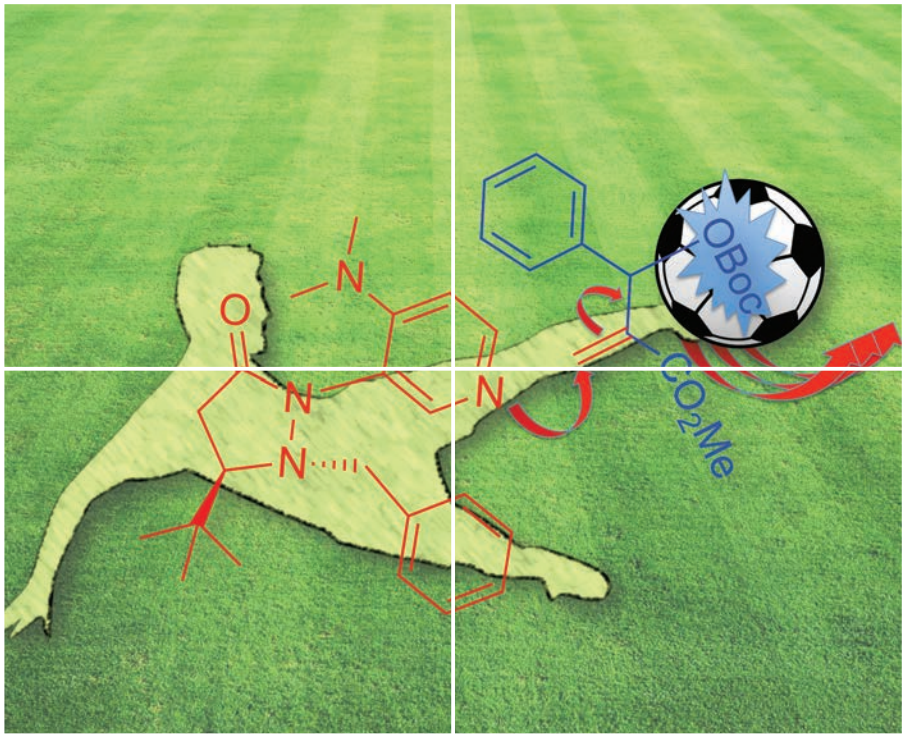
Volume 1 | Number 10 | December 2014



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Enantioselective allylic amination of MBH carbonates catalyzed by novel chiral 4-dialkylaminopyridine catalysts†‡

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Received 26th July 2014,
Accepted 9th September 2014

DOI: 10.1039/c4qo00210e

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We have investigated the asymmetric allylic amination of Morita–Baylis–Hillman (MBH) carbonates with nitrogen nucleophiles in the presence of newly designed chiral DMAP catalysts. A series of α-methylene β-amino esters were obtained with good yield and selectivities.

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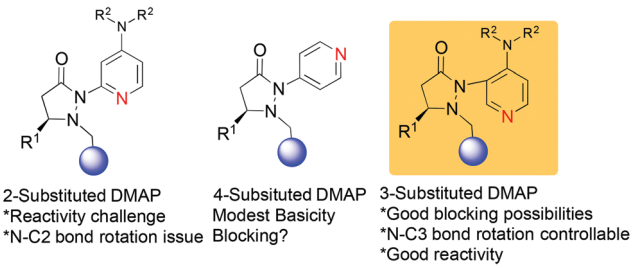
The super nucleophilic base, 4-dimethylaminopyridine (DMAP), and its derivatives have general applicability for the nucleophilic catalysis of a wide variety of reactions.[1] The range of applications using DMAP as a catalyst in organic synthesis has increased dramatically. In view of the versatility of DMAP, a significant step was to devise a chiral variant that could achieve asymmetric catalysis, and the first process toward attaining this objective was reported by Vedejs in 1996.[2] Following this pioneering study, several research groups successively developed chiral DMAP catalysts with a stereogenic center or a chiral axis and planar–chiral DMAP catalysts.[3] These catalysts have been successfully used in kinetic resolution of secondary alcohols and amines, desymmetrization of *meso* diols, asymmetric [3 + 2] cycloadditions, enantioselective protonation of ketenes, O-to-C rearrangements of acyl groups, *etc*.[4]

