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Tandem Synthesis of 2,3-Dihydro-4-iminoquinolines via Three-Component Alkyne-Imine Metathesis

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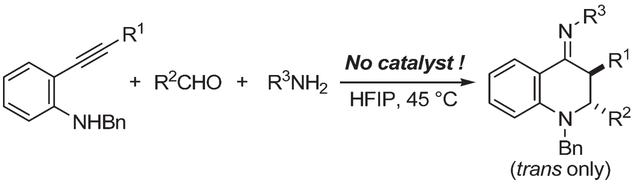
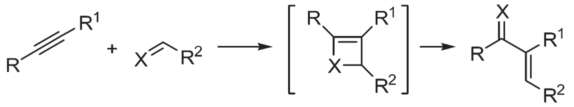
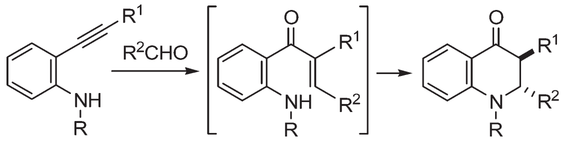


In the absence of any catalysts, *ortho*-alkynylanilines react with aldehydes and amines in HFIP to form *trans*-2,3-disubstituted 2,3-dihydro-4-iminoquinolines in a complete *trans*-selective manner via the three-component alkyne-imine metathesis.

Alkyne-carbonyl metathesis has received attention as a straightforward approach to the formation of highly substituted enones through a formal [2 + 2] cycloaddition of a C−C triple bond with a C−O double bond and the subsequent cycloreversion of an oxete intermediate (eq 1, X = O). The catalytic reaction can be used as an atom economical process alternative to the Wittig reaction.[1,2] In addition, the catalytic metathesis of ynamides (R = NR$'_2$) or alkynylcarcogenides (R = SR$'$, SeR$'$) with imine (X = NTs, NAr) provides us with the efficient synthetic procedure of α,β-unsaturated imidates via an azetin intermediate (eq 1).[3] Recently, Zr- or Ti-catalyzed formation of α,β-unsaturated imines from unactivated alkynes with imines was reported, albeit a different route from alkyne-imine metathesis.[4] Thus, alkyne-carbonyl metathesis and the related reactions have increasingly blossomed. We have developed a tandem synthesis of cyclic compounds via the alkyne-carbonyl metathesis.[5] For example, the SbF_5-alcohol complex-catalyzed metathesis of *o*-alkynylaniline derivatives and aldehydes leads to 2,3-dihydroquinolin-4(1*H*)-ones (eq 2),[5a,6] which possess attractive pharmacological properties[7] and also serve as important synthetic intermediates for the preparation of biologically active compounds.[8] Although the nitrogen analogues, 2,3-dihydro-4-iminoquinolines, are prevalent in various biologically and medicinally important compounds,[9] these compounds required many synthetic steps.[10] The imination of quinolinones has a limitation in the synthetic scope of the quinolinones.[9c,11] Our strategy inspired us to examine the formation of 2,3-dihydro-4-iminoquinolines from *o*-alkynylanilines with imines or with aldehydes and amines. We herein describe the tandem approach to the synthesis of 2,3-disubstituted iminoquinolines by the alkyne-imine metathesis or by the three-component-type metathesis *without any catalysts.*



(1)



(2)

At the outset, we focused on the screening of catalysts (10−20 mol %) for the formation of iminoquinolines **2aa** in

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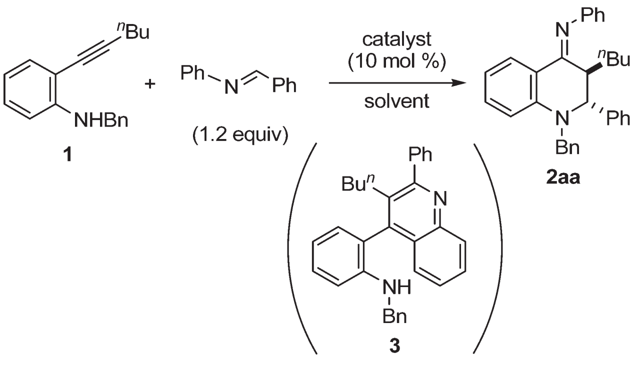
TABLE 1. Optimization for the Formation of 2aa from 1 with Imine



