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Catalytic imine–imine cross-coupling reactions†

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We report here efficient catalytic imine–imine cross-coupling reactions based on an umpolung strategy; an imine bearing a 9-fluorenyl moiety on its nitrogen atom, which acted as a nucleophile, reacted with another imine to afford an imine–imine cross-coupling adduct in high yield. Furthermore, a chiral guanidine acted as a chiral catalyst for these coupling reactions, and optically active 1,2-diamines were obtained in high yields with high enantioselectivities.

1,2-Diamine structures are often observed in many biologically important compounds, such as the anti-influenza agent, oseltamivir and anticancer agents, cisplatin derivatives, *etc.*[1,2] Imine–imine coupling reactions potentially provide the best route to 1,2-diamines because imines are easily prepared from the corresponding carbonyl precursors; however, in spite of many efforts, imine–imine cross-coupling reactions have been found to be very difficult. Indeed, almost all previous imine–imine coupling reactions relied on radical-mediated reactions and generally provided homo-coupling products.[3–14] In the literature, only two imine–imine cross-coupling reactions have been reported. One is a radical-mediated reaction, in which 2 equivalents of Zn–Cu, 2.2 equivalents of $BF_3{\cdot}OEt_2$ and 1 equivalent of $MeSiCl_3$ were used and some homo-coupling products were obtained as side products.[15] Including this, all previous radical-mediated reactions required more than stoichiometric amounts of metal reductants or promoters (lanthanide,[3–6] Al,[7] Ti,[8,9] Zr,[10] In,[11] Zn–Cu,[12,15] Mn,[13] Li,[14] *etc.*,[16] Fig. 1a), and thus large quantities of metal waste were formed after the reactions. In the other reaction an *in situ* generated titanium–imine[17] complex reacted with another imine to afford a cross-coupling adduct, where also more than one equivalent of organometallic species were required. To the best of our knowledge, no catalytic imine–imine cross-coupling reaction has been reported.

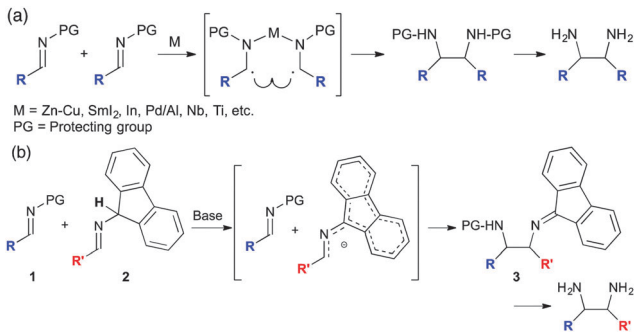

Fig. 1 Important 1,2-diamine structures and imine–imine coupling strategies for 1,2-diamine synthesis. (a) The traditional strategy for imine–imine coupling reactions using stoichiometric amounts of metal compounds to afford symmetrical 1,2-diamines. (b) Our strategy for imine–imine cross-coupling reactions affording unsymmetrical 1,2-diamines.

To develop imine–imine cross-coupling reactions, we planned to use an umpolung strategy.[18] An imine usually acts as an electrophile, but if an imine could act as a nucleophile, it would react with another imine that acts as an electrophile, and a nucleophile–electrophile coupling might be possible. For this purpose, we focused on an imine bearing a 9-fluorenyl moiety on its nitrogen atom (fluorenyl imine), previously known as an electrophile.[19–22] We thought that the hydrogen atom at the dibenzylic position of the fluorenyl imine was relatively acidic and that deprotonation of this hydrogen atom would be possible by a weak base. If deprotonation occurred, then a nucleophilic anion species would be formed, which could then react with an electrophilic imine, and thus an imine–imine cross-coupling might be realized (Fig. 1b). We have already reported that effective activation of an aminoalkane by using a 9-fluorenylidene substituent as a protecting and activating group was successfully carried out in the presence of a catalytic amount of a base.[23–26] In this system, the carbanion smoothly formed at the α-positions of the fluorenylideneamino groups *via* 14π electron stabilization[27] and catalytically reacted with imines to afford 1,2-diamine derivatives in high yields with high stereoselectivities. Based on these findings, we envisioned

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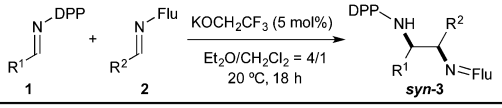
that if similar nucleophilic carbanion species were formed by deprotonation of *N*-9-fluorenyl imines, they might react with imines to realize imine–imine cross-coupling reactions.