We are interested in investigating DMAP catalysts that incorporate fluxional groups to provide steric control of reactivity. In the past few years, our group has examined a concept called "chiral relay" which utilizes fluxional chirality in achiral templates, ligands, and additives to provide a general method for the enhancement of enantioselectivity in a variety of transformations.[5] A body of work has demonstrated that stereochemical information can be conveyed from fluxional stereogenic centers to reaction sites to control diastereo- or enantioselectivities.[5,6]

We have recently reported on the development of novel chiral DMAP catalysts that incorporate a fluxional group to control stereoselectivity in kinetic resolutions.[7] The design criteria for the new chiral DMAP catalysts were based on well-established principles in the literature (Scheme 1). The initial evaluation involved the proper placement of the fluxional group on the pyridine ring. Early investigations showed that even a small group (methyl) adjacent to the pyridine nitrogen markedly erodes their activity as nucleophilic catalysts. Thus, 2-substituents in DMAP catalyst design are generally not desirable (structure A, Scheme 1).[8] Furthermore, 4-substituted pyridines are likely to provide minimal steric shielding due to the remote architecture between the catalytic center and the stereocontrol element (structure B, Scheme 1). Based on these considerations, we connected the 3-position of pyridine with the chiral pyrazolidinone template containing the fluxional group (structure C, Scheme 1). We expected that reactivity should be reasonable, and that the proximity between the fluxional group and the pyridine might afford conformational definition.



Scheme 1 Design of novel chiral DMAP catalysts with fluxional chirality.

Several chiral DMAP catalysts containing fluxional groups have been prepared from readily available pyrazolidinones **1** (Scheme 2).[7] The preparation of new DMAP catalysts started from enantiomerically pure pyrazolidinones **1** and required three steps, which afforded good overall yields. The methodology is amenable for scale up and diversity can be introduced in the fluxional group as well as the pyridine 4-substituent without much difficulty. Five catalysts were synthesized with different R^1, R^2 and R^3 substituents for evaluation.

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† This article is dedicated to Max Malacria on his 65th birthday.

‡ Electronic supplementary information (ESI) available. CCDC 1016533. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4qo00210e

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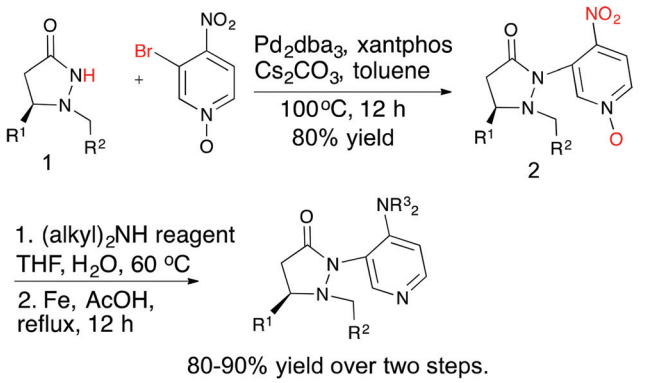
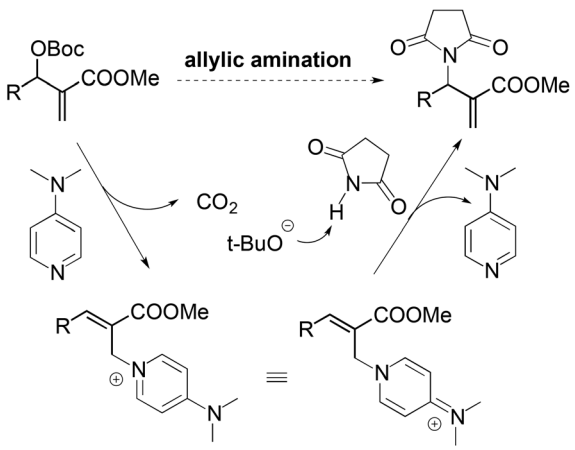


Scheme 2 Synthesis of chiral DMAP catalysts.

