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Review

Asymmetric catalytic anhydride openings *via* carbon-based nucleophiles

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ABSTRACT

The asymmetric desymmetrization of cyclic anhydrides *via* the addition of carbon-based nucleophiles has been the focus of considerable levels of interest because it leads to optically active products. Over the past 20 years, a variety of different catalytic asymmetric alkylation reactions have been developed for the desymmetrization of cyclic anhydrides using different metal reagents as nucleophiles and using chiral ligands. The purpose of this review is to provide an overview of significant developments in this field.

1. Introduction

The desymmetrization of meso cyclic anhydrides *via* the addition of carbon-based nucleophiles represents a well-established and powerful synthetic tool in asymmetric synthesis because it allows for the construction of multiple stereogenic centers in one symmetry-breaking operation [1]. Over the past two decades, the asymmetric opening of anhydrides with carbon-based nucleophiles has been extensively investigated because of the great potential for the application of this technique in the asymmetric synthesis of important chiral intermediates and optically active fine chemicals (Scheme 1) [2].

The asymmetric anhydride alkylation reaction using chiral Grignard reagents was pioneered by Real *et al.* [3] in 1993. Research in this area has been subsequently shifted to focus on the transition-metal catalyzed alkylation of anhydrides due to the mild reaction conditions and high stereoselectivity associated with these transformations. Nickel-, palladium- and rhodium-based systems have all been successfully applied as catalysts to the anhydride alkylation reaction. This review presents a comprehensive overview of both newly developed and well-established strategies in the field of asymmetric anhydride opening by the addition of carbon-based nucleophiles.

2. Asymmetric anhydride alkylation using organozinc reagents as nucleophiles

The ability of transition-metal complexes to mediate carbon–carbon bond-forming reactions makes them invaluable tools in organic synthesis [4]. Rovis *et al.* [5] provided a detailed description of the investigations involved in the asymmetric alkylation of anhydrides catalyzed by transition-metals. Nickel-, palladium- and rhodium-based catalysts have all been successfully applied to the desymmetrization of prochiral cyclic anhydrides.

2.1. Nickel-catalyzed anhydride alkylation

Non-stereoselective methods for the desymmetrization of cyclic anhydrides were initially studied by Rovis [5], providing a platform for the subsequent development of the asymmetric anhydride alkylation reaction. The 2,2′-bipyridyl (bipy) nickel complex was found to be highly effective in promoting the alkylation of succinic anhydrides, whereas the use of the (2-diphenylphosphino)ethylpyridine (pyphos)-derived nickel complex was successfully used to facilitate the alkylation of glutaric anhydrides to give the corresponding keto acids in high yields [5a,c]. Interestingly, the use of nickel allowed for the introduction of chiral ligands to provide enantioselectivity over the bond-forming event. As shown in Scheme 2, the use of the phosphino-oxazoline ligand (*i*-PrPHOX, **1**) afforded an active catalyst for the alkylation of cyclohexane-1,2-dicarboxylic anhydride (**2**) leading to the formation of the keto acid product in 85% yield and 79% *ee* [5a].

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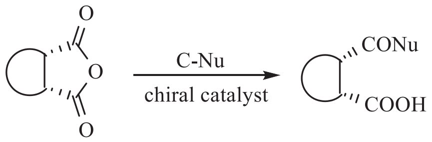
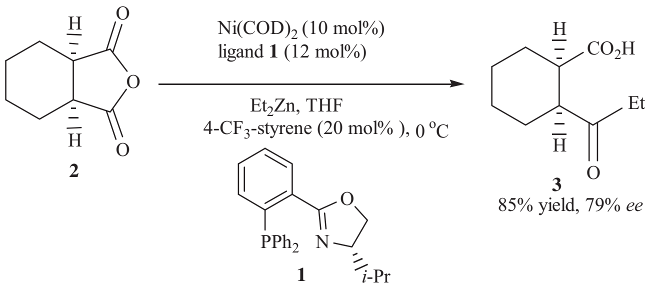
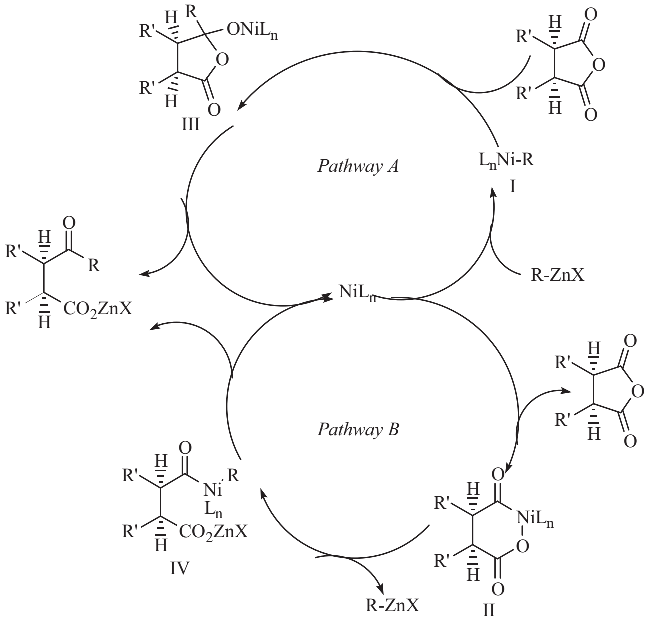


Scheme 1. Asymmetric anhydride openings *via* carbon-based nucleophiles.

