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Development of an N-heterocyclic carbene ligand based on concept of chiral mimetic

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Abstract—Development of a new N-heterocyclic carbene ligand based on the concept of a chiral mimetic is described. In Pd-catalyzed enantioselective intramolecular α-arylation of *N*-(2-bromophenyl)-*N*-methyl-2-arylpropanamide, (4*R*,5*R*)-4,5-diphenyl-1,3-diadamantylmethyl-4,5-dihydro-3*H*-imidazol-1-ium tetrafluoroborate is shown to function as a good N-heterocyclic carbene precursor.

We have recently been developing a novel chiral phosphine ligand **1** mimicking axial chirality, in which a chiral carbon center induces a preferred conformation **2a** by rotation around an N–Ar bond which is fixed by formation of a chelate structure with metal (Fig. 1).[1] In order to expand the scope of our chiral mimetic concept, we planned to develop a novel N-heterocyclic carbene ligand[2] **3**. The substituent R on the N group in the carbene ligand **3** may be conformationally flexible, but if the complexation of **3** and metal is reflected by the asymmetric center in **3**, a more stable complex **4a**, in which orientation of the substituent R on the N group is fixed, is expected to be selectively formed (Fig. 2). Herein, we would like to report our investigation on the enantioselective intramolecular α-arylation of amide **5** with the novel N-heterocyclic carbene ligands **3** (Scheme 1).

The synthesis of the imidazolium salt **7a** as an N-heterocyclic carbene precursor is representatively shown in Scheme 2.[3] Amidation of 1-adamantanecarboxylic acid (**10**) with (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (**9**), EDCI, Et_3N and DMAP in THF at 60 °C afforded the coupling product **11**. The carbonyl group in **11** was then reduced with BH_3 in THF under reflux to provide the diamine **12** in 54% yield (two steps). Finally, treatment of diamine **12** with $CH(OEt)_3$ and NH_4BF_4 under reflux gave the imidazolium salt **7a** in 98% yield. Other imidazolium salts **7b–d** and **8** are prepared in the same manner.

Hartwig[4] and Glorius[5] have reported the enantioselective α-arylation[6] of amide **5a**, giving oxindole **6a** in 57% ee and 43% ee, respectively (Scheme 3). We chose **5a** as a substrate and began to screen imidazolium salts **7a–d** and **8** as an N-heterocyclic carbene ligand precursor. The results are shown in Table 1, entries 1–5. Reactions were carried out with amide **5a** as a substrate, 10 mol % of $Pd(OAc)_2$, 20 mol % of imidazolium salts

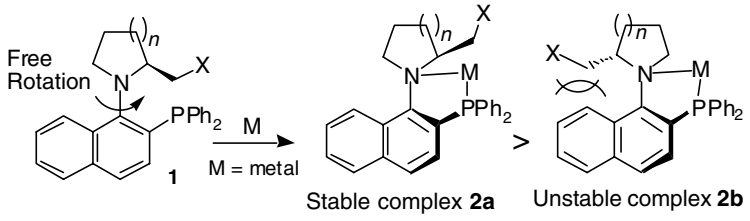

Figure 1.

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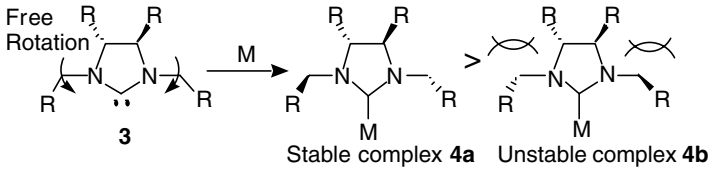
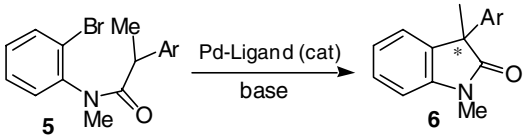
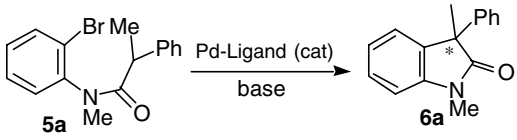


Figure 2.



Scheme 1. Enantioselective intramolecular α-arylation of amide **5**.



Scheme 3. Enantioselective intramolecular α-arylation of amide **5a**.

7a–d and **8**, and 2 mol equiv of NaO*t*-Bu in DME at 100 °C for 12 h. Among the imidazolium salts screened, **7a** possessing an adamantyl group as R substituent gave better asymmetric induction[7] (67% ee, entries 1), although reaction conversion was quite low. With **7a** as an N-heterocyclic carbene ligand precursor, the use of other solvents such as 1,4-dioxane, toluene and DMF gave less satisfactory results (entries 6–8). Other palladium and rhodium complexes were not good metal sources.

