NOVEL CARBAMATE-BASED P,O-LIGANDS FOR ASYMMETRIC ALLYLIC ALKYLATIONS

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ABSTRACT

Highly functionalized allylic compounds are invaluable intermediates for the pharmaceutical and agricultural industries. Since the early discovery of Trost and Takai, the field of Pd-catalyzed asymmetric allylic alkylation (AAA) was growing rapidly. Due to its indisputable advantages such as mild reaction conditions and operational simplicity, it is still one of the most relevant strategies for the synthesis of substituted allylic compounds [1]. One current state-of-the-art ligand family (Trost-type ligands) relies on a triazolium core, using a P-O bidentate motif for strong Pd-complexation, resulting in high catalytic activity and selectivity [1]. While such ligands are well established and studied, monophosphine analogues with P-O-chelation did not gain much attention. Hence, we report the synthesis of novel, chiral diamine-based O,O-ligands and their successful application in asymmetric allylic alkylation (AAA). After optimization of the reaction conditions, excellent yield and ee values have been obtained for aromatic and aliphatic substrates. The results show that such a new chelation concept can compete or even outperform the current state-of-art catalyst systems.

1. Asymmetric allylic alkylation

Palladium-catalyzed asymmetric allylic alkylation (AAA) provides an efficient and convenient alternative for the synthesis of highly substituted allylic intermediates. A wide range of allylic compounds can be reacted with a variety of soft nucleophiles under mild reaction conditions.

Based on various reports on the Trost-type ligands, it has been found that the two phosphine units are mainly responsible for the complex formation (Figure 1, left), however, a competition between the pure P,P-binding and P,O-chelation (Figure 1, right) is frequently mentioned as a major source of the limited enantioselectivity [2].

Encouraged by these shortcomings and the prior success with carbamate-based ligands in transition-metal catalysis [3], we aimed to synthesize novel P,O-monophosphine ligands for asymmetric allylic alkylation (Figure 1, right).

Starting from relatively cheap and easily accessible chiral pool of diamines (1-2), a small library of carbamate-protected monophosphine ligands (11-18) was synthesized following a straightforward two-step procedure (Scheme 1). After deprotection of the diamines 1-2 [3], the monophosphine unit was introduced via DCC/DMAP coupling. After purification, ligands 11-18 were obtained with good overall yields.

Reagents and conditions: (a) amines, benzyl alcohol in MeOH; (b) DCC, DMAP, ethyl CH₂CO₂Et

In order to experimentally investigate whether the carbonate carbonyl group plays a crucial role in the complexation, the unprotected analogues of compound 11 and 15 have been also synthesized:

TXMOL yield: 98% isolated yield > 99% ee

Scheme 3: Deprotection procedure for compounds 11 and 18

2. Ligand design

After identifying the optimal reaction conditions and the best ligand system, a series of different soft nucleophiles were used for the AAA reaction of (1)-diphenylallyl acetate (21) and dimethyl malonate.

Under the previously optimized reaction conditions, excellent enantioselectivities with high yields were observed for the AAA reaction of 22, while the corresponding products of acetate 23 could be obtained with high yields and good to excellent ee values.

3. Parameter optimization and ligand screening

After the successful synthesis and characterization of ligands 11-22, their catalytic activity and selectivity was investigated in the AAA reaction of (1)-diphenylallyl acetate (21) and dimethyl malonate.

4. Scope and limitations

Novel P,O-ligands with unique coordination mode have been synthesized in a straightforward two-step procedure with good overall yields. After parameter optimization, the carbamate-monophosphine ligand 11 was found to be an excellent catalyst for asymmetric allylic alkylation, providing high catalytic activities and good to excellent enantioselectivities for different substrates and nucleophiles.

5. Conclusion

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