entry	catalyst	solvent[a]	conditions	yield (%)[b] 2aa	3
1	$Yb(OTf)_3$	DCE	90 °C, 20 h	41	21
2	$Sc(OTf)_3$	DCE	90 °C, 20 h	40	21
3	$BF_3 \cdot OEt_2$[c]	DCE	90 °C, 20 h	43	24
4	HBF_4	DCE	90 °C, 43 h	49	25
5	$SbF_5 \cdot 5MeOH$[d]	DCE	90 °C, 18 h	46	19
6	$TfOH \cdot 5MeOH$[d]	DCE	90 °C, 18 h	32	17
7	TfOH	DCE	90 °C, 20 h	43	21
8	TfOH	HFIP	70 °C, 44 h	57	13
9		HFIP	70 °C, 44 h	57	13
10[e]		HFIP	45 °C, 20 h	73	17
11[e]		HFIP-DCE[f]	45 °C, 20 h	70	14
12[e]		HFIP-DCE[g]	45 °C, 20 h	61	13
13[e]		HFIP-DCE[h]	45 °C, 20 h	24	9

[a] DCE = 1,2-dichloroethane, HFIP = hexafluoroisopropanol. [b] Yields were determined by ^{1}H NMR analysis. [c] With 20 mol %. [d] Catalyst/MeOH = 1:5 mixture. [e] **1**/imine = 3:1; the yield of **2aa** was based on imine. [f] HFIP/DCE = 3:1. [g] HFIP/DCE = 1:1. [h] HFIP/DCE = 1:3.

the reaction of *o*-alkynylaniline **1** with benzylideneaniline (1.2 equiv) in 1,2-dichloroethane (DCE, Table 1). It turned out that the employed Lewis acids and Brønsted acids gave the desired **2aa** in 32−49% yields (entries 1−7). In all cases, quinoline **3**, which would be considered to be formed by the aza-Diels−Alder reaction of alkyne moiety of **1** with 2-aza-diene part of imine,[12] was detected in 13−25% yields. Although $SbF_5 \cdot 5MeOH$ (1:5 mixture of SbF_5 and MeOH) was an outstanding catalyst for the formation of 2,3-dihydroquinolin-4(1*H*)-ones from *o*-alkynylanilines and aldehydes,[5] it did not bring about a significant result in the present reaction (entry 5). Under the trifluoromethanesulfonic acid (TfOH)-catalyzed conditions, an addition of MeOH was ineffective (entries 6 and 7). The use of hexafluoroisopropanol (HFIP) as a solvent, however, exerted a marked effect on the formation of **2aa** (entries 8−10). Thus, in HFIP, **2aa** was obtained in 57% yield even without any catalysts (entry 9). Furthermore, the increasing amount of **1** (3 equiv to benzylideneaniline) improved the yield of **2aa** up to 73% at 45 °C within 20 h (entry 10). On the other hand, when HFIP was used with DCE as a cosolvent, the decrease in the ratio of HFIP caused the drop of the yield of **2aa** (entries 11−13).

TABLE 2. Optimization for the Three-Component Formation of 2aa

$$\mathbf{1} + PhCHO + PhNH_2 \xrightarrow[\text{HFIP, 45 °C, 20 h}]{} \mathbf{2aa} + \mathbf{3}$$

entry	1	mixture ratio PhCHO	$PhNH_2$	additive	yield (%)[a] 2aa	3
1	1	1	1		51	13
2	1	1	1	$MgSO_4$	50	13
3	1	1	1	MS 4Å	61	13
4	1	2	2		59	18
5[b]	2	1	1		64	18
6[b]	2	1	1	MS 4Å	68	13
7[b]	3	1	1		65	21
8[b]	3	1	1	MS 4Å	77	21

[a] Yields, which were based on **1**, were determined by ^{1}H NMR analysis. [b] Yields were based on aldehyde.

Since HFIP has been known to be a hydrogen-bond donor (pK_a = 9.3) for heteroatomic functional group,[13] such an activity of HFIP would be primarily a result of the efficient interaction with imine. This is supported by ^{13}C NMR studies using a 1:1 mixture of **1** and benzylideneaniline in HFIP-$CDCl_3$ (3:2) at rt. Compared with ^{13}C NMR spectrum (75 MHz) in neat $CDCl_3$, the spectrum in HFIP-$CDCl_3$ (3:2) showed the larger shifts of imine-carbons of benzylideneaniline ($\Delta\delta = 5.7$)[14] than the other carbons such as the shift of the *sp*-carbons ($\Delta\delta = 2.3$ and -1.0)[14] of **1**. Thus, the present conditions would preferentially activate imine rather than alkyne, and a similar observation has been reported in the reaction of alkyne and aldehyde catalyzed by SbF_5-alcohol complex.[5]

The effect of HFIP solvent was also exhibited on the three-component formation of **2aa** from **1**, PhCHO, and $PhNH_2$ (Table 2). In particular, the addition of MS 4Å (entries 3, 6, and 8) and the increasing amount of **1** (entries 5−8) brought about good results. In the presence of MS 4Å, the 3:1:1 mixture of **1**, PhCHO, and $PhNH_2$ in HFIP at 45 °C for 20 h afforded **2aa** as a single *trans*-isomer in 77% yield (entry 8).

