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Parallel Copper Catalysis: Diastereoselective Synthesis of Polyfunctionalized Azetidin-2-imines

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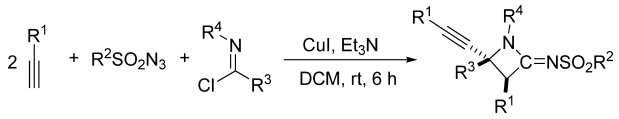
ABSTRACT



An efficient and diastereoselective synthesis of highly functionalized azetidin-2-imines has been achieved through a parallel catalysis strategy, including a copper-catalyzed azide−alkyne cycloaddition, a copper-catalyzed $C_{sp}-C_{sp^2}$ cross-coupling reaction, and an intermolecular [2 + 2] cycloaddition. The products could be conveniently converted into the structurally interesting dihydroazeto[1,2-*a*]benzo[*e*]azepin-2(4*H*)-imines.

As a new concept, cascade catalysis[1] or concurrent tandem catalysis[2] is becoming a rapid, efficient, and convenient strategy in organic synthesis. This strategy integrates multiple catalytic cycles in a single procedure and allows sophisticated compounds to be easily prepared from commercially available starting materials.[3] Since both time and resources can be efficiently saved by simplifying the operating procedures, this concept fits the basic requirements of green chemistry and is of unique importance for unstable intermediates.

Recently, copper-catalyzed azide−alkyne cycloadditions (CuAACs) were developed for the formation of ketenimines,[4,5] which could be efficiently transformed into a variety of nitrogen-containing heterocyclic compounds with economic and ecological values.[6,7] Inspired by our previous success with ketenimine chemistry[3d,7] and the literature on the copper-catalyzed $C_{sp}-C_{sp^2}$ cross-coupling reaction,[8] we became interested in cascade reactions that can combine a copper-catalyzed azide−alkyne cycloaddition and a copper-catalyzed $C_{sp}-C_{sp^2}$ cross-coupling in a parallel catalysis approach (Figure 1).

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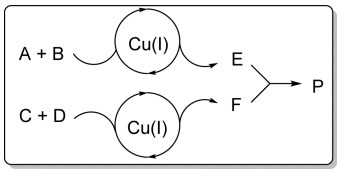
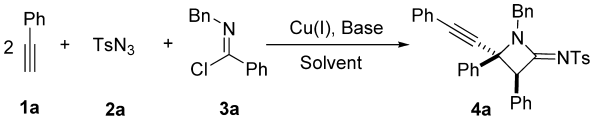


Figure 1. Cascade strategy involving parallel catalysis.

Our investigation started with the reaction of phenylacetylene (**1a**), 4-methylbenzenesulfonyl azide (**2a**), and imidoyl chloride (**3a**) as the model reaction using CuI as a single catalyst source (Table 1, entry 1). Primarily, a four-component adduct **4a** was isolated in 64% yield after the reaction was conducted in THF at room temperature for 6 h. The relative configuration of **4a** was comparatively confirmed by X-ray crystallographic analysis of its analogs **4b** and **4q** as well as its derivative **7a**,[9] while an 85:15 *cis*/*trans* ratio for **4a** was determined with ^{1}H NMR spectroscopy. Since **4a** contains an azetidin-2-one core, which is the key structure unit of a large class of antibiotics and might potentially possess biological activity,[10] we screened the reaction conditions to develop an efficient approach to the azetidin-2-one ring system. As shown in Table 1, the best yield and stereoselectivity were obtained when the reaction was carried out in dichloromethane (DCM) using 10 mol % CuI as the catalyst and 3 equiv of Et_3N as the base (Table 1, entries 5 and 13).