We are interested in evaluation of the newly designed DMAP catalysts in enantioselective transformations. To evaluate the nucleophilic characteristics of the new DMAP catalysts we have chosen the allylic amination of Morita–Baylis–Hillman (MBH) carbonates. The transformation of MBH adducts has attracted a lot of attention since they are synthetically important synthons.[9] Although there are a number of reports which utilize chiral palladium complexes, chiral tertiary amines and phosphines for the transformation of MBH adducts,[10] to the best of our knowledge there is no example of using chiral DMAP for such a transformation.

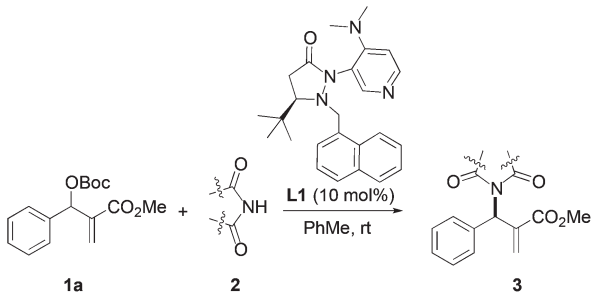
For the nucleophilic allylic amination of MBH adducts, a commonly accepted tandem S_N2'–S_N2' mechanism is illustrated in Scheme 3. The nucleophilic catalyst (DMAP) first adds to the MBH adduct in an S_N2' fashion, followed by elimination of the *tert*-butyl carbonate anion. After elimination of carbon dioxide, the *tert*-butoxy anion deprotonates the pronucleophile. Then the *in situ* formed anionic nucleophile attacks the olefinic bond of the cation intermediate to afford the observed amination products.[11]

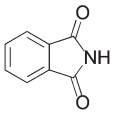
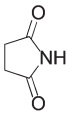
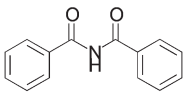
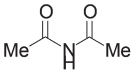
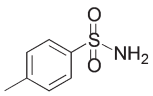
We began our investigation by screening MBH carbonates **1a** with a variety of nitrogen nucleophiles **2** in toluene in the presence of 10 mol% **L1** at room temperature to furnish the amination product. The results are summarized in Table 1. In



Scheme 3 Allylic amination of MBH carbonates catalyzed by DMAP.

Table 1 Screening studies of nitrogen nucleophiles[a]



Entry	Nitrogen Nu	Product	Time	Yield[b] (%)	ee[c] (%)
1		**3a**	24 h	76	31
2		**3b**	24 h	75	39
3		**3c**	36 h	26	3
4		**3d**	7 d	16	11
5		**3e**	3 d	17	25

[a] Reaction conditions: the reactions were performed with 1 equiv. of **1**, 1.5 equiv. of **2** and 10 mol% of catalyst in toluene at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

general, better yield as well as enantioselectivity was obtained when cyclic imide pronucleophiles were used (Table 1, entries 1, 2). Succinimide was slightly better than phthalimide (compare entry 2 with 1). Both the yield and enantioselectivity in reactions with acyclic benzoylbenzamide and acetylacetamide were lower than cyclic nitrogen nucleophiles (entries 3 and 4). Benzenesulfonamide as a nucleophile was better than acyclic pronucleophiles but inferior to cyclic imides (entry 5). A variety of solvents were screened for the reaction and of these toluene gave the best result (see ESI‡).

Next we examined MBH adducts with different leaving groups (OR^2) and different electron withdrawing substituents (OR^1) using succinimide as an aminating agent and **L1** as the catalyst (Table 2). We found that the *tert*-butoxycarbonyloxy group was optimal as a leaving group compared to an acetate or a benzoate group (compare entry 1 with entries 2 and 3). The *t*-BOC group which produces a *tert*-butoxide anion *in situ* generates a nucleophile from the pronucleophile more effectively, leading to the amination product in good yield (75%). Of the different electron withdrawing groups evaluated, the methyl ester gave the product with the highest selectivity (compare entry 1 with entries 4, 5, and 6). In contrast, ethyl

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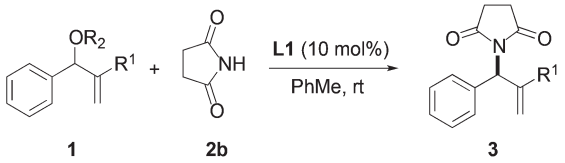
Table 2 Optimization studies of MBH carbonates[a]



