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Cobalt(III)-catalyzed synthesis of isoquinolines from oximes and alkynes in deep eutectic solvents

Liang Wang,* Lingfeng Zhang and Ling Gong

School of Chemical and Pharmaceutical Engineering, Changzhou Vocational Institute of Engineering, 213164 Changzhou, P. R. China. Fax: +86 5198 633 2059; e-mail: lwcczu@126.com

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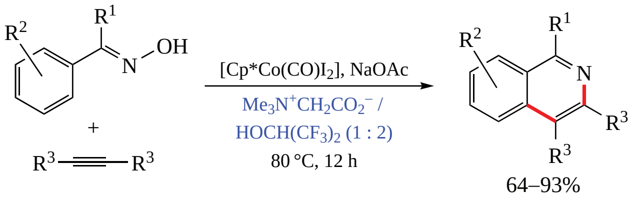
A cobalt-catalyzed redox-neutral [4 + 2] annulation of oximes and alkynes in deep eutectic solvents comprising quaternary ammonium compounds and hydrogen bond donors has been developed, the best system being $Me_3N^+CH_2CO_2^-/HOCH(CF_3)_2$. No external oxidizing reagent was required, and only water was generated as the secondary product. The catalytic system can be reused in three consecutive cycles.

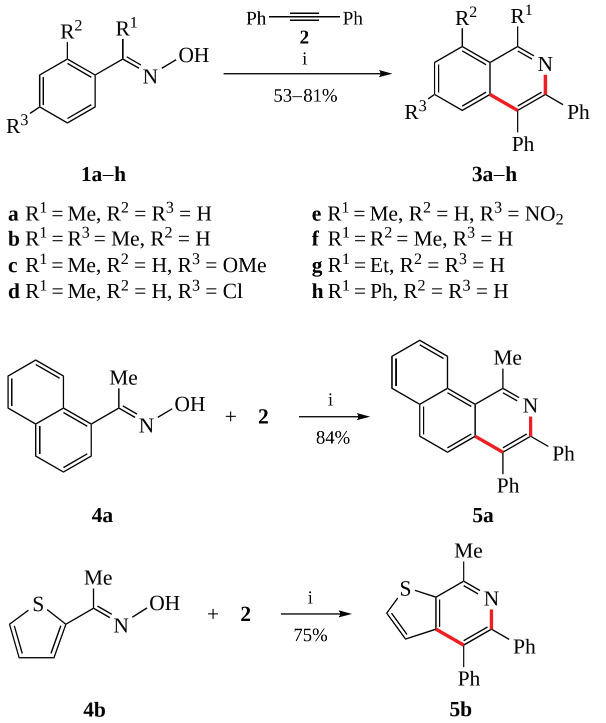


Keywords: C−H activation, annulation, oximes, alkynes, cobalt catalysis, isoquinolines.

Isoquinolines are prevalent scaffolds existing in many pharmaceuticals and natural products.[1–3] Traditional synthetic methods such as the Bischler–Napieralski cyclization,[4] the Pictet–Gams reaction[5] and the Pomeranz–Fritsch reaction[6,7] often require laborious multistep procedures and harsh reaction conditions. Recently, transition metal-catalyzed C–H activation/annulation strategy has emerged as an effective tool to construct isoquinolines. However, in early procedures stoichiometric amounts of external oxidants were applied.[8–10] Subsequently, some oxidizing directing groups containing N–O,[11–17] N–N,[18–20] N–S[21] and N–Cl[22] bonds were employed allowing the reactions under redox-neutral and mild conditions to proceed. Despite the significant progress, the reported procedures were limited to relatively costly Rh or Ru catalysts. In recent years, sustainable C–H activation reaction using earth-abundant metal catalysts or green solvents has aroused widespread interest. Among them, cost-effective cobalt catalysts have shown complementary activity to the Rh or Ru congeners in the isoquinoline synthesis.[14,21,23–26] Also, C–H activation in ‘green’ media such as water, biomass-derived solvents and deep eutectic solvents has been disclosed.[27–33]

