Tandem Reactions

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Diastereo- and Enantioselective Catalytic Tandem Michael Addition/Mannich Reaction: Access to Chiral Isoindolinones and Azetidines with Multiple Stereocenters**

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Construction of multiple contiguous stereogenic centers in acyclic compounds by asymmetric catalysis represents a particularly difficult challenge.[1] For the success of such a catalytic process, carbon–carbon bond-forming tandem reactions using well-known reactions as key transformation steps that give high diastereo- and enantiocontrol are a prerequisite.[2] The asymmetric Mannich-type reaction is a popular method for preparing optically active β-aminocarbonyl frameworks, which are interesting structures found in many useful biologically active compounds.[3] This type of reaction has been frequently used as a fundamental step for establishing tandem protocols,[2] and in those processes, the catalytic generation of chiral enolates is crucial for achieving high activity and selectivity.

It is widely appreciated that copper-catalyzed conjugate addition of R_2Zn to α,β-unsaturated carbonyl compounds is one of the most attractive way for constructing a carbon–carbon bond,[4] in which the chiral zinc enolate is generated in situ. In the case when an appropriate electrophile is added to the reaction system, the tandem conjugate addition/electrophilic trapping reaction might be realized. Based on this concept, various electrophiles such as aldehydes, ketones, esters, nitriles, oxocarbenium ions, carboxylates, alkyl halides, nitrosos, and tosylates have been used in the intermolecular or intramolecular conjugate addition/electrophilic trapping reactions for the construction of complex molecular frameworks through tandem processes.[5] As with the carbon electrophile, imines might be another attractive substrate for the conjugate addition/electrophilic trapping reaction. However, to the best of our knowledge, the use of this type of synthetically versatile aldimine as the terminal electrophile for this kind of reaction remains unexplored—presumably owing to their relatively lower electrophilicity in comparison with aldehydes and other carbonyl-containing electrophiles.[5] Moreover, most of the stereoselective tandem reactions of this kind install the stereogenic centers on cyclic compounds. This limitation is probably due to difficulty in the stereoselective construction of contiguous stereogenic centers in acyclic compounds as compared to cyclic systems. Herein we report a highly diastereo- and enantioselective construction of three contiguous acyclic stereogenic centers through a copper-catalyzed tandem conjugate addition/Mannich reaction of organozinc reagents and acyclic α,β-unsaturated ketones in the presence of imines to afford β-aminocarbonyl derivatives (Scheme 1). Thus, allowing the asymmetric synthesis of chiral azetidines in high enantioselectivity. Notably, in a one-pot manipulation, chiral isoindolinones can also be obtained with high levels of relative and absolute stereochemical control by using this method.

First, we investigated the reactivity of several types of imines as electrophiles toward the chalcone **1** and Et_2Zn in the presence of $Cu(CH_3CN)_4BF_4$ (1 mol%) and with (*S*,*S*)-**L1** (1.2 mol%) as a chiral ligand in toluene at −10°C for 12 hours—these are the same reaction conditions that previously led to good results for the copper-catalyzed conjugate Michael addition protocol.[6] The desired tandem reactions did not proceed with either *N*-arylimine or *N*-alkylimine, and only the 1,4-conjugate addition products were obtained. However, the use of *N*-tosyl aldimine **2a** as an electrophile under the same reaction conditions gave the desired tandem adduct in 72% yield with good enantioselectivity (76% *ee*) for the major diastereomer (Table 1, entry 1). Also, only two of the four possible diastereomers were detected. This exceptionally high reactivity may be attributed to the higher electrophilicity of the *N*-tosyl aldimine or the strong coordination of the copper ion to the *N*-tosyl aldimine through a 1,3-binding mode of the nitrogen atom of the imine moiety and the oxygen atom of the sulfonyl group.[7]