Table 1. Optimization of the Reaction Conditions[a]

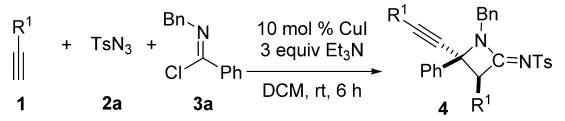


entry	solvent	base	cat.	yield (%)[b]	*dr*[c]
1	THF	Et_3N	CuI	64	85:15
2	CH_3CN	Et_3N	CuI	44	84:16
3	toluene	Et_3N	CuI	53	>95:5
4	DCE	Et_3N	CuI	67	>95:5
5	DCM	Et_3N	CuI	76	>95:5
6	DCM	pyridine	CuI	<10	_
7	DCM	DBU	CuI	<10	_
8	DCM	K_2CO_3	CuI	<10	_
9	DCM	DABCO	CuI	NF	_
10	DCM	Et_3N	CuCl	39	>95:5
11	DCM	Et_3N	CuBr	47	>95:5
12[d]	DCM	Et_3N	CuI	59	>95:5
13[e]	DCM	Et_3N	CuI	78	>95:5

[a] Reaction conditions: **1a** (2.5 mmol), **2a** (1.2 mmol), **3a** (1 mmol), base (3 mmol), and Cu(I) (0.1 mmol), solvent (5 mL), room temperature, 6 h. [b] Isolated yield based on **3a**. [c] Determined from the ^{1}H NMR spectra of the crude product. [d] For 3 h. [e] For 12 h.

Under the optimized reaction conditions, we investigated the scope of substrates. A variety of terminal alkynes **1a**–**1f** were examined for this transformation (Table 2). Both aromatic alkynes (Table 2, entries 1–5) and aliphatic alkynes (Table 2, entry 6) reacted smoothly with **2a** and **3a** to afford the corresponding azetidin-2-ones **4a**–**4f** in yields

Table 2. Preparation of Azetidin-2-imines **4**: Scope with Respect to the Terminal Alkyne Component[a]



entry	**1** (R^1)	product	yield (%)[b]	*dr*[c]
1	**1a** (C_6H_5)	**4a**	76	>95:5
2	**1b** (*p*-MeC_6H_4)	**4b**	70	84:16
3	**1c** (*p*-$MeOC_6H_4$)	**4c**	68	77:23
4	**1d** (*p*-PhC_6H_4)	**4d**	71	>95:5
5	**1e** (*p*-BrC_6H_4)	**4e**	63	>95:5
6[d]	**1f** (*n*-C_5H_{11})	**4f**	76	>95:5

[a] Reaction conditions: **1** (2.5 mmol), **2a** (1.2 mmol), **3a** (1 mmol), Et_3N (3 mmol), and Cu(I) (0.1 mmol), DCM (5 mL), room temperature, 6 h. [b] Isolated yield based on **3a**. [c] Determined from the ^{1}H NMR spectra of the crude product. [d] 40 °C, 12 h.

between 63% and 76%. The electronic effect of the substituent on aromatic ring of aromatic alkynes was not apparent. However, it indeed affected the diastereomeric ratio (*dr*) of the products. 1-Ethynyl-4-methylbenzene (**1b**) and 1-ethynyl-4-methoxybenzene (**1c**) produced **4b** and **4c** with *dr* values of 84:16 and 77:23, respectively, while excellent diastereoselectivity (*dr* > 95:5) was observed for **4a** and **4d**–**4f**.

Both aryl sulfonyl azides (Table 3, entries 1–6) and alkyl sulfonyl azide (Table 3, entry 7) worked for the reaction to afford the desired products **4g**–**4m** in moderate to excellent yields. Among these tested azides, naphthalene-2-sulfonyl azide furnished **4k** in the best yield (95%) with the highest *dr* value (>95:5) (Table 3, entry 5), while 2,4,6-trimethylbenzenesulfonyl azide produced **4j** in the lowest yield (60%) with the lowest *dr* value (77:23) although a higher reaction temperature and a longer reaction time were applied (Table 3, entry 4).