1 2b 3

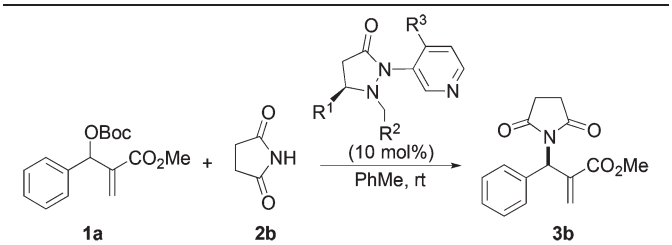
Entry	R^1	R^2	Product	Time	Yield[b] (%)	ee[c] (%)
1	CO_2Me	Boc	**3b**	24 h	75	39
2	CO_2Me	Ac	**3b**	7 d	30	39
3	CO_2Me	4-No_2–PhCO	**3b**	6 d	9	33
4	CO_2Et	Boc	**3f**	36 h	88	29
5	CO_2Bn	Boc	**3g**	36 h	80	29
6	COMe	Boc	**3h**	36 h	90	27

[a,b,c] See Table 1.

and benzyl esters as well as the methyl ketone gave adduct **3** in high yields but with only modest enantioselectivity (entries 4–6).

Based on the above results, reaction between MBH carbonates **1a** and succinimide **2b** was chosen as a model reaction. A number of chiral relay DMAP catalysts were examined next, and these results are summarized in Table 3. In general, all the DMAP catalysts examined in this study were able to catalyze the enantioselective amination of MBH carbonates and provided the product in yields ranging from 75 to 95% (entries 1–6). The catalysts examined in this study varied in the size of the fluxional group and the nature of the dialkylamino substituent on the pyridine ring (catalysts **L1–L5**). Generally, catalysts with a dimethylamino substituent at pyridine-4 gave higher selectivity (compare **L1** with **L2** and **L4** with **L5**). Interestingly, catalyst **L1** with a bulkier 1-naphthyl fluxional group was less effective than a smaller phenyl group (**L4**) with respect to

Table 3 Catalyst optimization studies[a]



1a 2b 3b

Catalysts	Time (h)	Yield[b] (%)	ee[c] (%)
L1 R^1 = *t*-Bu, R^2 = 1-naphthyl, R^3 = dimethylamino	24	75	39
L2 R^1 = *t*-Bu, R^2 = 1-naphthyl, R^3 = pyrrolidine	40	95	29
L3 R^1 = i-Pr, R^2 = phenyl, R^3 = dimethylamino	48	95	33
L4 R^1 = *t*-Bu, R^2 = phenyl, R^3 = dimethylamino	40	85	59
L5 R^1 = *t*-Bu, R^2 = phenyl, R^3 = pyrrolidine	36	90	43

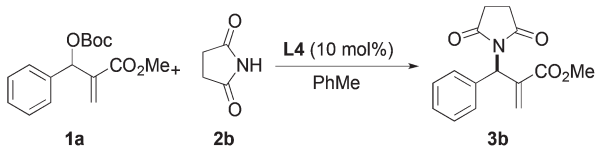
[a,b,c] See Table 1.

enantioselectivity. Catalyst **L3** with a smaller chiral i-Pr group gave the product in a lower selectivity than **L4** with a bigger *t*-Bu chiral group (33% *vs.* 59%). Based on these results, catalyst **L4** was chosen for further studies.

After identifying catalyst **L4** that gave high yield and good selectivity, we evaluated the effect of reaction temperature and catalyst loading on the amination reaction. Results from these experiments are tabulated in Table 4. Reactions with 5, 10, and 25 mol% **L4** gave the product with similar enantioselectivities and yields (entries 1–3). However, using 5 mol% catalyst, a relatively longer reaction time was required for good conversion (entry 3). Lowering the temperature to −10 °C led to improvement in enantioselectivity up to 67% *vs.* 59%, although the yield suffered slightly (63% *vs.* 85%, entry 4).