We conducted the reaction of *N*-fluorenyl imine **2a** derived from benzaldehyde with imine **1a** bearing a diphenylphosphinyl (DPP) substituent as an *N*-protecting group in the presence of a catalytic amount of a base (Table S1, ESI†). In the presence of potassium *tert*-butoxide (KO^{t}Bu) and 18-crown-6 ether, the reaction proceeded in THF at room temperature to afford the desired cross-coupling product in 60% yield with moderate diastereoselectivity. It should be noted that the fluorenyl imine worked as a nucleophile and reacted with another imine, and that no homo-coupling product was produced. The effect of solvents was then examined. Diethyl ether (Et_2O) showed better selectivity but lower conversion was observed due to low solubility of **1a**. The reaction proceeded smoothly in a mixed solvent of Et_2O/CH_2Cl_2 (4/1) to afford the desired 1,2-diamine compound in high yield with high *syn* selectivity (90% yield, *syn*/*anti* = 99/1). It was also found that weaker Brønsted bases were successfully employed in the coupling reaction, and among them, potassium 2,2,2-trifluoroethoxide ($KOCH_2CF_3$) worked well and higher *syn* selectivity (*syn*/*anti* = >99/1) was obtained with 97% yield. While the desired cross-coupling product was obtained in excellent yield, there were no homo-coupling products.

We then investigated the substrate scope of this imine–imine cross-coupling reaction (Table 1). First, a variety of *N*-DPP imines were investigated. *Ortho* to *para* substitution on the benzene ring by a methyl group did not have any significant effect on reactivities and selectivities, and high yields and high *syn* selectivities were obtained (entries 2–4). Electronic effects of the substituents were then examined. When *N*-DPP imine **1e** prepared from *p*-methoxybenzaldehyde was used, the diastereoselectivity decreased slightly (entry 5). Imine **1f** bearing an electron-withdrawing group was also found to be applicable to the reaction system (entry 6). *N*-DPP imines **1g** and **1h** prepared from heteroaromatic aldehydes were successfully employed (entries 7 and 8). The imines prepared from aliphatic aldehydes could also be employed in this coupling reaction. *N*-DPP imine **1i** derived from cyclohexanecarboxyaldehyde reacted smoothly to afford the desired product in high yield (entry 9). Imines **1j–1k** derived from primary aliphatic aldehydes were also found to react with *N*-fluorenyl imine **2a** in moderate to high yields (entries 10 and 11). These results are remarkable because imines derived from aliphatic aldehydes generally cause many side reactions, and successful examples of even aliphatic imine–imine homo-coupling reactions are very rare.

Next, the scope of the *N*-fluorenyl imine was examined. As was the case when the DPP imines were investigated, the steric effect of the imine was not significant, and high yields and high *syn* selectivities were observed (entries 12–15). When fluorenyl imine **2f** bearing an electron-withdrawing substituent, Cl, was employed, high yield and high *syn* selectivity were obtained (entry 16). Imines **2g** and **2h** derived from heteroaromatic aldehydes were also successfully employed (entries 17 and 18). Aliphatic *N*-fluorenyl imines **2i–l** were also examined, and good yields and high *syn* selectivities were obtained (entries 19–22). *N*-Fluorenyl imine **2m** derived from ethyl glyoxylate could be successfully employed by

