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New 5,5′-disubstituted BINAP derivatives: Syntheses and pressure and electronic effects in Rh asymmetric hydrogenation

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Abstract

A library of 5,5′-disubstituted BINAP derivatives were synthesized in good yield from optically pure BINAP and evaluated for the Rh-catalyzed homogeneous asymmetric hydrogenation of (α)-acylaminoacrylate ester, with ee of up to 77% being obtained with the phenyl derivative. The enantiomeric excess variation was followed according to the groups introduced in the 5,5′-position of BINAP and for a range of pressure from 5 to 30 bar.

Keywords: Asymmetric catalysis; Rhodium; Hydrogenation; Ligand effect

Chiral diphosphines have been known for more than 30 years [1,2], to be the most efficient type of ligands for the asymmetric hydrogenation of C=C and C=O bonds, one of the most important application of enantioselective catalysis [3]. The first developments by Knowles and Sabacky [4], Horner et al. [5], and Kagan and coworkers [6] were rapidly followed by the first successful commercial application of the Rh-catalyzed hydrogenation of prochiral enamides in the Monsanto L-DOPA process [7] and the preparation of pharmaceuticals, agrochemicals, fragrances, and flavours [8]. In 1980, Noyori and coworkers published the synthesis of BINAP [9,10] (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), which has further open the field of application of asymmetric hydrogenation. Since then, the mechanism of the reaction [11] has been elucidated, thousands of chiral ligands and their transition-metal complexes have been reported [12]. Many of them, closely related to the BINAP itself, are highly effective in the asymmetric formation of C–H, C–C, C–O, and C–N bonds and for transition-metal-catalyzed asymmetric synthesis in general [13–15].

The research undertaken to date in asymmetric hydrogenation relates almost exclusively to the development of new chiral inductors to improve the selectivity of the reactions. The key/hole concept generally used to adapt the chiral catalyst to the prochiral substrate is however, often not operating properly. On the contrary, many examples demonstrate the importance of the operating conditions, such as the hydrogen pressure, on the ee during enantioselective catalytic hydrogenations [16a]. Kinetic factors rather than thermodynamic account for such observations, as demonstrated from the determination of the reaction mechanism [17]. This study pointed that a small and achiral molecule like hydrogen, can indeed exert a very strong influence on measured ee. With regard to the asymmetrical reductions of "enamide" type substrates by molecular hydrogen, it is noteworthy that most of hydrogen pressure effects lead to a *decrease* of the enantioselectivity. The situation is even more complex since it is the dissolved hydrogen concentration and not the pressure which is responsible for ee variations. The reactor, being in charge of gas–liquid mixing, is also involved somehow [16,18]. The situation is complex but rather clear: the pathway to further understand the structure/enantioselectivity relationship, that would ultimately leads to more general predictive tools, must go through the decoupling of possible pressure and conversion effects on ee while proceeding with a systematic approach of intrinsic (molecular) effects. Obviously, because many tests are being performed, such an approach

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needs specific tools able to handle small quantities of expensive chiral inductors (BINAP ≈ 80,000 € kg^{-1}) [16] within a broad range of operating conditions [19,20].

In order to extend the scope of our first studies, a library of 5,5′-disubstituted BINAP derivatives have been synthesised and a significant number of catalytic systems of the type Rh/BINAP-derivatives (seven catalytic systems) with various electronic and steric properties, all featuring the same ligand backbone, have been screened for the asymmetric hydrogenations of three prochiral(acylamino)acrylic esters within a range of pressure from 5 to 30 bar.