We then focused our attention on this type of imine as the electrophilic tapping reagent and examined several catalytic systems. We used chalcone **1a**, *N*-tosyl aldimine **2a**, and Et_2Zn as the reactants, and the reaction was performed at −10°C in toluene for 12 hours. With **L1** as a ligand, we screened a variety of copper sources including copper(I) and copper(II) species, and found the stereoselectivity was significantly affected by the nature of the counterion of the copper salts (Table 1, entries 1–8). The more coordinating counterions proved to be more suitable, and among those tested, CuBr led to the best results with respect to reactivity and stereoselectivity (Table 1, entry 3). Among the solvents

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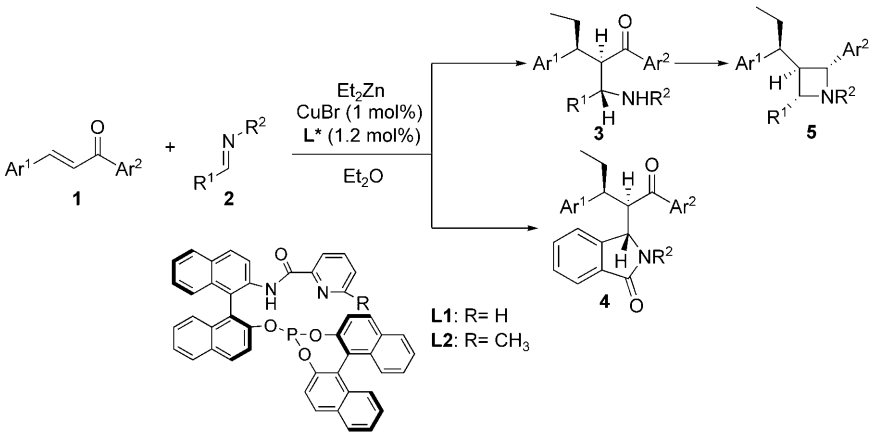
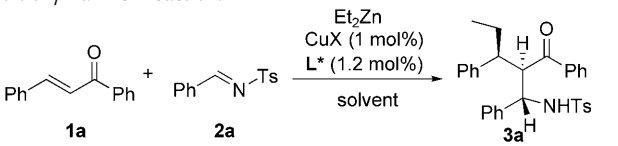


Scheme 1. Copper-catalyzed tandem conjugate addition/Mannich reaction. L* = chiral ligand.

To extend the application of the reaction, a variety of *N*-sulfonyl aldimines were subjected to the optimal reaction conditions using chalcone **1a** and Et_2Zn. As summarized in Table 2, the desired optically active tandem adducts—with three contiguous acyclic stereogenic centers—were obtained in up to 99% yield, 95% *ee*, and 95:5 d.r.. It appeared that the electronic nature of the *para* and *meta* substituents on the phenyl ring of the imine did not have a strong influence on the reactivity and stereoselectivity. Substrates with both electron-rich methyl and methoxyl substituents as well as electron-deficient halogen substitutents all reacted smoothly and gave moderate to high yield, 91–95% *ee*, and 82:18–91:9 d.r. (Table 2, entries 1–7). Besides the substituted phenyl *N*-sulfonyl aldimine, the naphthyl *N*-sulfonyl aldimine also gave the tandem product in high yield and good stereoselectivity (Table 2,

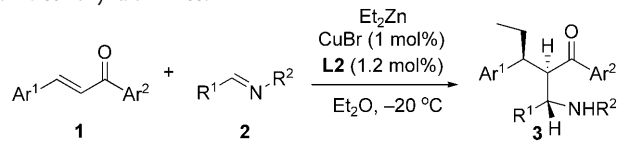
Table 1: Optimized reaction conditions for the tandem conjugate addition/Mannich reaction.[a]



Entry	CuX	Solvent	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	$Cu(CH_3CN)_4BF_4$	toluene	−10	72	75:25	76
2	$Cu(OTf)_2$	toluene	−10	62	70:30	66
3	CuBr	toluene	−10	85	81:19	90
4	$CuBr_2$	toluene	−10	77	70:30	84
5	CuCl	toluene	−10	81	82:18	90
6	$CuCl_2$	toluene	−10	89	72:28	90
7	CuI	toluene	−10	56	65:35	92
8	$Cu(OAc)_2$	toluene	−10	84	75:25	88
9	CuBr	CH_2Cl_2	−10	44	54:46	68
10	CuBr	THF	−10	23	81:19	−4
11	CuBr	Et_2O	−10	98	90:10	84
12	CuBr	nBu_2O	−10	78	85:15	92
13	CuBr	MTBE	−10	84	86:14	86
14	CuBr	CPME	−10	80	83:17	84
15	CuBr	Et_2O	−20	97	91:9	87
16[e]	CuBr	Et_2O	−20	96	91:9	92