Table 1 Catalytic imine–imine cross-coupling reactions



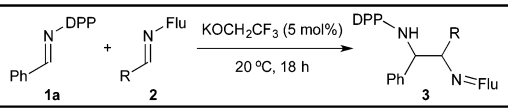
Entry	R^1	R^2		Yield[a] (%)	*syn*/*anti*[b]
1	Ph (**1a**)	Ph (**2a**)	**3aa**	97	>99/<1
2[c,d]	*p*-MeC_6H_4 (**1b**)	Ph (**2a**)	**3ba**	99	94/6
3[c,f]	*m*-MeC_6H_4 (**1c**)	Ph (**2a**)	**3ca**	97	96/4
4[c,f]	*o*-MeC_6H_4 (**1d**)	Ph (**2a**)	**3da**	91	97/3
5[c,f]	*p*-MeOC_6H_4 (**1e**)	Ph (**2a**)	**3ea**	90	84/16
6[c]	*p*-BrC_6H_4 (**1f**)	Ph (**2a**)	**3fa**	99	96/4
7	Furfuryl (**1g**)	Ph (**2a**)	**3ga**	>99	>99/<1
8	3-Py (**1h**)	Ph (**2a**)	**3ha**	93	99/1
9	Cy (**1i**)	Ph (**2a**)	**3ia**	99	90/10
10[f]	^{i}Bu (**1j**)	Ph (**2a**)	**3ja**	92	97/3
11[g,h,i]	^{n}Bu (**1k**)	Ph (**2a**)	**3ka**	91	>99/<1
12	Ph (**1a**)	*p*-MeC_6H_4 (**2b**)	**3ab**	>99	98/2
13	Ph (**1a**)	*m*-MeC_6H_4 (**2c**)	**3ac**	99	98/2
14	Ph (**1a**)	*o*-MeC_6H_4 (**2d**)	**3ad**	>99	>99/<1
15	Ph (**1a**)	2-Naph (**2e**)	**3ae**	92	>99/<1
16[e]	Ph (**1a**)	*p*-ClC_6H_4 (**2f**)	**3af**	99	95/5
17	Ph (**1a**)	Furfuryl (**2g**)	**3ag**	83	96/4
18	Ph (**1a**)	2-Thienyl (**2h**)	**3ah**	>99	97/3
19[f]	Ph (**1a**)	^{n}Bu (**2i**)	**3ai**	81	93/7
20[e,f]	Ph (**1a**)	^{i}Bu (**2j**)	**3aj**	79	85/15
21[f]	Ph (**1a**)	Cy (**2k**)	**3ak**	82	90/10
22[f]	Ph (**1a**)	^{t}Bu (**2l**)	**3al**	78	>99/<1
23[j]	Ph (**1a**)	COOEt (**2m**)	**3am**	83	91/9
24[g,k,h]	Cy (**1i**)	^{i}Bu (**2j**)	**3ij**	81	99/1
25[l]	Ph (**1a**)	Ph (**2a**)	**3aa**	92	3/97

DPP = diphenylphosphinyl; Flu = fluorenyl. [a] Isolated yield. [b] Determined by ^{1}H NMR analysis. [c] At −40 °C. [d] For 24 h. [e] At −20 °C. [f] KO^{t}Bu (5 mol%) and 18-crown-6 (5.5 mol%) were employed as catalysts. [g] In DMF. [h] At 0 °C. [i] KO^{t}Bu (5 mol%) and PhOH (5.5 mol%) were employed as catalysts. [j] DBU (10 mol%) was used instead of $KOCH_2CF_3$. the reaction was performed at 25 °C. [k] KO^{t}Bu (10 mol%) and 18-crown-6 (11 mol%) were employed as catalysts. [l] In toluene at 20 °C.

using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base catalyst (entry 23). It is noted that a combination of aliphatic *N*-DPP imine **1i** and aliphatic *N*-fluorenyl imine **2j** in DMF at lower temperature successfully afforded the desired compound **3ij** in 81% yield with excellent *syn* selectivity (*syn*/*anti* = 99/1, entry 24).

During the investigation of the substrate scope, it was surprisingly found that the reaction of **1a** with **2a** in toluene gave the opposite diastereomer with high selectivity (Table 1, entry 25). Thus, the diastereoselectivity dramatically changed from *syn* to *anti* when the solvent Et_2O–CH_2Cl_2 was replaced with toluene (Table 2, entries 1 and 2). We further examined the switch of diastereoselectivity of other substrates. In the reactions with 4-chlorophenyl fluorenyl imine **2f**, the same *anti* selectivity was obtained in both Et_2O–CH_2Cl_2 and toluene (entries 3 and 4), while the *syn* isomer was obtained with high selectivity when the reaction was conducted in Et_2O–CH_2Cl_2 at −20 °C (entry 5). In the reactions with 4-methylphenyl fluorenyl imine **2b**, *syn* selectivity was obtained in both Et_2O–CH_2Cl_2 and toluene (entries 6 and 7), although the selectivity in toluene was moderate. In the case of imine **2n** bearing a stronger electron-withdrawing substituent, 4-nitrophenyl fluorenyl imine, only *anti*-selectivity was obtained in both solvents (entries 8 and 9). On the other hand, 3-chlorophenyl fluorenyl imine **2o** gave a *syn* adduct in Et_2O–CH_2Cl_2 at 20 °C (entry 10). A substitution at the 3-position provided a less electronic influence on the selectivity. This interesting