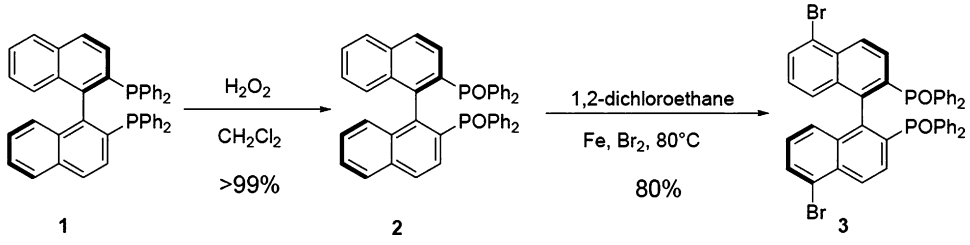
1. Results and discussion

1.1. Synthesis

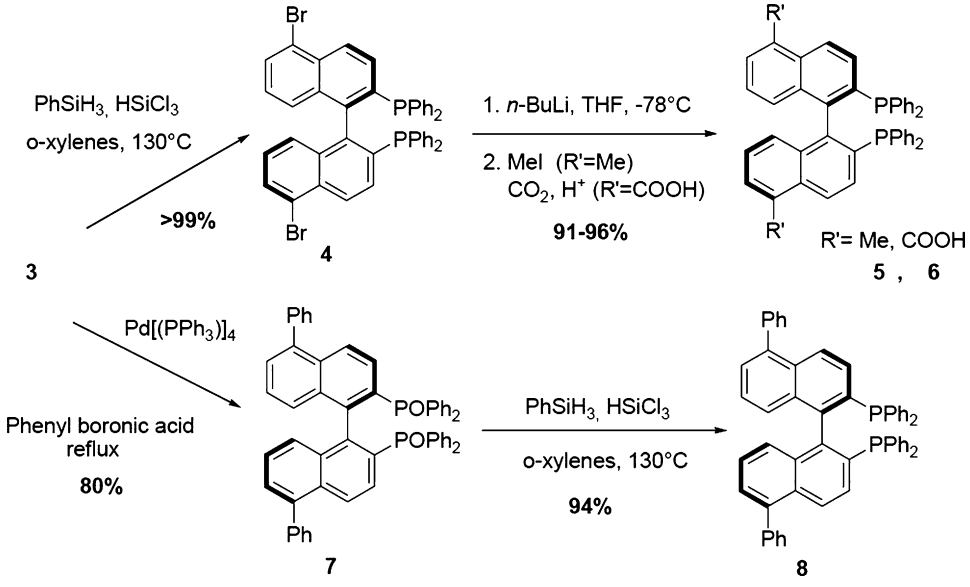
Most of the BINAP derivatives were usually prepared from BINOL or protected BINOL with a phosphination reaction at the end of the synthesis [21]. Lemaire and coworkers [22] described a new strategy to obtain BINAP derivatives directly from BINAP itself. Firstly, optically pure (*R*)-BINAP was transformed (Scheme 1) into its corresponding dioxide **2** followed by a regioselective bromination. The 4,4′-positions were brominated in the presence of pyridine [23] according to Kockritz and coworkers while the 5,5′-positions were brominated in the presence of iron as catalyst. In both cases, brominations were regioselective, with only a trace of monobrominated by-products. The dibrominated phosphines were both obtained in 80% isolated yield [24]. In the literature, the only way to functionalize the 5,5′-position is nitration [25] or sulfonation [26]. Our method required a strong Lewis acid. Phosphine oxides are Lewis bases [27] and are complexed during electronic substitution in presence of Lewis acid. Although the 4,4′-positions, close to the phosphine oxide, were the most reactive, the presence of a Lewis acid deactivate this position by complexing the phosphine oxide; Br_2 (activated by the presence of Fe) would brominate the less deactivated 5,5′-position. To our knowledge, this method is the first report, which leads to a dibrominated BINAP at the 5,5′-positions [28]. In order to study electronic effect in the Rh-catalyzed homogeneous asymmetric hydrogenation of (α)-acylaminoacrylate ester we were interested in the synthesis of new 5,5′-disubstituted BINAP derivatives by this method.

Our synthesis began from readily available BINAP (**1**), which was treated with H_2O_2 in dichloromethane to give BINAPO (**2**) and the treatment of (**2**) with bromine and iron at 80 °C in 1,2-dichloroethane give 5,5′-dibromoBINAPO (**3**) (Scheme 1).

The 5,5′-disubstituted BINAP derivatives were synthesized starting from (**3**) by two different approaches (Scheme 2). Firstly, compound (**4**) was synthesized from (**3**) in excellent yields by reduction with a mixture of $PhSiH_3$ and $HSiCl_3$ at 130 °C. Then, compounds (**5**) and (**6**) were obtained in very good yield (91–96%) by lithiation of (**4**) with *n*-butyl lithium followed by



Scheme 1. Synthesis of 5,5′-dibromoBINAPO.



Scheme 2. Synthesis of 5,5′-(diphenyl, dimethyl, diacides)BINAP.