[a] Reaction conditions: chalcone **1a** (0.5 mmol), Et_2Zn (0.75 mmol), imine **2a** (0.6 mmol), CuX (0.005 mmol), **L1** (0.006 mmol), solvent (2.0 mL), 12 h. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] The *ee* value was determined by HPLC on a chiral stationary phase and is quotes only for the main product. [e] **L2** was used as the chiral ligand. CPME = cyclopentyl methyl ether, MTBE = methyl *tert*-butyl ether, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

Table 2: Copper-catalyzed tandem conjugate addition/Mannich reaction of *N*-sulfonyl aldimines.[a]



Entry	**1** (Ar^1, Ar^2)	**2** (R^1, R^2)	Yield of **3** [%][b]	d.r.[c]	*ee* [%][d]
1	Ph, Ph	Ph, Ts	**3a**, 96	91:9	92
2	Ph, Ph	4-ClC_6H_4, Ts	**3b**, 92	91:9	91
3	Ph, Ph	4-BrC_6H_4, Ts	**3c**, 89	91:9	93
4	Ph, Ph	4-FC_6H_4, Ts	**3d**, 66	88:12	95
5	Ph, Ph	4-$CH_3C_6H_4$, Ts	**3e**, 92	86:14	93
6	Ph, Ph	4-$MeOC_6H_4$, Ts	**3f**, 99	82:18	91
7	Ph, Ph	3-ClC_6H_4, Ts	**3g**, 83	91:9	92
8	Ph, Ph	1-naphthyl, Ts	**3h**, 90	93:7	94
9	Ph, Ph	*c*-C_6H_{11}, Ts	**3i**, 72	83:17	92
10	Ph, Ph	2-furyl, Ts	**3j**, 77	67:33	95
11	Ph, Ph	4-$CH_3OC_6H_4$, Ns	**3k**, 84	93:7	92
12	Ph, Ph	4-$CH_3C_6H_4$, Ns	**3l**, 80	92:8	93
13	4-$CH_3C_6H_4$, Ph	Ph, Ts	**3m**, 95	92:8	94
14	4-$MeOC_6H_4$, Ph	Ph, Ts	**3n**, 94	95:5	92
15	4-ClC_6H_4, Ph	Ph, Ts	**3o**, 93	86:14	93
16	4-BrC_6H_4, Ph	Ph, Ts	**3p**, 85	89:11	94
17	4-FC_6H_4, Ph	Ph, Ts	**3q**, 90	88:12	89
18	3-ClC_6H_4, Ph	Ph, Ts	**3r**, 76	81:19	87
19	Ph, 4-ClC_6H_4	Ph, Ts	**3s**, 95	88:12	88
20	4-BrC_6H_4, Ph	2-$CO_2MeC_6H_4$, Ts	**3t**, 88	70:30	95
21	4-ClC_6H_4, Ph	2-$CO_2MeC_6H_4$, Ts	**3u**, 86	71:29	93
22	Ph, 4-ClC_6H_4	2-$CO_2MeC_6H_4$, Ts	**3v**, 85	78:22	90

[a] Reaction conditions: chalcone **1** (0.5 mmol), Et_2Zn (0.75 mmol), imine **2** (0.6 mmol), CuBr (0.005 mmol), **L2** (0.006 mmol), Et_2O (2.0 mL), −20 °C, 12 h. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy, other diastereomers less than 1%. [d] Determined by HPLC on a chiral stationary phase. Ns = 2-nitrobenzenesulfonyl.