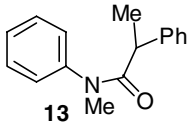
Using the best $Pd(OAc)_2$-**7a** catalyst in DME, we screened various bases as shown in Table 2. As can be seen, the choice of base played an important role in reaction conversion. The use of LiO*t*-Bu gave the best reaction conversion with 61% enantioselectivity (entry 2).[8]

Finally, we examined the enantioselective α-arylation with amides **5b** and **5c** possessing electron-withdrawing and donating groups on the benzene ring as shown in Scheme 4. The reactions with amide **5b** and **5c** were found to exhibit 65% and 54% enantioselectivity[7], respectively.

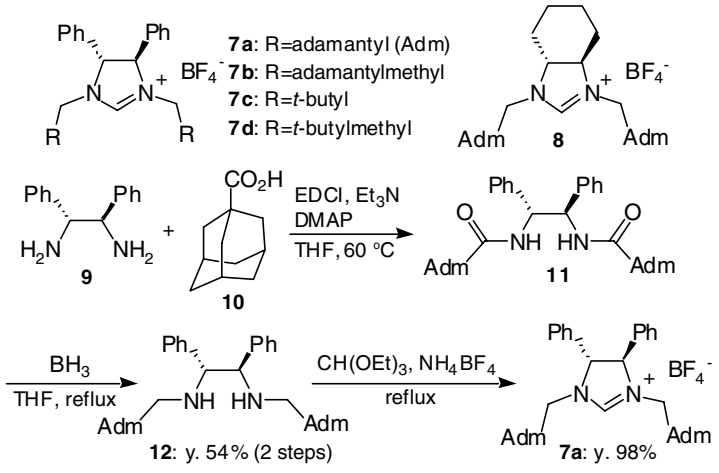
Table 1. Effects of ligands and solvents[a]

Entry	Ligand	Solvent	Yield of **6a** (%)	ee[b] of **6a** (%)	Absolute configuration
1	**7a**	DME	14[c]	67	*S*
2	**7b**	DME	16[c]	45	*S*
3	**7c**	DME	8[c]	41	*S*
4	**7d**	DME	13[c]	36	*S*
5	**8**	DME	7[c]	23	*S*
6	**7a**	1,4-Dioxane	17[c]	50	*S*
7	**7a**	Toluene	8[c]	46	*S*
8	**7a**	DMF	0[d]	—	—

[a] The reactions of **5a** were performed using 10 mol % of $Pd(OAc)_2$, 20 mol % of the imidazolium salts and 2 mol equiv of NaO*t*-Bu in the shown solvent at 100 °C for 12 h.
[b] Determined by HPLC analysis.
[c] Remainder of mass balance was the unreacted starting amide **5a**.
[d] The debrominated product **13** was obtained in 90% yield.



In summary, we have developed a new class of N-heterocyclic carbene ligands for asymmetric catalysis, conformation of N-substituents of which was reflected by chirality on the carbones of heterocyclic moiety and

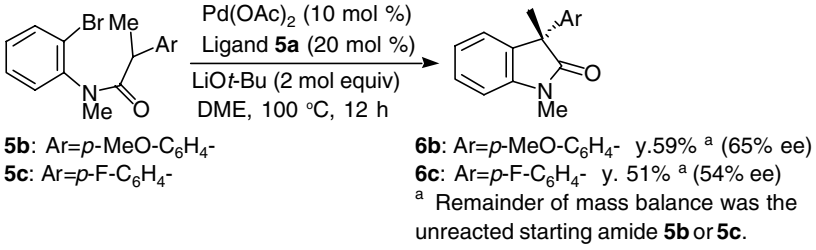


Scheme 2. Representative synthesis of imidazolium salt.

Table 2. Effects of bases[a]

Entry	Base[b]	Yield of **6a** (%)	ee[c] of **6a** (%)	Absolute configuration
1	NaO*t*-Bu	14[d]	67	*S*
2	LiO*t*-Bu	62[d]	61	*S*
3	KO*t*-Bu	5[d]	41	*S*
4	NaOH	16[d]	62	*S*

[a] The reactions of **5a** were performed using 10 mol % of $Pd(OAc)_2$, 20 mol % of imidazolium salt **7a** and 2 mol equiv of the shown base in DME at 100 °C for 12 h.
[b] LHMDS, KHMDS and LiOH gave less satisfactory results.
[c] Determined by HPLC analysis.
[d] Remainder of mass balance was the unreacted starting amide **5a**.



5b: Ar=*p*-MeO-C_6H_4-
5c: Ar=*p*-F-C_6H_4-

6b: Ar=*p*-MeO-C_6H_4- y.59% [a] (65% ee)
6c: Ar=*p*-F-C_6H_4- y. 51% [a] (54% ee)
[a] Remainder of mass balance was the unreacted starting amide **5b** or **5c**.

Scheme 4. Enantioselective intramolecular α-arylation of amides **5b** and **5c**.

fixed to be C_2-symmetric by complexation with metal. Further application to other catalytic asymmetric reactions is now in progress.