Deep eutectic solvents (DESs) mainly composed of quaternary ammonium salts with hydrogen bond donors (urea, amides, acids, or polyols) possess good availability and biodegradability, low flammability and low toxicity.[34,35] Although DESs have found wide applications, very few examples on C–H activation reaction in DESs have been reported.[31–33] In this study, we envision that C–H activation/annulation of oximes and alkynes leading to isoquinolines under cobalt catalysis in DESs undoubtedly has some advantages compared with the reported procedures. Herein we would report on a cobalt-catalyzed redox-neutral [4 + 2] annulation of oximes and alkynes in DES in detail.

Initially, acetophenone oxime **1a** and diphenylacetylene **2** were selected as the model substrates to screen the reaction conditions (Scheme 1, Table 1). A series of DESs comprising various ammonium and protic compounds were evaluated (entries 1–7). Among them, $Me_3N^+CH_2CO_2^-$ (betaine) with $(CF_3)_2CHOH$ (hexaflouorispopropanol) provided the desired product **3a** with excellent conversion (entry 7, 93%). No reaction was observed in the absence of any catalyst (entry 8). Switching the $[Cp^*Co(CO)I_2]$ catalyst to $[Cp^*CoI_2]_2$ or $[Cp^*CoCl_2]_2$ led to low yields of **3a** (entries 9,10). A moderate yield was obtained in the absence of AcONa (entry 11, 75%). Use of AcOK or Na_2CO_3 instead of AcONa as additives reduced the yield of product **3a** (entries 12,13). Lowering the temperature to 60 ºC gave **3a** in only 63% yield, whereas increasing the temperature to 100 ºC



a R^1 = Me, R^2 = R^3 = H
b R^1 = R^3 = Me, R^2 = H
c R^1 = Me, R^2 = H, R^3 = OMe
d R^1 = Me, R^2 = H, R^3 = Cl
e R^1 = Me, R^2 = H, R^3 = NO_2
f R^1 = R^2 = Me, R^3 = H
g R^1 = Et, R^2 = R^3 = H
h R^1 = Ph, R^2 = R^3 = H

Scheme 1 *Reagents and optimized conditions*: i, oxime **1** or **4** (0.2 mmol), alkyne **2** (0.24 mmol), $[Cp^*Co(CO)I_2]$ (10 mol%), AcONa (20 mol%), betaine/$(CF_3)_2CHOH$ (1 : 2, mol/mol, 1 ml), 80 ºC, 12 h, isolated yields.

Table 1 Optimization of reaction conditions.[a]

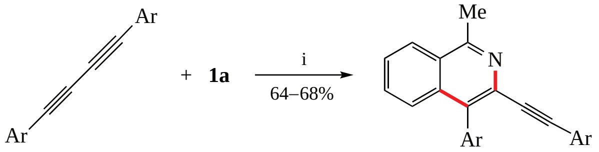
Entry	[Co]	Solvent[b]	Additive	*T*/°C	Yield of **3a** (%)[c]
1	$[Cp^*Co(CO)I_2]$	TBAB/$HO(CH_2)_2OH$	AcONa	80	0
2	$[Cp^*Co(CO)I_2]$	ChCl/urea	AcONa	80	10
3	$[Cp^*Co(CO)I_2]$	ChCl/$HO(CH_2)_2OH$	AcONa	80	31
4	$[Cp^*Co(CO)I_2]$	ChCl/glycerol	AcONa	80	45
5	$[Cp^*Co(CO)I_2]$	ChCl/$MeC(O)NH_2$	AcONa	80	73
6	$[Cp^*Co(CO)I_2]$	betaine/lactic acid	AcONa	80	17
7	$[Cp^*Co(CO)I_2]$	betaine/$(CF_3)_2CHOH$	AcONa	80	93 (70[d])
8	none	betaine/$(CF_3)_2CHOH$	AcONa	80	0
9	$[Cp^*CoI_2]_2$	betaine/$(CF_3)_2CHOH$	AcONa	80	36
10	$[Cp^*CoCl_2]_2$	betaine/$(CF_3)_2CHOH$	AcONa	80	29
11	$[Cp^*Co(CO)I_2]$	betaine/$(CF_3)_2CHOH$	none	80	75
12	$[Cp^*Co(CO)I_2]$	betaine/$(CF_3)_2CHOH$	AcOK	80	80
13	$[Cp^*Co(CO)I_2]$	betaine/$(CF_3)_2CHOH$	Na_2CO_3	80	65
14	$[Cp^*Co(CO)I_2]$	betaine/$(CF_3)_2CHOH$	AcONa	60	63
15	$[Cp^*Co(CO)I_2]$	betaine/$(CF_3)_2CHOH$	AcONa	100	85
16	$[Cp^*Co(CO)I_2]$	$(CF_3)_2CHOH$	AcONa	80	62