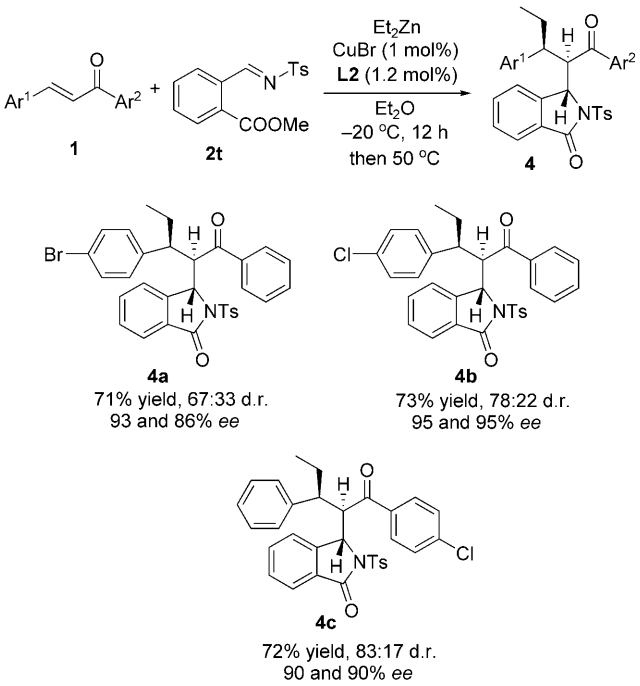
examined, Et_2O gave the highest yield and diastereoselectivity (Table 1, entry 11). Although we observed a little erosion in asymmetric induction with Et_2O compared to the other solvents tested. The temperature also influenced the diastereoselectivity and enantioselectivity of the reaction, but not the reactivity (Table 1, entry 11 vs. 15). Furthermore, the product was formed in higher yield with a higher *ee* value when **L2** instead of **L1** was used as the chiral ligand (Table 1, entry 15 vs. 16).

entry 8). Aliphatic and heteroaromatic aldehyde-derived imines were also tested, and these gave high *ee* values but relatively lower yields and diastereoselectivities (Table 2, entries 9 and 10). When the protecting group on the nitrogen center of **2** was changed from Ts to Ns, then high enantioselectivity and diastereoselectivity could also be realized (Table 2, entries 11 and 12).

Further broadening of the substrate scope indicated that the tandem reaction of *N*-tosyl aldimine **2a** with a series of substituted chalcones and Et_2Zn could also be achieved to produce the desired tandem adducts under the optimal reaction conditions. As shown in Table 2, high yields and enantioselectivities of up to 95% *ee* were obtained regardless of the electronic and steric nature of the substituted chalcones examined here (Table 2, entries 13–19). Notably, the synthetically more versatile, but less reactive aldimine **2t** (see Scheme 2 for structure) was also compatible with this tandem reaction. Under the optimized reaction conditions, **2t** was subjected to the tandem reaction with different chalcones and the corresponding tandem adducts were obtained in good yields with high stereoselectivities (up to 95% *ee*; Table 2, entries 20–22). The configuration of the major isomer of **3t** was determined to be 1*S*,2*R*,3*S* by single-crystal X-ray analysis,[8] and the other products were tentatively assigned by analogy.

Given the importance of chiral isoindolinone and isoindoline derivatives in biological science and medicinal chemistry,[9] the synthesis of these compounds is of great interest.[10] The substrate **2t** could also be used for the synthesis of chiral isoindolinones. Under the optimized reaction conditions, **2t** underwent the tandem reaction with different chalcones and Et_2Zn. The corresponding formation of the tandem adducts and subsequent in situ lactamization at 50 °C gave the chiral 3-substituted *N*-tosylphthalimidines **4a–c** in good yields and with high enantioselectivities (90–95% *ee*; Scheme 2). Crystals of enantiopure **4a** were obtained and single-crystal X-ray analysis also revealed the configuration to be 1*S*,2*R*,3*S* (Figure 1, left).[8]