Table 2 Switch of diastereoselectivity



Entry	R (2)	Conditions	3	Yield[a] (%)	*syn*/*anti*[b]
1	Ph (**2a**)	Et_2O/CH_2Cl_2 (4/1)	**3aa**	97	>99/1
2	Ph (**2a**)	Toluene	**3aa**	92	3/97
3	*p*-ClC_6H_4 (**2f**)	Et_2O/CH_2Cl_2 (4/1)	**3af**	92	13/87
4	*p*-ClC_6H_4 (**2f**)	Toluene	**3af**	95	4/96
5[c]	*p*-ClC_6H_4 (**2f**)	Et_2O/CH_2Cl_2 (4/1)	**3af**	99	95/5
6	*p*-MeC_6H_4 (**2b**)	Et_2O/CH_2Cl_2 (4/1)	**3ab**	>99	98/2
7	*p*-MeC_6H_4 (**2b**)	Toluene	**3ab**	>95[d]	59/41
8	*p*-$NO_2C_6H_4$ (**2n**)	Et_2O/CH_2Cl_2 (4/1)	**3an**	70	7/93
9	*p*-$NO_2C_6H_4$ (**2n**)	Toluene	**3an**	90	2/98
10	*m*-ClC_6H_4 (**2o**)	Et_2O/CH_2Cl_2 (4/1)	**3ao**	>99	99/1

[a] Isolated yield. [b] Determined by ^1H NMR analysis. [c] At −20 °C. [d] NMR yield.

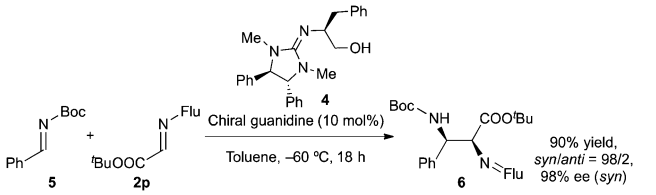
phenomenon could be explained by a solvent effect and an epimerization mechanism. DPP-imine **1a** was attacked by fluorenyl imine **2** *via* deprotonation by a base catalyst to afford the cross-coupling product **3** in a *syn* selective manner. When the fluorenyl imine has an electron-withdrawing substituent on the phenyl ring, further deprotonation at the α-hydrogen of the product might occur (Scheme S1, ESI†). Moreover, it is noted that the pK_a value of the hydrogen may change in different solvents and at different temperatures.

To verify if the epimerization did occur, a diastereomeric mixture of the isolated product **3aa** was treated in toluene under the reaction conditions (Scheme S2, ESI†). After 18 h, the diastereomer ratio changed dramatically, and the *anti* product was obtained as a major compound. This result indicated that the *anti* product was thermodynamically stable and strongly supported the epimerization mechanism.

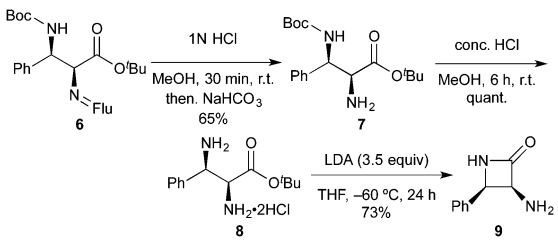
Further investigations on the epimerization were conducted in toluene by using different bases (Table S2, ESI†). When the reaction of **1a** with **2a** utilizing KO^{t}Bu and 18-crown-6 ether was quenched in a shorter reaction time (0.5 h), *ca.* a 1 : 1 *syn*/*anti* mixture of product **3aa** was obtained (entry 2). Other weaker bases could also support our hypothesis. When KOPh or DBU was employed, the *syn* isomer was obtained with good to high selectivities (entries 4 and 5). These results indicated that the epimerization could be suppressed by using a weaker base.

The above experiments indicated that epimerization of the fluorenylidene amino group by a base catalyst occurred during the reaction process, and thermodynamically stable *anti* isomers were obtained with high selectivities under the reaction conditions. The epimerization was faster in toluene than in Et_2O–CH_2Cl_2, and was suppressed by using weak bases and performing reactions at lower temperature.

In the imine–imine coupling strategy, chiral modification of a base catalyst might lead to a catalytic asymmetric coupling reaction. However, no such examples, even in homo-coupling reactions, are reported. We thought that chiral organobase species[28] with aromatic moieties could be promising catalysts for the formation of asymmetric environments around these types of substrates *via* π–π interactions. Because of the low pK_a value of the active hydrogen



Scheme 1 Substrate scope of asymmetric catalysis.