Having established the optimal reaction conditions for the asymmetric allylic amination with succinimide, a variety of MBH carbonates were synthesized to study the substrate scope. Results from these experiments are shown in Table 5. MBH carbonates with electron-deficient aromatics were facile

Table 4 Temperature and catalyst loading studies[a]

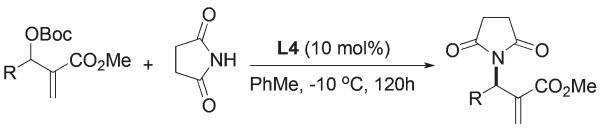


1a 2b 3b

Entry	Temp. (°C)	Cat. loading (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	rt	10%	40	85	59
2	rt	25%	48	88	57
3	rt	5%	72	80	57
4	−10	10%	120	62	67

[a] Reaction conditions: the reactions were performed with 1 equiv. of **1a**, 1.5 equiv. of **2b** and **L4** in toluene at a given temp. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Table 5 Substrate scope of the asymmetric allylic amination of MBH carbonates[a]



1 2b 3

Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	C_6H_5	**3b**	62	67
2	4-$NO_2C_6H_4$	**3i**	90	62
3	4-CNC_6H_4	**3j**	81	61
4	3-$MeOC_6H_4$	**3k**	70	63
5	3,5-$(MeO)_2C_6H_4$	**3l**	78	72
6	2-BrC_6H_4	**3m**	61	39
7	*n*-C_4H_9	**3n**	27	16

[a] Reaction conditions: the reactions were performed with 1 equiv. of **1**, 1.5 equiv. of **2b** and 10 mol% of **L4** in toluene at −10 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

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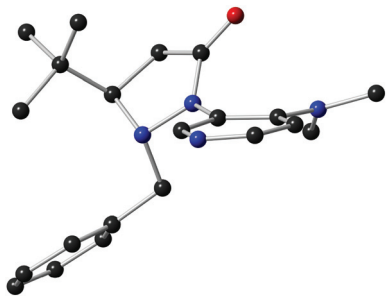

Fig. 1 Single crystal X-ray structure of **L4**.

giving the products in excellent yield and good selectivity (entries 2 and 3). Reaction with an electron-rich aromatic proceeded with comparable enantioselectivity (entry 4). An MBH carbonate with a disubstituted aromatic produced the product with good yield and the highest enantioselectivity was observed in this series (entry 5, 72% ee). A substrate containing an *ortho* substituent was less efficient, giving the product with low enantioselectivity (entry 6). Allylic amination of an alkyl substituted MBH substrate gave low yield and low enantioselectivity (entry 7).

Several groups have developed chiral amines and phosphines as efficient organocatalysts for asymmetric substitutions of MBH adducts. High yields and enantioselectivities were achieved with a wide range of MBH adducts.[11c,d] Similar to *cinchona* alkaloid-based tertiary amine or chiral tertiary phosphine catalysts, the chiral DMAP catalysts are also effective for the allylic amination of MBH carbonates. Although the selectivities for the DMAP catalyzed reactions are slightly lower, it offers new insights into chiral DMAP catalysis, especially organo-DMAPs with fluxional chirality.

The structure and absolute configuration of **L4** were ascertained by single crystal X-ray analysis (Fig. 1). The X-ray crystal structure unambiguously shows that the *tert*-butyl group could control the stereochemistry of the adjacent benzyl group because of its fluxionality resulting in an anti orientation. The fluxional benzyl group appears to block the back as well as the bottom side of the DMAP pyridine ring, which facilitates enantiocontrol.

Conclusions

In conclusion, we have developed the first DMAP catalyzed enantioselective allylic substitution reaction of MBH carbonates. We have also shown that the new DMAP catalysts containing fluxional groups as stereocontrol units can be effectively applied as nucleophilic catalysts in asymmetric allylic aminations. The catalyst preparation is highly tunable and up to 72% ee was achieved using **L4** and a range of α-methylene β-amino esters were obtained with good yield and selectivities. Higher selectivity obtained with catalyst **L4** with a bulky chiral C-5 substituent in comparison with a reaction with **L3** with a smaller C-5 substituent demonstrates that the 'chiral relay' concept is operative. Further applications of chiral relay DMAP catalysts in asymmetric catalysis are in progress.

Acknowledgements

We thank NSF-CHM-0709061 and the AC Cope Scholar award for financial support. We also thank NSF-CRIF (CHE-0946990) for the purchase of the departmental X-ray diffractometer and Dr Angel Ugrinov for solving the single crystal XRD structures.

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