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# Asymmetric hydrogenation of tri-substituted alkenes with Ir-NHC-thiazole complexes

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**Abstract**—An efficient chiral N-heterocyclic carbene ligand for the Ir-catalyzed asymmetric hydrogenation of largely unfunctionalized tri-substituted olefins has been developed. The Ir-NHC-thiazole catalyst is able to reduce a large variety of substrates with excellent conversions and good enantioselectivities with ee's ranging from 34% to 90%, depending on the geometry around the double bond of the substrates.
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## 1. Introduction

N-Heterocyclic carbenes (NHCs) and their transition metal complexes have recently attracted much interest in organic and organometallic chemistry.[1] Due to strong carbon–metal σ-bonds, NHCs are well suited to act as ligands in various transition metal catalyzed reactions. The organometallic complexes derived from NHCs tend to be air stable and the carbene binds to the metal more strongly than electron rich phosphines.[2] Their powerful σ-donating and weak π-accepting properties result in metal centers that are electron rich when compared to the corresponding phosphine complexes.[3]

Complexes containing carbene based ligands tend to be highly active in oxidative addition reactions and hence are attractive alternatives to phosphine based ligand systems.

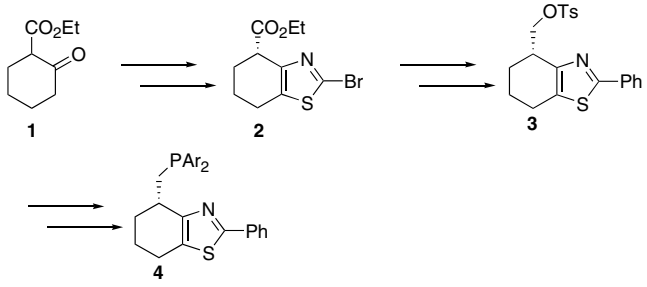
Recently, Burgess and co-workers reported that chiral Ir-imidazol-2-ylidene-oxazoline complexes can be used for the asymmetric hydrogenation of olefins with great success, enantiomeric excesses over 99% were obtained.[4]

Chiral imidazolylidenes were first reported several decades ago by Müller and co-workers[5] and several others have been reported more recently.[6–8] Even so there have been relatively few reports on optically active electron rich carbene ligands in asymmetric catalysis, some examples include Ru-catalyzed metathesis,[8,9] Rh-catalyzed hydrosilylation[10] and conjugate addition of arylboronic acid derivatives to enones.[11]

Ever since Pfaltz first reported the successful Ir-catalyzed hydrogenation of largely unfunctionalized olefins using the Ir–PHOX complex,[12] a chiral mimic of Crabtree's catalyst,[13] there have been a number of reports in the literature employing chiral N,P-ligands for this type of hydrogenation.[14] However, Ir-catalyzed asymmetric hydrogenation is still highly substrate dependent and the development of new efficient chiral ligands that tolerate a broad range of substrates remains a challenge.

Inspired by this, we decided to synthesize an imidazole analogue of our recently published phosphine-thiazole ligand **4** (Scheme 1).[15]

We reasoned that exchanging the phosphine moiety with a NHC functionality would produce an interesting




**Scheme 1.** Synthetic route leading to the phosphine–thiazole ligand.

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ligand structure that might perform well in various asymmetric catalytic reactions, especially in the Ir-catalyzed hydrogenation of olefins.

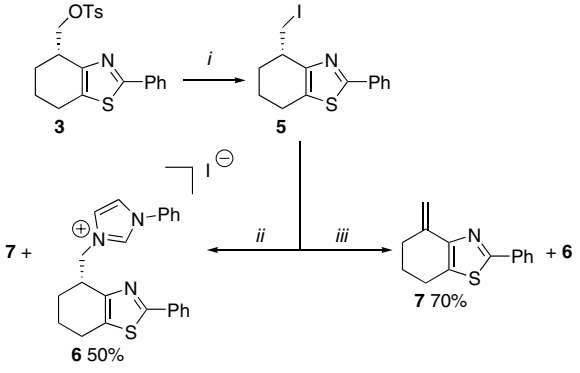
The synthesis of the NHC ligand **6** started from the previously described tosylate **3** (Scheme 1), which in turn can be prepared in enantiomerically pure form by a previously reported synthetic protocol (Scheme 1).[15] The tosylate is first converted into the iodide **5** via a Finkelstein reaction, by treatment with 5 equiv of NaI in refluxing acetone. Nucleophilic substitution with *N*-phenylimidazole (1 equiv) proceeded smoothly in DMF at 60 °C (48 h), giving **6** in reasonable yield. The major by-product observed in this reaction was the elimination product **7**. In an attempt to reduce the reaction time, the temperature was increased (80 °C), resulting in 70% of **7** (Scheme 2). However, decreasing the temperature below 60 °C did not produce the desired product **6** in higher yield.