It was anticipated that the tandem adducts **3** could be employed for the efficient preparation of chiral 2,3,4-trisubstituted *N*-tosylazetidines (Scheme 3). Azetidines are four-membered nitrogen-containing heterocyclic compounds, and they possess various important biological properties such as activity against influenza virus A as well as anti-HIV, anti-HSV-1, and anti-HSV-2 activity.[11] Despite their indisputable importance as bioactive compounds and pharmaceutical building blocks, the methods for the preparation of chiral azetidines are currently limited which is probably due to their strained nature and the difficulty of formation of the four-membered ring.[12] Thus, this transformation was carried out as follows: product **3a** was obtained on gram scale through the newly developed tandem reaction, and the crude compound was recrystallized to afford the enantiomerically pure product with 98% *ee* and more than 95:5 d.r. The purified **3a** was converted into the β-amino alcohol **6a** as one diastereomer with four contiguous stereogenic centers by Pd/C-catalyzed hydrogenation, and was subsequently treated with TsCl/KOH under reflux in THF[12e,f] to furnish the desired *N*-tosylazetidine **5a** as a single isomer with 62% overall yield in three steps. By using a similar method, **3e** was converted into the corresponding *N*-tosylazetidine **5b** as a single isomer with 65% overall yield. The structure of **5a** was confirmed unambiguously by single-crystal X-ray analysis, and the newly formed chiral center was determined to have *R* configuration (Figure 1, right).[8]



Scheme 2. Catalytic synthesis of chiral isoindolinone derivatives by a tandem reaction.

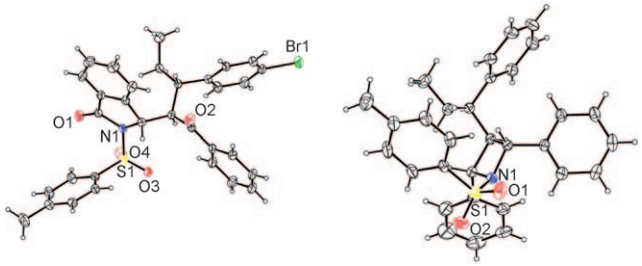


Figure 1. X-ray structures of the enantiomerically pure isoindolinone **4a** (left) and azetidine **5a** (right). The thermal ellipsoids are drawn at the 50% probability level. Blue N, green Br, red O, yellow S.

In summary, we have developed an efficient asymmetric tandem conjugate addition/Mannich reaction for the construction of multiple contiguous acyclic stereogenic centers in product with high diastereo- and enantioselectivity. This protocol provides a reliable and rapid approach for the synthesis of chiral *N*-tosyl isoindolinones and 2,3,4-trisubstituted *N*-tosylazetidines. Further investigation to extend the reaction scope and applications of this process in organic synthesis are underway.

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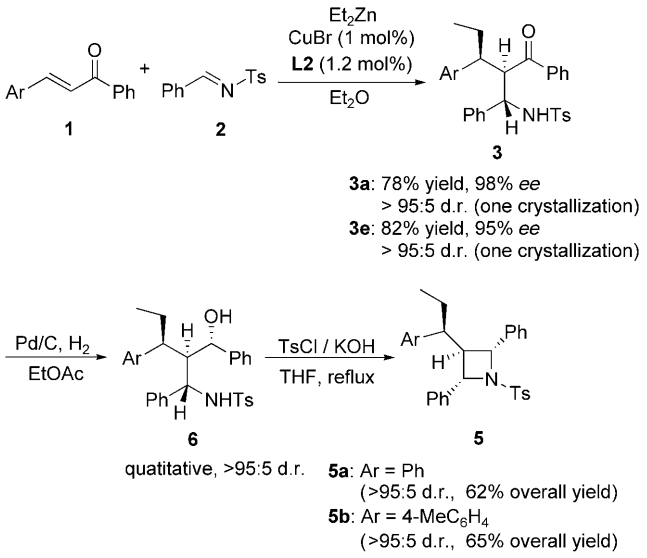

Scheme 3. Synthesis of chiral *N*-tosylazetidine derivatives.

Keywords: asymmetric catalysis · Mannich reaction · Michael addition · tandem reactions

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[8] CCDC 757909 (**3t**), 757908 (**4a**), and 757907 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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