a] All data are the average of two runs. Ring openings in toluene provide higher *ee* than reactions in Et_2O or THF. At temperatures above −78 °C, slightly lower enantioselection is observed. [b] PhMgBr and PhMgCl furnish the same level of enantioselectivity.

We have also investigated the scope with respect to the anhydride, and we have established that the reaction tolerates a wide range of substituents and provides uniformly high *ee* values (Table 3). Thus, substrates that bear hindered aromatic (88% *ee*; entry 2) and heteroaromatic groups (91% *ee*; entry 3) undergo desymmetrization with good enantioselectivity. Benzyl-substituted (92% *ee*; entry 4), as well as a sterically diverse array of alkyl-substituted (90–92% *ee*; entries 5–8), anhydrides react to furnish ketoacids with excellent enantioselectivity. The enantioselective ring-opening of heteroatom-substituted anhydrides also proceeds with high stereoselection (87% *ee*; entry 9).

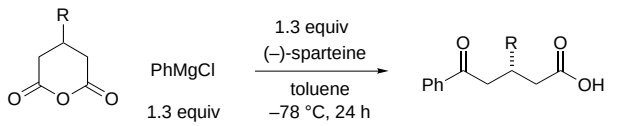
We can effectively desymmetrize not only monocyclic, but also bicyclic anhydrides. Thus, meso **6** reacts with PhMgCl/(−)-sparteine to generate the chiral ketoacid in good enantiomeric excess [Eq. (2)].

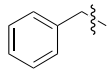
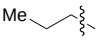
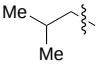


(2)

In summary, we have described the first enantioselective desymmetrizations of anhydrides with carbon-based nucleophiles by employing (−)-sparteine as a chiral ligand. These C–C bond-forming reactions proceed in good enantioselectivity for a range of anhydrides. To the best of our knowledge, this is the first general method wherein (−)-sparteine, which exhibits remarkable versatility in enantioselective reactions of organolithium compounds, has provided excellent stereocontrol in reactions of Grignard reagents. We anticipate that this discovery will stimulate a wide array of studies of applications of (−)-sparteine-complexed Grignard reagents in asymmetric synthesis.

Table 3. Desymmetrization of anhydrides: scope.[a]



Entry	R	*ee* [%]	Yield [%]
1		92	91
2		88	87
3		91	74
4		92	87
5		90	74
6		91	76
7		92	70
8		91	84
9[b]	TBSO	87	51

[a] All data are the average of two runs. [b] TBS = *tert*-butyldimethylsilyl.

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A Stereospecific Ruthenium-Catalyzed Allylic Alkylation**

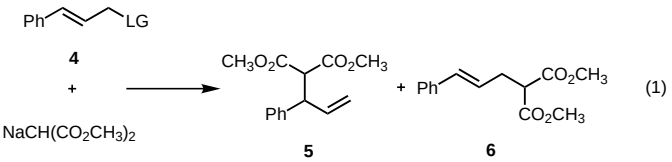
Barry M. Trost,* Pierre L. Fraisse, and Zachary T. Ball

Metal-catalyzed allylic alkylations provide a powerful tool for the construction of complex molecules. One of the benefits of such substitutions is the prospect that the regioselectivity with unsymmetrical allyl substrates can be controlled by the catalyst rather than the position of the allylic substituent serving as the leaving group. Palladium-catalyzed allylic alkylations normally favor nucleophilic addition to the less substituted allyl terminus although ligands can influence this selectivity.[1] Early results demonstrate the effectiveness of Mo[3] and W[4] catalysts and, more recently, their ability to induce enantioselectivity.[5] Such catalysts normally do not work with heteroatom nucleophiles. Iridium catalysts have been reported to favor attack on the more substituted carbon with a carbon—and most recently nitrogen—nucleophile, but the use of an oxygen nucleophile like phenol has not been reported.[6] Rhodium catalysis has proven to be very interesting in that the regioselectivity of the substitution is determined by the position of the leaving group.[7] Herein, we report our preliminary observations that the ruthenium-catalyzed reaction favors attack at the more substituted carbon atom regardless of the regioisomeric nature of the substrate and does so with complete retention of enantiomeric purity when a chiral scalemic substrate is employed. This study has led to a facile synthetic strategy to antidepressants like fluoxetine,[8] the active ingredient of prozac, from ephedrine.

Pioneering work in ruthenium-catalyzed allylic alkylation by Watanabe et al. with the [Ru(cod)(cot)] (cod = 1,5-cyclooctadiene; cot = 1,3,5-cyclooctatriene) complex has indicated a bias for attack at the more substituted terminus with some nucleophiles, although only a 50:50 regioisomeric mixture was obtained by using a cinnamyl carbonate and malonate anion.[9] $[CpRu(cod)Cl]$[10] (**1**) and $[CpRu(PPh_3)_2Cl]$[11] (**2**) have been employed together with heteroatom nucleophiles, but the regioselectivity has not been satisfactorily addressed.

Our recent work on cyclocondensations of allenes and vinyl ketones using $[CpRu(NCCH_3)_3]PF_6$ (**3**) induced us to examine this complex as a catalyst for regioselective allylic alkylation.

We chose the reaction shown in Equation (1) as a standard. In contrast to the earlier reports in which **1** or **2** were used and which required elevated temperatures, complex **3** effected the



(1)

a: LG = OCO_2tBu
b: LG = OCO_2CH_3
c: LG = Cl

reaction of carbonate **4a** at ambient temperature in DMF to give a 1:2 ratio of **5**:**6** in nearly quantitative yield. Attempts to increase this selectivity by varying the reaction conditions failed and thus we examined changes in the ligand. We reasoned that a more sterically demanding catalyst might favor the monosubstituted olefin adduct initially formed from "branched" attack to afford **5**. Under identical conditions with carbonate **4a**, $[Cp^*Ru(NCCH_3)_3]PF_6$ (**7**) ($Cp^* = \eta^5$-C_5Me_5) gave a 9:1 ratio of **5**:**6** (96% yield) in 2 h. In acetone, the selectivity increased to 19:1 (quantitative yield). Reactions of the methyl carbonate **4b** are generally faster. Indeed, in DMF within 30 min, a quantitative yield of alkylation products was obtained in a 14:1 ratio of **5**:**6** with only 1 mol% of catalyst **7**.

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