To further examine the generality of this method, various imidoyl chlorides **3** were allowed to react with **1a**–**1b** and **2a** under the established conditions (Table 4). Imidoyl chlorides **3** were prepared from the corresponding amides and sulfonyl chlorides at refluxing temperature for 3 h. When the imidoyl chlorides **3b**–**3f** derived from *N*-benzyl amides were used as the substrates, **4n**–**4r** were obtained in yields between 66% and 83% with excellent diastereoselectivities (Table 4, entries 1–5). For the imidoyl chlorides

(9) For ORTEPs of products **4b**, **4q**, and **7a**, please see the Supporting Information. CCDC 930258 (**4b**), CCDC 930259 (**4q**), and CCDC 930262 (**7a**) contain 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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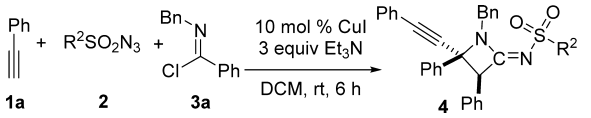
Table 3. Preparation of Azetidin-2-imines **4**: Scope with Respect to the Azide Component[a]



entry	**2** (R^2)	product	yield (%)[b]	*dr*[c]
1	**2b** (C_6H_5)	**4g**	89	>95:5
2	**2c** (*p*-$MeOC_6H_4$)	**4h**	92	84:16
3	**2d** (*p*-ClC_6H_4)	**4i**	87	>95:5
4[d]	**2e** (2,4,6-$Me_3C_6H_2$)	**4j**	60	77:23
5	**2f** (2-naphthalenyl)	**4k**	95	>95:5
6	**2g** (*p*-$NO_2C_6H_4$)	**4l**	88	>95:5
7	**2h** (CH_3)	**4m**	66	>95:5

[a] Reaction conditions: **1a** (2.5 mmol), **2** (1.2 mmol), **3a** (1 mmol), Et_3N (3 mmol), and Cu(I) (0.1 mmol), DCM (5 mL), room temperature, 6 h. [b] Isolated yield based on **3a**. [c] Determined from the ^1H NMR spectra of the crude product. [d] 40 °C, 12 h.

3g–**3j** derived from benzamides with different substituents at the nitrogen atom, **4s**–**4v** were prepared in 73–93% yields with *dr* values varied from 77:23 to >95:5 (Table 4, entries 6–9).

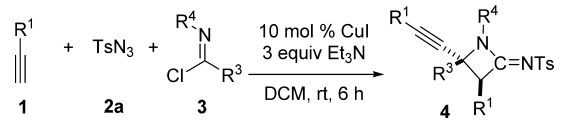
We assumed that the ynimine **5**, generated in situ from terminal alkyne **1** and imidoyl chloride **3** via a copper-catalyzed coupling, might be a key intermediate in this transformation. Therefore, we prepared ynimine **5** from **1b** and **3j** in the presence of CuI and then employed **5** for the subsequent reaction with **2a** and **1b** (Scheme 1). As we expected, the desired **4v** was obtained with the same *dr* value as the one obtained from the one-pot procedure (Table 4, entry 9).

Since 2 equiv of the terminal alkynes **1** were used in this transformation, two different terminal alkynes were sequentially added. As shown in Scheme 2, after the reaction of **1a** with **3a** was conducted in dichloromethane in the presence of CuI at room temperature for 2 h, 1-heptyne (**1f**), **2a**, and additional CuI were sequentially added in one pot to allow the reaction to proceed for an additional 6 h. Finally, **6** was obtained in 61% yield with excellent diastereoselectivity (>95:5 *dr*).

The stereochemistry of this transformation is attractive. Two aryl groups in the azetidin-2-imine rings are in *cis*-configurations (for **4f** and **6**, heptyl and phenyl are in a *cis*-configuration). These results prompted us to look for theoretical support. **4a**, **4h**, and **4u** were therefore selected as three representatives, which have excellent (>95:5 *dr*), good (84:16 *dr*), and moderate (77:23 *dr*) diastereoselectivities, respectively (Figure 2). We calculated these three pairs of azetidin-2-imines and found that the energy difference between *cis*-**4a** and *trans*-**4a** is the largest, while the energy difference between *cis*-**4u** and *trans*-**4u** is the smallest. The tendency for the energy difference eventually supported what we observed in the diastereoselectivity and implied that *cis*-azetidin-2-imines (*cis*-**4**) were the thermodynamically favored products.