Complex formation was accomplished by dissolving the ligand **6**, $[IrCl(COD)]_2$, and $^t$BuOLi in THF, then refluxing for 1 h to generate the carbene and then stirring at rt overnight. The solvent was then evaporated and the residue was dissolved in $CH_2Cl_2$ (5 ml). Ion exchange was accomplished by addition of $H_2O$ (2 ml) followed by 1.2 equiv of $NaBAr_F$ and stirring vigorously for 30 min, yielding complex **8** in 30% isolated yield (Scheme 3).

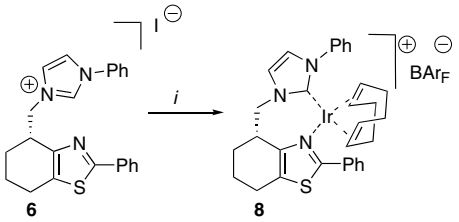
The new complex **8** proved to be efficient in the hydrogenation of various standard substrates with ee's ranging from 34% to 90% (Table 1). The hydrogenation of **9** at different pressures of $H_2$ showed 50 bar to be optimal for this substrate and this pressure was therefore used for all subsequent experiments (Table 1).

All the substrates evaluated showed good activity and full conversions were obtained for almost all substrates within two hours.

Substrate **9** (entry 1) proved to be the best substrate in terms of enantioselectivity. The *trans* and *cis* isomers of (1-methylpropenyl)benzene **10** and **11** (entries 2 and




**Scheme 2.** Finkelstein reaction and nucleophilic substitution reaction between iodide **5** and *N*-phenylimidazole. Reagents and conditions: (i) NaI, Acetone, 60 °C, overnight, quantitative; (ii) *N*-phenylimidazole, DMF, 60 °C, 48 h, 50%; (iii) *N*-phenylimidazole, DMF, 80 °C, 12 h, 25%.




**Scheme 3.** Synthesis of Ir-complex **8**. Reagents and conditions: (i) $[IrCl(COD)_2]$, $^t$BuOLi, THF, reflux, 1 h, then rt overnight, then $H_2O$, $NaBArF{\cdot}3H_2O$, rt, 1 h, 30%.

3), resulted in products having opposite absolute configurations, also the observed enantioselectivity for the *cis* conformation was lower. Introducing an electron donating group in the *para* position, that is, substrate **12** (entry 4) proved to be beneficial, 79% ee. Substrate **13** (entry 5) was reduced with better enantioselectivity than for the previously reported phosphine thiazole complexes, 55% ee.[15] Interestingly, moving the methyl group to the β-position, that is, substrate **14** (entry 6) did not increase the enantioselectivity, 70% ee.

Also, *trans*- and *cis*-β-methyl cinnamates **15** and **16** (entries 7 and 8) show reversed enantiofacial selectivity when compared to our phosphine thiazole complexes.[15] With this complex, tetra-substituted olefins showed no conversion at all under the conditions used.

Unfortunately, substrate **18** (entry 10) was reduced with both low selectivity and conversion. The differences in enantioselectivity compared to our previously published phosphine-thiazole complex may be a result of either two factors, the *N*-phenylimidazole provides a less efficient chiral environment around the Ir atom, or that the complex formed coordinates through a seven-membered chelate resulting in a more open structure compared to the phosphine-thiazole ligand **4**.

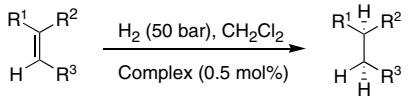
In conclusion, we have synthesized a new NHC ligand applying the same chiral scaffold as earlier reported by us. The Ir-NHC thiazole complex was tested and evaluated in the asymmetric hydrogenation of olefins. This new complex proved to be efficient in the hydrogenation of various tri-substituted olefins, with ee's ranging from 34% to 90% depending on the geometry around the double bond in the substrates. We have also shown that this new complex was more selective for substrates containing bulky substituents, such as **13**.