According to the optimized conditions, we next examined the three-component formation of various substituted 2,3-dihydro-4-iminoquinolines (Table 3). In the absence of any catalysts, alkyne **1** or **4** successfully reacted with various aromatic aldehydes and various anilines to give the corresponding iminoquinolines **2** or **5** in moderate to high yields. In all cases, complete *trans*-selectivities were observed. In the reaction with *p*-nitrobenzaldehyde or anilines bearing a strongly electron-withdrawing group (R^3 = *p*-$NO_2C_6H_4$, *p*-CNC_6H_4), however, ketone **6** was detected (7−15%) in place of the desired iminoquinolines (entries 7, 12, and 13).[15] Although **6** would be expected to be formed from alkyne **1** and H_2O, the reaction of **6** instead of **1** with PhCHO and $PhNH_2$ did not yield **2aa** but yielded benzylideneaniline along with recovery of **6**.

Under the present conditions, the treatment of *o*-alkynylaniline **7** with benzaldehyde (1 equiv) and aniline (1 equiv) in

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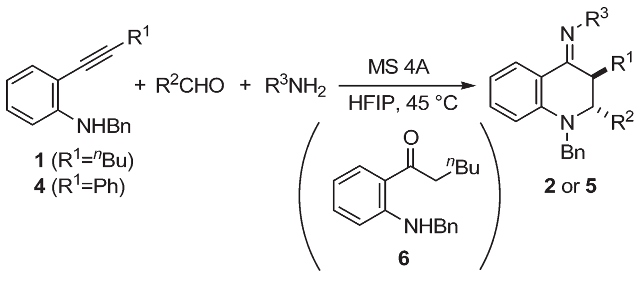
[14] The chemical shift difference $\Delta\delta$ showed the shift to a lower field. The shift to a higher field is stated in minus figures.

[15] The present conditions could not be applied to the reactions of aliphatic aldehydes (R^2 = *n*-hexyl, cyclohexyl, *t*-butyl) instead of aromatic aldehydes or aliphatic amines (R^3 = *n*-butyl, *t*-butyl) instead of aromatic amines. In the absence of aniline, the reaction of **1** and PhCHO with or without MeOH did not afford the corresponding 2,3-dihydroquinolin-4(1*H*)-one and 1,2-dihydro-4-methoxyquinoline.

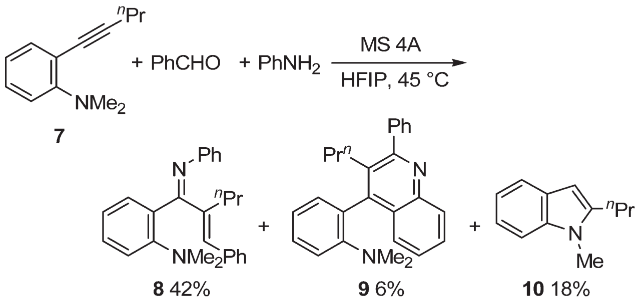
TABLE 3. Three-Component Formation of Iminoquinolines



entry	alkyne	R^2	R^3	(h)	yield (%)[a]	
1	**1**	Ph	Ph	20	**2aa**	75
2	**1**	*p*-$MeOC_6H_4$	Ph	18	**2ba**	68
3	**1**	*m*-$MeOC_6H_4$	Ph	20	**2ca**	64
4	**1**	*o*-$MeOC_6H_4$	Ph	20	**2da**	56
5	**1**	*p*-MeC_6H_4	Ph	21	**2ea**	69
6	**1**	*p*-FC_6H_4	Ph	20	**2fa**	67
7	**1**	*p*-$NO_2C_6H_4$	Ph	42	**2ga**	0
8	**1**	Ph	*p*-$MeOC_6H_4$	20	**2ab**	32
9	**1**	Ph	*p*-MeC_6H_4	18	**2ac**	38
10	**1**	Ph	*p*-FC_6H_4	18	**2ad**	70
11	**1**	Ph	*p*-ClC_6H_4	18	**2ae**	70
12	**1**	Ph	*p*-$NO_2C_6H_4$	42	**2af**	0
13	**1**	Ph	*p*-CNC_6H_4	42	**2ag**	0
14	**4**	Ph	Ph	20	**5aa**	80

[a] Isolated yield.