Based on these results, a possible mechanism is outlined in Scheme 3. In the presence of a base, the copper-catalyzed

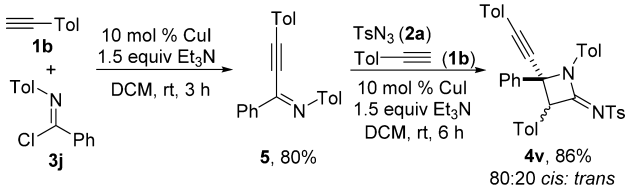
Table 4. Preparation of Azetidin-2-imines **4**: Scope with Respect to the Imidoyl Chloride Component[a]



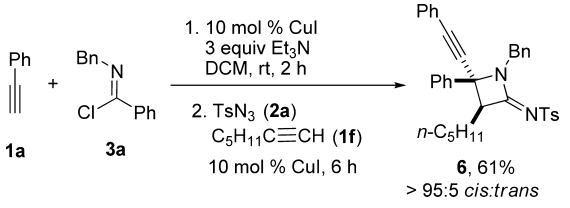
entry	**1**	**3** (R^3, R^4)	product/yield (%)[b]	*dr*[c]
1	**1a**	**3b** (*p*-MeC_6H_4, Bn)	**4n**/72	>95:5
2	**1a**	**3c** (*m*-ClC_6H_4, Bn)	**4o**/66	>95:5
3	**1a**	**3d** (*p*-$MeOC_6H_4$, Bn)	**4p**/83	>95:5
4	**1a**	**3e** (*o*-BrC_6H_4, Bn)	**4q**/69	>95:5
5	**1a**	**3f** (*p*-BrC_6H_4, Bn)	**4r**/75	>95:5
6	**1a**	**3g** (C_6H_5, *n*-C_4H_9)	**4s**/87	>95:5
7	**1a**	**3h** (C_6H_5, *o*-ClBn)	**4t**/93	>95:5
8	**1a**	**3i** (C_6H_5, *c*-C_6H_{11})	**4u**/88	77:23
9	**1b**	**3j** (C_6H_5, *p*-MeC_6H_4)	**4v**/73	80:20

[a] Reaction conditions: **1** (2.5 mmol), **2a** (1.2 mmol), **3** (1 mmol), Et_3N (3 mmol), and Cu(I) (0.1 mmol), DCM (5 mL), room temperature, 6 h. [b] Isolated yield based on **3**. [c] Determined from the ^1H NMR spectra of the crude product.

Scheme 1. Preparation of Azetidin-2-imine **4v** Step-by-Step



Scheme 2. Preparation of Azetidin-2-imine **6** from Mixed Alkynes



C_{sp}–C_{sp^2} coupling reaction between terminal alkyne **1a** and imidoyl chloride **3a** forms the ynimine intermediate **A**.[11] Meanwhile, the copper-catalyzed alkyne–azide cycloaddition occurs to form the ketenimine intermediate **B**.[4,5] Subsequently, a [2 + 2] cycloaddition between **A** and **B** takes place to furnish azetidin-2-imine **4a**. The remarkable diastereoselectivity for the formation of *cis*-**4a** can be contributed to the thermodynamic stability of the *cis*-product.