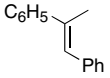
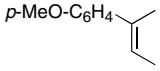
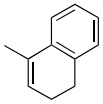
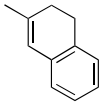
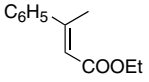
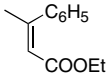
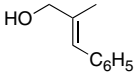
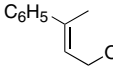
## 2. Experimental

### 2.1. 4-Iodomethyl-2-phenyl-4,5,6,7-tetrahydro-benzothiazole (5)

Compound **3** (0.43 g, 1.1 mmol) was dissolved in acetone (13 ml), and NaI (0.83 g, 5.5 mmol) was added. The resulting mixture was stirred at 60 °C overnight. The solvent was removed, the residue dissolved in toluene and the solution was poured into aq $NaHCO_3$ (10%, 20 ml). The organic layer was washed with brine (20 ml)

**Table 1.** Ir-catalyzed hydrogenation of substrates **9**–**18**




| Entry | Substrate | | Conversion (%) | ee (%) | Absolute configuration |
|---|---|---|---|---|---|
| 1 |  | **9** | >99 | 90[a] (>99)[d] | (*S*) |
| 2 |  | **10** | >99 | 70[b] (99)[d] | (*S*) |
| 3 |  | **11** | 76 | 34[b] | (*R*) |
| 4 |  | **12** | >99 | 79[b] (99)[d] | (*S*) |
| 5 |  | **13** | >99 | 70[b] (55)[d] | (*R*) |
| 6 |  | **14** | >99 | 70[b] (98)[d] | (*S*) |
| 7 |  | **15** | >99 | 63[b] (98)[d] | (*R*) |
| 8 |  | **16** | >99 | 34[b] (rac.)[d] | (*S*) |
| 9 |  | **17** | >99 | 80[c] (99)[d] | (*S*) |
| 10 |  | **18** | 30 | rac.[b] | |

[a] HPLC (Chiralcel-OJ column, hexane: *i*-PrOH, 99:1).
[b] GC–MS (G-Ta, 60 °C, 30 min, 5 °C/min, 75 °C, 100 kPa).
[c] GC (CP-Chirasil-Dex CB, isotherm 130 °C).
[d] Values within brackets refer to the ee obtained with Ir-**4** complex.[15]

and $H_2O$ (20 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Purification by flash chromatography (toluene–EtOAc 9:1) yielded pure **5**, as a yellow solid in quantitative yield (0.39 g); mp 52.5–53.9 °C; $R_f$ 0.89 (toluene–EtOAc 9:1); $[\alpha]_D^{20}$ +40.2 (*c* 0.90, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 1.75–1.89 (m, 2H, $CH_2$),1.93–2.03 (m, 1H, $CH_2$), 2.10–2.19 (m, 1H, $CH_2$), 2.72–2.85 (m, 2H, $CH_2$), 3.08–3.15 (m, 1H, CH), 3.43 (dd, $J = 9.4$, 9.7 Hz, 1H, $CH_2I$), 3.42 (dd, $J = 3.3$, 9.7 Hz, 1H, $CH_2I$), 7.35–7.44 (m, 3H, ArH), 7.85–7.90 (m, 2H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 21.5, 25.6, 31.7, 39.7, 71.1, 126.0, 127.9, 128.4, 144.6, 150.6, 160.3, 172.3; MS (EI) (*m*/*z*) (rel intensity) 356.3 ($MH^+$, 20%), 228.1 (100%).

### 2.2. 2-Phenyl-4-(3-phenyl-3*H*-imidazol-1-ylmethyl)-4,5,6,7-tetrahydro-benzothiazole iodide (6)

Compound **5** (0.147 g, 0.41 mmol) was dissolved in DMF (1.0 ml), and *N*-phenylimidazole (0.059 g, 0.41 mmol) was added. The resulting mixture was heated at 60 °C for 48 h. The solvent was removed under vacuum. Purification by flash chromatography ($CH_2Cl_2$–MeOH 9:1) yielded **6**, as a pale yellow solid in 50% yield (0.102 g, 0.21 mmol); mp: decomposed at 278 °C; $R_f$ 0.22 ($CH_2Cl_2$–MeOH 9:1); $[\alpha]_D^{20}$ +25.2 (*c* 0.70, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 1.55–1.72 (m, 1H, $CH_2$), 1.75–1.92 (m, 1H, $CH_2$), 1.98–2.12 (m, 1H, $CH_2$), 2.21–2.34 (m, 1H, $CH_2$), 2.70–2.83 (m, 2H, $CH_2$)

3.46–3.58 (m, 1H, CH), 4.93 (dd, $J = 7.1$, 13.7 Hz, 1H, $CH_2I$), 5.02 (dd, $J = 5.1$, 13.7 Hz, 1H, $CH_2I$), 7.22–7.37 (m, 3H, ArH), 7.42–7.55 (m, 3H) 7.59–7.75 (m, 6H, ArH), 10.53 (s, 1H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$: 21.5, 23.5, 26.4, 37.7, 53.5, 120.1, 121.9, 124.1, 125.9, 128.9, 129.9, 130.2, 130.5, 132.7, 133.4, 134.3, 136.1, 149.5, 165.2.; MS (EI) ($m/z$) (rel intensity) 499.5 ($M^+$, 100%).

## Acknowledgements

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