# Enantioselective rhodium-catalysed 1,4-additions of 2-heteroarylzinc donors using Me-DUPHOS†

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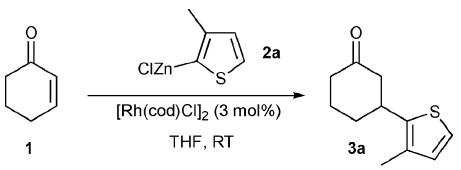
**The enantioselective 1,4-addition of 2-(substituted)thienylzinc and 2-furanylzinc reagents has been achieved (up to 99 : 1 er) using a complex derived from $[Rh(C_2H_4)_2Cl]_2$ and Me-DUPHOS.**

The transition-metal catalysed conjugate addition of organometallics to activated alkenes is an important tool for organic synthesis.[1] For the addition of aryl and alkenyl groups, the elegant rhodium-catalysed addition of organoboron reagents to α,β-unsaturated carbonyl acceptors, pioneered by Hayashi and Miyaura, offers high enantioselectivities in a predictable fashion.[2] In each case, the sense of asymmetric induction can be reliably predicted by means of simple stereochemical models when using enantiopure BINAP (or related ligands).[3] The process hinges on an efficient transmetallation to rhodium followed by carbometallation to afford an $\eta^3$-oxa-π-allylrhodium complex that is protonated to afford the product. A significant side-reaction is the protodeboronation pathway that necessitates the use of two to five equivalents of the organoboron donor to achieve satisfactory yields of product.[4] Other organometallics are known to participate in the key transmetallation to rhodium and are becoming more widely-used in enantioselective synthesis (notably arylzinc reagents and arylsiloxanes).[5] More recently, the palladium-catalysed addition of arylboronic acids and arylsiloxanes has emerged as a practical alternative.[6]

Despite the advances in catalyst design and substrate (acceptor) diversity, the structure of the donor remains surprisingly limited to aryl and a small number of alkenyl derivatives (*alkyl* organometallics are not currently viable donors as the rhodium alkyl complexes are kinetically unstable and rapidly undergo β-hydride elimination). A conspicuous limitation is the general application of heteroaromatic donors and particularly 2-heteroaryl donors in the rhodium-catalysed addition reaction. Our initial experiments with 2-heteroarylboronic acids under the standard aqueous conditions returned the protonated heteroarene as the major product.[7] It appeared the rate of protodeboronation is significantly faster than the rate of carbometallation and this undesirable pathway predominates. As organozinc reagents do not require water for catalyst turnover and transmetallate at room temperature, we therefore decided to examine 2-heteroarylzinc donors (available as commercially available solutions or prepared by directed metallation–zincation).†

At the outset we examined the addition of the thienylzinc reagent **2a** to cyclohexenone **1**, as shown in Scheme 1. In the absence of any additives, the reaction resulted in a complex mixture including oligomeric products from subsequent conjugate additions of the intermediate zinc enolate. The introduction of chlorotrimethylsilane (1.5 equivalents) in the reaction mixture suppressed the tandem conjugate addition reactions by forming a more stable enolate and side reactions are avoided.[8] The product **3a** was obtained in high isolated yield. Interestingly, Woodward *et al.* have reported a detailed study of a related cascade process that occurs in the copper-catalysed addition of alkylzinc reagents to cyclohexenone.[9]

With the conjugate addition of **2a** demonstrated in good yield, we immediately initiated work on developing an enantioselective reaction (selected results shown in Table 1). A number of enantiopure ligands were identified that afforded product **3b** with good enantioselectivity, including (*R*)-BINAP (93 : 7 er) and (*S*)-SYNPHOS (17 : 83 er). The optimal ligands turned out to be Carreira's (*R*,*R*,*R*)-DOLEFIN ligands (up to 98 : 2 er) and (*R*,*R*)-Me-DUPHOS (up to 98 : 2 er) with (*R*,*R*)-Me-DUPHOS providing higher isolated yields of products (Table 1, entry 11). Remarkably, the addition of 2-thienylzinc bromide afforded product with excellent enantioselectivity (98 : 2 er) in the presence of $[Rh(C_2H_4)_2Cl]_2$ and (*R*,*R*)-Me-DUPHOS despite there being a significant conversion to product (41%, Table 1, entry 1) in the absence of the rhodium catalyst.[10] Preliminary kinetic studies have revealed that the catalytic reaction stalls after one hour suggesting some catalyst decomposition to inactive species over longer reaction times (Table 1, entries 12–16). The addition of extra $[Rh(C_2H_4)_2Cl]_2$ (2 mol%) and (*R*,*R*)-Me-DUPHOS (2.2 mol%) after one hour led to an increased conversion to product of 86% after three hours. The observed enantioselectivity remained constant over time with (*R*,*R*)-Me-DUPHOS affording predominantly the