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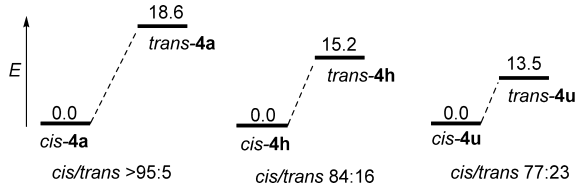
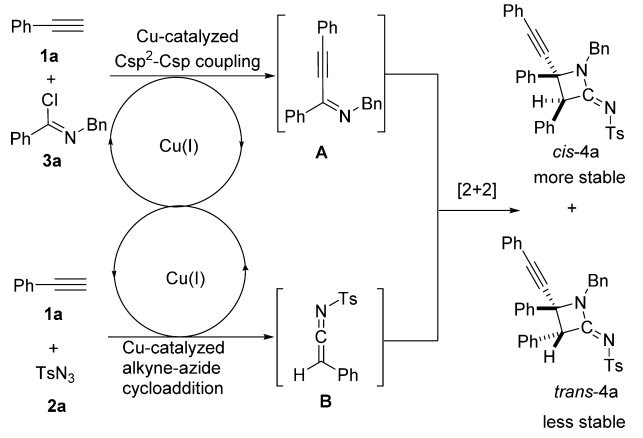


Figure 2. Rrelative potential energy (kJ/mol) of *cis*/*trans*-**4a**, *cis*/*trans*-**4h**, and *cis*/*trans*-**4u**, calculated by Spartan 10, using the DF B3LYP/6-31G* method.

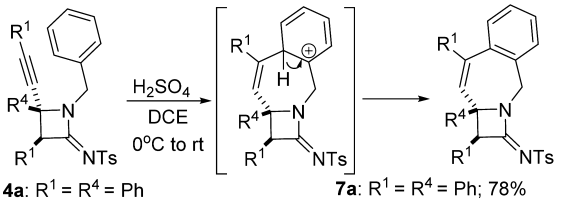
Scheme 3. Proposed Mechanism for the Formation of Azetidin-2-imines



As a synthetic application of this method, the synthesized azetidin-2-imines **4** were conveniently converted into dihydroazeto[1,2-*a*]benzo[*e*]azepin-2(4*H*)-imines **7** via an electrophilic cyclization using 10 equiv of H_2SO_4 in DCE (Scheme 4). The structure of **7a** was unambiguously confirmed by the X-ray crystallographic analysis.[9]

In conclusion, we have developed a Cu-catalyzed four-component reaction of imidoly chlorides, sulfonyl azides, and two terminal alkynes, which afforded polyfunctionalized

Scheme 4. Preparation of Dihydroazeto[1,2-*a*]benzo[*e*]azepin-2(4*H*)-imines **7** from **4**



4a: $R^1 = R^4$ = Ph
4e: R^1 = *p*-BrC_6H_4, R^4 = Ph
4q: R^1 = Ph, R^4 = *o*-BrC_6H_4
4r: R^1 = Ph, R^4 = *p*-BrC_6H_4

7a: $R^1 = R^4$ = Ph; 78%
7b: R^1 = *p*-BrC_6H_4, R^4 = Ph; 81%
7c: R^1 = Ph, R^4 = *o*-BrC_6H_4; 67%
7d: R^1 = Ph, R^4 = *p*-BrC_6H_4; 90%

azetidin-2-imines in good to excellent yield with high diastereoselectivity. Starting materials are easily accessible. This one-pot reaction proceeded smoothly at room temperature with easy operation. It occurred in a parallel catalysis manner, including a copper-catalyzed C_{sp}–C_{sp^2} coupling, a copper-catalyzed alkyne–azide cycloaddition, and a [2 + 2] cycloaddition. All of these separate reactions represent the frontier of modern organic chemistry and fit the basic requirements of green chemistry with high atom economy. Moreover, the synthesized azetidin-2-imines could be conveniently converted into the structurally interesting dihydroazeto[1,2-*a*]benzo[*e*]azepin-2(4*H*)-imines. Further research on synthetic applications of this method is underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data as well as ^1H and ^{13}C NMR spectra for all products, and crystallographic information files (CIF) for compounds **4b**, **4q**, and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.