[a] Reaction conditions: oxime **1a** (0.2 mmol), alkyne **2** (0.24 mmol), Co catalyst (10 mol%), additive (20 mol%), DES (1 ml), heating, 12 h. [b] TBAB stands for tetrabutylammonium bromide, ChCl stands for choline chloride, the betaine stands for $Me_3N^+CH_2CO_2^-$; except for entry 16, ratios of ammonium/hydrogen donor components are 1 : 2. [c] Isolated yield. [d] With 5 mol% of [Co].

had no more benefit to the reaction (entries 14,15). Furthermore, with lower catalyst loading the yields dropped to 70% (entry 7). The model reaction was also performed in pure $(CF_3)_2CHOH$ when a lower conversion of the starting material was observed (entry 16). It was worth noting that no expensive silver salt (for example $AgSbF_6$) that is usually employed in other C–H activation reactions[24] was required in the present protocol.

With the optimized reaction conditions in hand, the scope of oxime was then explored (see Scheme 1).[†] The annulation of various acetophenone oximes **1a**–**e** and diphenylacetylene **2** proceeded efficiently to provide the desired isoquinolines **3a**–**e** in good to excellent yields. Both electron-withdrawing and electron-donating groups were well tolerated. Substituent on the *ortho* position allowed the C–H activation to occur on the less hindered position (product **3f**). Other ketoximes such as (*E*)-1-phenyl-propan-1-one oxime **1g**, benzophenone oxime **1h** and (*E*)-1-(naphthalen-1-yl)ethan-1-one oxime **4a** also showed good reactivities to afford the desired products **3g**,**h** and **5a**. In addition, heterocyclic ketoxime **4b** also reacted smoothly to give product **5b** in 75% yield. Subsequently, two diaryl diynes **6a**,**b** were explored, and regioisomeric mixtures of the products were obtained. Compounds **7a** and **7b** were found as the major products and were isolated in moderate yields (68 and 64%, respectively). When aliphatic alkynes or unsymmetrical alkynes were tested, complex mixtures were formed.

One of the main advantages of the DESs use as solvents lies in that DESs enable recycling of transition metal catalysts.[36,37] Once the reaction was finished, the organic compounds were extracted, and the DES [betaine/$(CF_3)_2CHOH$] was dried under vacuum. A new batch of fresh starting materials and NaOAc were then added to the recovered DES without the addition of more Co catalyst. The process could be repeated up to three consecutive cycles with slight loss in the yield (93, 90 and 85%, respectively). However, the yield dropped down to 62% after the fourth cycle. It was assumed that the presence of noticeable amounts of different salts may influence the intrinsic structure of DES, or essentially volatile $(CF_3)_2CHOH$ could be partially evaporated despite its hydrogen bonding to the betaine.