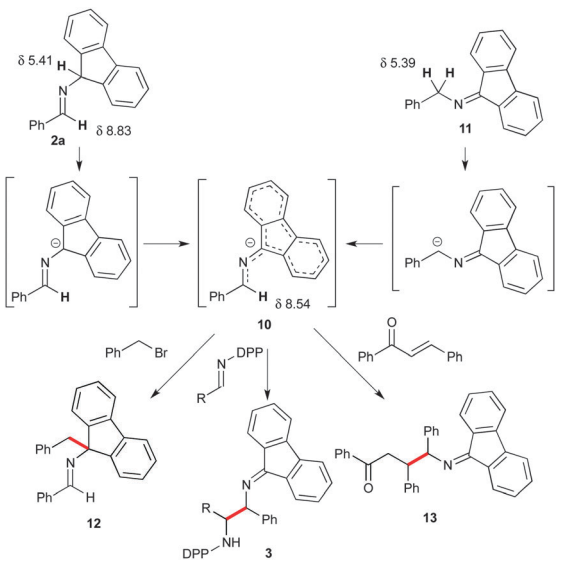


Scheme 2 Transformation of the coupling product to 3-amino-β-lactam.

on the *N*-fluorenyl group, an *N*-fluorenylglyoxylateimine was selected as a model substrate. It was found that the reaction of *N*-Boc protected imine **5** with *N*-fluorenyl imine **2p** bearing a *tert*-butyl ester proceeded in toluene at −60 °C for 18 h using a catalytic amount of chiral guanidine **4** to afford the desired adduct in 90% yield with excellent diastereo- and enantioselectivities (Scheme 1).[29]

The reaction was successfully applied to a concise synthesis of 3-amino-β-lactam, a useful intermediate for the synthesis of monobactams (Scheme 2).[30] The coupling product **6** was hydrolyzed under acidic conditions to afford the corresponding α,β-diamino ester **8**, which was further cyclized to afford the desired 3-amino-β-lactam **9** in high yield.[31]

It was assumed that carbanion **10**, which was formed from *N*-fluorenyl imine **2a**, reacted with DPP imines **1** or Boc imines to afford cross-coupling products (Scheme 3). Since DPP imines and Boc imines are much more reactive than *N*-fluorenyl imines



Scheme 3 Assumed reaction pathways.

as electrophiles, no homo-coupling products were obtained. Formation of carbanion **10** was confirmed by ^{1}H NMR analysis. *N*-Fluorenyl imine **2a** was treated with a stoichiometric amount of $KN(SiMe_3)_2$ at ambient temperature in THF-d_8 to form carbanion **10**. There are two key protons in **2a**, observed by ^{1}H NMR analysis, at δ 8.83 and δ 5.41, and one reacted with the base to form **10**, whose remaining proton was observed at δ 8.54. These results suggest that the anion of **10** is located on the fluorenyl group stabilized by the 14π electron system. The deprotonation step was very fast and no intermediate was observed by ^{1}H NMR analysis. We further conducted the deprotonation using other bases such as $KOCH_2CF_3$, and KO^{t}Bu, and the same results were obtained. Formation of **10** was also observed from aminoalkane **11** and a base. Namely, **11** was treated with a base at ambient temperature in THF-d_8 to form the same carbanion **10**. The formation of **10** was also very fast and no intermediate was observed by ^{1}H NMR analysis. It is assumed that the benzylic anion formed from **11** and a base tautomerized to **10** immediately.

As already mentioned, **10** reacted with DPP imines or Boc imines at the benzylic position to make carbon–carbon bonds (**3**). On the other hand, while chalcone also reacted with **10** at the benzylic position (**13**), benzyl bromide reacted with **10** at the other position (**12**) exclusively. The origin of the difference in the regioselectivity is not clear at this stage and is under investigation.[32]

In conclusion, we have developed the first catalytic imine–imine cross-coupling reaction, which proceeds under mild conditions to afford 1,2-diamines in high yields with high diastereoselectivities. Distinguishing features of this novel reaction are as follows: (1) only a catalytic amount of a base is required; (2) only cross-coupling occurs and no homo-coupling products are obtained; and (3) high yields and high stereoselectivity are realized even when aliphatic imines are used. Asymmetric catalysis was also achieved using a chiral nonmetal catalyst, and the reaction was successfully applied to the synthesis of a biologically important β-lactam. Moreover, the key carbanion **10** formed from *N*-fluorenyl imine **2a** and a base was characterized by ^{1}H NMR analysis and was found to react with another imine at the benzylic position to afford the cross-coupling product. It was also confirmed that the same carbanion **10** was formed from aminoalkane **11**. A synthetic advantage of the present cross-coupling reactions is that various commercially available aldehydes can be used as starting materials, and that various 1,2-diamines, some of which could not be synthesized from amino alkanes, can be prepared in high yields with high diastereoselectivities. It should be noted from a viewpoint of organic reactions that unprecedented catalytic imine–imine cross-coupling reactions have been accomplished. Further investigations utilizing the key carbanion **10** for other synthetic reactions are now under way in our laboratories.

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