**Scheme 1**

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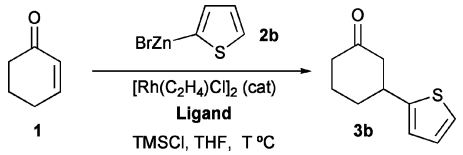
**Table 1** Developing an enantioselective process[a]



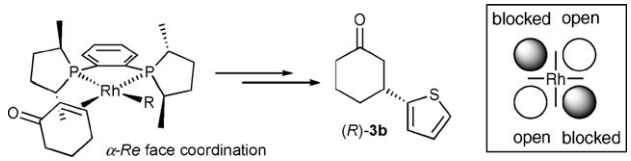

| Entry | Ligand[b] | Temp./°C | Time/h | Conversion (yield%)[c] | Er **3b**[d] (*R* : *S*) |
|---|---|---|---|---|---|
| 1[e] | — | RT | 16 | 41 | 1 : 1 |
| 2 | (*R*)-DIOP | 50 | 4 | 33 (26) | 55 : 45 |
| 3 | (*R*)-BINAP | 50 | 4 | 89 (70) | 93 : 7 |
| 4 | (*S*)-SYNPHOS | 50 | 4 | 30 (22) | 17 : 83 |
| 5 | (*R*,*R*,*R*)-DOLEFIN[f] | 50 | 4 | >99 (80) | 93 : 7 |
| 6 | (*R*,*R*)-Me-DUPHOS | 50 | 4 | 44 (36) | 97 : 3 |
| 7 | (*R*,*R*)-$^{i}$Pr-DUPHOS | 35 | 16 | 50 (41) | 91 : 9 |
| 8 | (*R*,*R*)-Me-DUPHOS | RT | 16 | 78 (71) | 98 : 2 |
| 9 | (*R*,*R*,*R*)-DOLEFIN | RT | 16 | 33 (33) | 98 : 2 |
| 10 | (*S*,*S*,*S*)-DOLEFIN | RT | 16 | 35 (32) | 3 : 97 |
| 11[g] | (*R*,*R*)-Me-DUPHOS | RT | 4 | 76 (71) | 98 : 2 |
| 12[h] | (*R*,*R*)-Me-DUPHOS | RT | 0.5 | 38 | 95.5 : 4.5 |
| 13[h] | (*R*,*R*)-Me-DUPHOS | RT | 1 | 61 | 96 : 4 |
| 15[h] | (*R*,*R*)-Me-DUPHOS | RT | 4 | 65 | 97 : 3 |
| 16[h] | (*R*,*R*)-Me-DUPHOS | RT | 8 | 67 | 96.5 : 3.5 |

[a] Reaction conditions: **1** (1.0 equiv.), **2b** (0.5 M in THF, 1.5 equiv.), chlorotrimethylsilane (1.5 equiv.), $[Rh(C_2H_4)_2Cl]_2$ (3 mol%), ligand (3.6 mol%) in THF (1 ml). [b] Ligand structures shown in ESI. [c] Isolated yields after column chromatography. [d] Determined by HPLC analysis using Chiralcel OJ column, hexane : $^{i}$PrOH = 98 : 2, flow rate 1.0 ml min$^{-1}$. [e] No catalyst or ligand added. [f] (1*R*,4*R*,8*R*)-5-Benzyl-8-methoxy-1,8-dimethyl-2-(2′-methylpropyl)bicyclo[2.2.2]octa-2,5-diene. [g] $[Rh(C_2H_4)_2Cl]_2$ (5 mol%), ligand (6 mol%). [h] Kinetic study.