SCHEME 1. Three-Component Metathesis of 7, PhCHO, and $PhNH_2$



HFIP afforded the α,*β*-unsaturated imine **8** in 42% yield along with [4 + 2] adduct **9** and indole **10** (Scheme 1). On the basis of the previously reported synthesis of α,*β*-unsaturated imidates from alkynes and imines,[3] the result suggested that the present conditions promoted the formal alkyne-imine metathesis of **7** with benzylideneaniline generated in situ to afford **8**. Therefore, the present pathway to 2,3-dihydro-4-iminoquinoline derivatives from *o*-alkynylanilines, aldehydes, and amines would be considered to involve the intramolecular addition of the NH group of α,*β*-unsaturated imines (such as **8**) generated in situ by an alkyne-imine metathesis.

In summary, we have demonstrated the tandem preparation of 2,3-dihydro-4-iminoquinolines via three-component metathesis of *o*-alkynylanilines, aromatic aldehydes, and anilines. *The effect of HFIP solvent is noteworthy in the respect that any catalysts were not demanded.* Since our approach is a highly stereoselective procedure for the synthesis of *trans*-2,3-disubstituted iminoquinolines, the present reaction would raise new possibilities for the construction of quinoline frameworks. Synthetic applications and detailed mechanistic studies of the present reaction are underway.

Experimental Section

Typical Experimental Procedure for the Formation of 2,3-Dihydro-4-iminoquinolines (2aa): To a solution of *o*-alkynylaniline **1a** (316 mg, 0.4 mmol), benzaldehyde (41 μmL, 0.4 mmol), and aniline (37.2 mg, 0.4 mmol) in HFIP (2.0 mL) was added the predrying MS 4Å by microwave. After being stirred at 45 °C for 20 h, the reaction mixture was concentrated to dryness. The purification of the residue by silica gel column chromatography (hexane/AcOEt = 50/1) and the subsequent MPLC (hexane/AcOEt = 99/1) gave **2aa** (136.0 mg, 77% yield) and **3** (37.1 mg, 21% yield). **2aa**: yellow solid; mp 96−98 °C; IR (KBr) ν cm^{-1} 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, 3H, $J = 7.1$ Hz), 1.07−1.14 (m, 4H), 1.58−1.69 (m, 2H), 2.82 (td, 1H, $J = 7.4, 1.8$ Hz), 4.21 (d, 1H, $J = 17.1$ Hz), 4.52 (d, 1H, $J = 1.8$ Hz), 4.80 (d, 1H, $J = 17.1$ Hz), 5.94−5.97 (m, 2H), 6.70−6.72 (m, 1H), 6.76−6.82 (m, 1H), 6.88−6.94 (m, 1H), 7.03−7.09 (m, 1H), 7.28−7.38 (m, 9H), 8.01 (dd, 1H, $J = 7.6, 1.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.4, 28.9, 32.2, 43.8, 53.6, 65.5, 111.0, 116.6, 119.4, 119.4, 122.5, 126.4, 127.2, 127.3, 127.6, 128.3, 128.7, 128.9, 132.6, 138.4, 141.3, 147.1, 150.8, 164.3; FAB-LM m/z 445 ($M^+ + H$); FAB-HM calcd for $C_{32}H_{33}N_2$ 445.2644, found 445.265. Anal. Calcd for $C_{32}H_{32}N_2$: C, 86.44; H, 7.25; N, 6.30. Found: C, 86.53; H, 7.15; N, 6.36. **3**: Yellow solid; mp 147−148 °C; IR (KBr) ν cm^{-1} 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 0.51 (t, 3H, $J = 7.4$ Hz), 0.93 (qt, 2H, $J = 7.4, 7.4$ Hz), 1.14−1.26 (m, 2H), 2.46−2.56 (m, 1H), 2.63−2.73 (m, 1H), 3.67 (br s, 1H), 4.29 (s, 2H), 6.75−6.78 (m, 1H), 6.83−6.89 (m, 1H), 7.04−7.07 (m, 1H), 7.17−7.34 (m, 5H), 7.41−7.58 (m, 7H), 7.65−7.71 (m, 1H), 8.18−8.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 22.6, 30.0, 32.3, 47.9, 111.05, 117.2, 122.1, 125.8, 126.6, 127.0, 127.1, 128.0, 128.3, 128.5, 128.7, 129.0, 129.4, 129.6, 130.3, 133.9, 139.4, 141.6, 144.3, 145.1, 146.5, 161.7; FAB-LM m/z 443 ($M^+ + H$); FAB-HM calcd for $C_{32}H_{31}N_2$ 443.2487, found 443.2497.

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Supporting Information Available: Experimental procedures and physical data for novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.