Acknowledgements

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3. Representative procedure for the synthesis of imidazolium salt **7a**: To a stirred solution of (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (**9**) (1.50 g, 7.07 mmol) in THF (30.0 mL) were added 1-adamantanecarboxylic acid (**10**) (3.18 g, 17.7 mmol), DMAP (173 mg, 1.41 mmol), Et_3N (2.46 mL, 1.79 g, 17.7 mmol) and EDCI (3.39 g, 17.7 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 60 °C, diluted with water, and extracted with EtOAc. The organic extracts were successively washed with 10% HCl, water, saturated aq $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated. Purification by silica gel column ($CHCl_3$/hexane, 1:2) gave a mixture (2.86 g) of coupling product **11** and small amounts of impurities. This mixture was used for the next step without further separation. This mixture was dissolved in THF (20.0 mL), and to this mixture BH_3 (26.7 mL, 26.7 mmol, 1.0 M solution in THF) was added at 0 °C. The reaction mixture was heated under reflux for 4 h. After being cooled to 0 °C, MeOH was carefully poured into the reaction mixture. The whole mixture was heated under reflux overnight and concentrated. The residue was dissolved in water and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by silica gel column ($CHCl_3$) gave diamine **12** (1.96 g, 54% in two steps) as colorless needles of mp 146 °C ($CHCl_3$–hexane). $[\alpha]_D^{23}$ −5 (*c* 3.30, THF). IR (nujol): $\nu = 3315\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 1.44$–2.16 (m, 36H), 3.47 (s, 2H), 6.92–7.02 (m, 4H), 7.04–7.16 (m, 6H). ^{13}C NMR ($CDCl_3$): $\delta = 28.64$, 33.85, 37.40, 40.95, 60.44, 70.67, 126.39, 127.53, 127.75, 142.03.

EIMS $m/z = 508$ (M^+), 373, 254 (bp). Anal. Calcd for $C_{36}H_{48}N_2$: C, 84.98; H, 9.51; N, 5.51. Found: C, 85.05; H, 9.50; N, 5.26. A suspension of diamine **12** (965 mg, 1.90 mmol) and NH_4BF_4 (239 mg, 2.28 mmol) in $(EtO)_3CH$ (2.0 mL) was refluxed overnight. The suspension was cooled to rt and concentrated. Purification by silica gel column ($MeOH/CHCl_3$, 1:30) gave (4*R*,5*R*)-4,5-diphenyl-1,3-diadamantylmethyl-4,5-dihydro-3*H*-imidazol-1-ium tetrafluoroborate (**7a**) (1.13 g, 98%) as a colorless amorphous. $[\alpha]_D^{24}$ +127 (*c* 1.21, THF). IR (nujol): $\nu = 1634\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 1.42$–1.84 (m, 12H), 1.58 (d, $J = 12.7$ Hz, 6H), 1.70 (d, $J = 12.7$ Hz, 6H), 1.99 (s, 6H), 2.78 (d, $J = 14.7$ Hz, 2H), 3.54 (d, $J = 14.7$ Hz, 2H), 5.02 (s, 2H), 7.23–7.32 (m, 4H), 7.48–7.58 (m, 6H), 8.86 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 27.96$, 34.98, 36.41, 40.25, 57.53, 75.90, 126.2, 130.1, 130.2, 135.1, 160.1. FABMS: $m/z = 520$ ($M^+ - BF_4^- + 1$). Anal. Calcd for $C_{37}H_{47}N_2BF_4$: C, 73.26; H, 7.81; N, 4.62. Found: C, 73.31; H, 7.56; N, 4.51. Representative procedure for the enantioselective intramolecular α-arylation of amide **5a** with imidazolium salt **7a** (Table 2, entry 2). To a stirred solution of *N*-(2-bromophenyl)-*N*-methyl-2-phenylpropanamide (**5a**) (63.6 mg, 0.200 mmol) in DME (1.0 mL) were added imidazolium salt **7a** (24.3 mg, 0.0400 mmol), $Pd(OAc)_2$ (4.5 mg, 0.0200 mmol) and LiO*t*-Bu (48.0 mg, 0.600 mmol) at rt and the mixture was stirred for 12 h at 100 °C. After being cooled to rt, the mixture was filtered through a layer of silica gel and evaporated. Purification by silica gel column (EtOAc/hexane, 1:8) gave (3*S*)-1,3-dimethyl-3-phenyl-1,3-dihydro-indol-2-one (**6a**) (29.3 mg, 62%, 61% ee). The spectral data of **6a** were comparable to those reported.[4]

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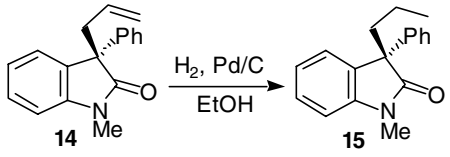
7. The absolute configurations of oxindoles **6a**–**c** were determined by comparison with the CD spectrum of **15** derived from **14**, whose absolute configuration was known.[9]



8. The good reaction conversion with a weaker base such as LiO*t*-Bu might be due to the suppression of decomposition of carbene ligand **7a**.
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