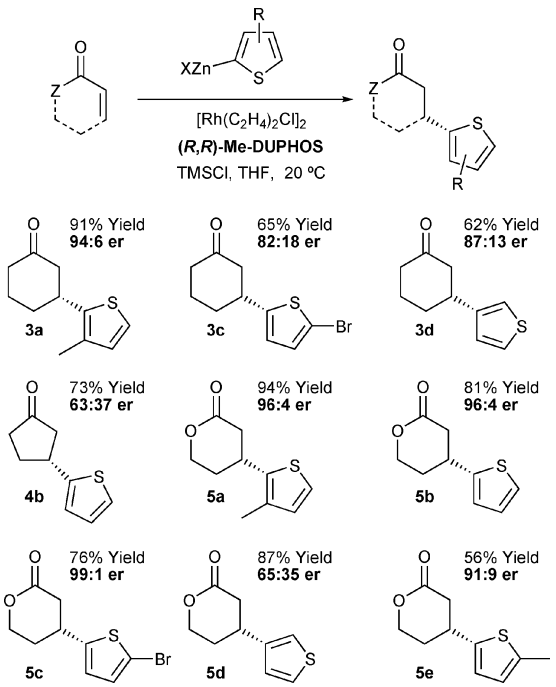
(*R*)-enantiomer of product **3b**. The sense of asymmetric induction is the same as with (*R*)-BINAP and implies steric blocking of the upper left and bottom right quadrants by the methyl substituents leading to α-*Re*-face coordination of cyclohexenone to rhodium as shown in Scheme 2.

Following the success of the initial experiments, the scope of the 2-thienylzinc donor and the acceptor was investigated to establish the versatility of the reaction (Scheme 3). In the addition to cyclohexenone, a selection of donors were found to provide products with good enantioselectivities (**3a–3d**). In the addition to cyclopentenone, the addition of **2b** afforded product **4b** with low enantioselectivity (63 : 37 er).[11] However, in the absence of catalyst, a quantitative conversion to product was noted with this substrate. Clearly, the rate of the enantioselective carbometallation, the rate of the background addition reaction and the rate of catalyst decomposition are intimately linked to the overall enantioselectivity obtained. An attractive solution was to switch to a less reactive substrate that did not undergo the addition reaction in the absence of a catalyst. A suitable acceptor was the cyclic lactone 5,6-dihydro-2*H*-pyran-2-one; pleasingly this was found to undergo highly enantioselective additions of 2-heteroarylzinc donors (**5a**, **5b**, **5c** and **5e** up to 99 : 1 er). The use of 3-thienylzinc bromide as the donor resulted in appreciably lower enantioselectivity compared to 2-thienylzinc bromide, particularly in the case of **5d**. This may indicate that secondary interactions between the sulfur donor and either zinc or another rhodium complex is important in dictating the transition state leading to high enantioselectivity.[12]

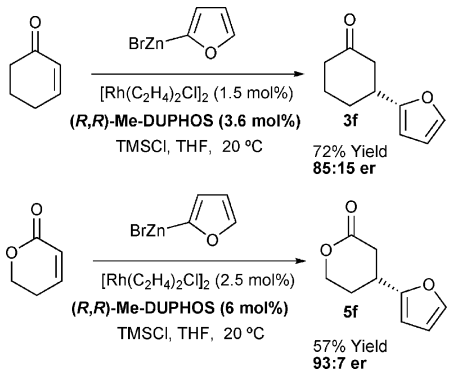
To extend the utility of this method, we have explored the use of 2-furanylzinc reagents in the addition reaction. Using




**Scheme 2**




**Scheme 3**




**Scheme 4**

the established conditions, the products **3f** and **5f** were obtained in reasonable yields and good enantioselectivities (Scheme 4). To our knowledge, these are the first examples of enantioselective rhodium-catalysed conjugate additions involving furan as a donor.

In summary, we have successfully demonstrated that 2-heteroarylzinc donors can be utilised in the enantioselective rhodium-catalysed conjugate addition reaction. Furthermore, we have revealed that a complex derived from $[Rh(C_2H_4)_2Cl]_2$ and Me-DUPHOS is superior to established catalyst systems for this challenging transformation. We are continuing to explore the scope of this process with a broader range of heteroaromatic donors.

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