The alkylation of cyclic anhydrides with diorganozinc reagents can be efficiently catalyzed by adding nickel in conjunction with an appropriate ligand. There are limitations to this protocol, including the fact that only one of the two zinc substituents is transferred during the reaction. To address this issue and conduct a thorough investigation of the Ni-catalyzed alkylation of anhydride, Rovis *et al.* employed mixed zinc reagents [6] as nucleophiles and evaluated their effects on the levels of enantioselectivity in the products. As shown in Table 1, particularly high levels of selectivity for Ph transfer were achieved when *i*-Pr_2Zn or $(TMSCH_2)_2Zn$ were used as the second zinc reagents (Table 1, entries 6–9), and even higher levels of enantioselectivity were observed when Et_2Zn was used as the second zinc reagent (Table 1, entries 3–5). It is noteworthy that the asymmetric alkylation of anhydrides was proceeded with a lower enantioselectivity when Ph_2Zn prepared *in situ* from the reaction of ArBr and *n*-BuLi with $ZnCl_2$ as the zinc reagent [7].

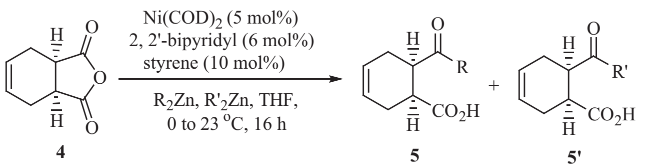


Scheme 2. Ni-catalyzed asymmetric alkylation of **2**.



Scheme 3. The proposed mechanistic pathways.

Table 1
Ni-catalyzed asymmetric opening of **4**.



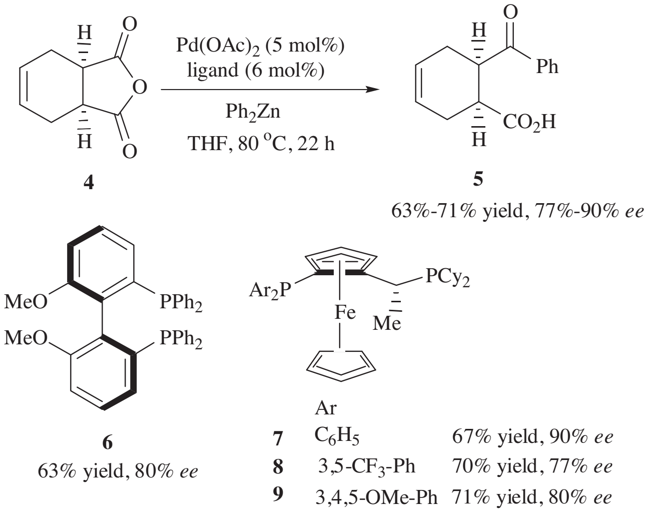
Entry	R	R'	Products (R:R')	Yield (%)[a]	*ee* (%)[b]
1	Ph			81	65
2	Ph			79	22
3	Ph	Et	10:1	78	75
4	Ph	Et	10:1	73	63
5	Ph	Et	1.3:1	69	74
6	Ph	$TMSCH_2$	>20:1	77	33
7	Ph	$TMSCH_2$	>20:1	72	44
8	Ph	*i*-Pr	>20:1	77	35
9	Ph	*i*-Pr	>20:1	73	40

[a] The yield of **5** and **5**′.
[b] The *ee* of **5.**

In 2005, two possible mechanistic routes to this asymmetric reaction were proposed by Rovis group [5c]. As shown in Scheme 3, Pathway A involves the initial formation of an alkyl nickel intermediate I from direct alkyl group transfer from the zinc reagent to the catalyst, whereas pathway B involves oxidative addition of the low-valent nickel complex to the electron-deficient C–O bond of the cyclic anhydride to provide carboxylate II. Intermediate I could then react with the anhydride directly yielding intermediate III which would provide the desired product upon collapse. Transmetalation of II yields IV which can then provide the final product along with regeneration of the active catalyst by reductive elimination.

2.2. Palladium-catalyzed anhydride alkylation

An improved protocol for the enantioselective desymmetrization of cyclic anhydrides using palladium-based catalysts was also reported (Scheme 4) [8]. The enantioselective ring-opening of cyclic anhydrides was initially investigated using (S)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(S)-BINAP] as the ligand and $Pd(OAc)_2$ as the palladium source, with the corresponding keto



Scheme 4. Ligand screen for the asymmetric arylation of **4**.