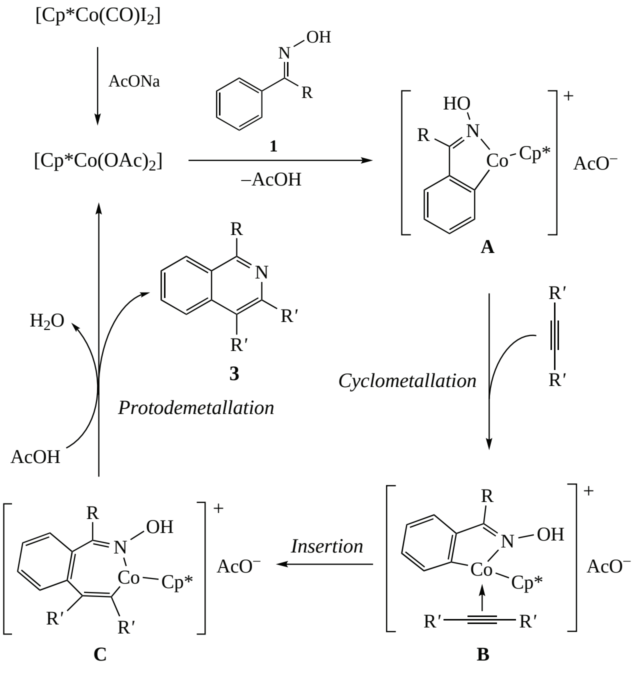


6a,**b**

a Ar = Ph
b Ar = 4-$MeOC_6H_4$

7a,**b**
(major regioisomer)

Scheme 2 *Reagents and optimized conditions*: i, oxime **1a** (0.2 mmol), diyne **6a**,**b** (0.24 mmol), $[Cp^*Co(CO)I_2]$ (10 mol%), AcONa (20 mol%), betaine/$(CF_3)_2CHOH$ (1 : 2, mol/mol, 1 ml), 80 °C, 12 h, isolated yields.



Scheme 3

Since this kind of annulation was well established,[23–25] we propose the following mechanism (Scheme 3). Initially, $[Cp^*Co(CO)I_2]$ readily undergoes decarbonylation in the presence of NaOAc to afford species $[Cp^*Co(OAc)_2]$. Coordination of oxime **1** followed by cyclometallation–deprotonation provides intermediate **A**. Subsequently, coordination of alkyne (species **B**) followed by migratory insertion of an alkyne gives **C**. Finally, reductive elimination followed by protodemetallation affords product **3** and meanwhile regenerates the catalytically active species.

In summary, a cobalt-catalyzed redox-neutral [4 + 2] annulation of oximes and alkynes in deep eutectic solvent has been developed. The reactions proceed smoothly to give isoquinolines in moderate to excellent yields. No external oxidizing reagent is required, and water is released as the only secondary product. The DES consisting of betaine and hexafluoroisopropanol is readily available and cost effective. Moreover, the catalyst and the solvent can be used for three consecutive cycles.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.030.

References

1 K. W. Bentley, *Nat. Prod. Rep*., 2006, **23**, 444.
2 J. D. Scott and R. M. Williams, *Chem. Rev*., 2002, **102**, 1669.
3 K. Bhadra and G. S. Kumar, *Med. Res. Rev.*, 2011, **31**, 821.
4 R. D. Larsen, R. A. Reamer, E. G. Corley, P. Davis, E. J. J. Grabowski, P. J. Reider and I. Shinkai, *J. Org. Chem.*, 1991, **56**, 6034.
5 A. Pictet and A. Gams, *Ber. Dtsch. Chem. Ges*., 1909, **42**, 2943.
6 C. Pomeranz, *Monatsh. Chem*., 1893, **14**, 116.
7 P. Fritsch, *Ber. Dtsch. Chem. Ges*., 1893, **26**, 419.
8 N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc*., 2010, **132**, 6908.
9 N. Guimond and K. Fagnou, *J. Am. Chem. Soc*., 2009, **131**, 12050.
10 T. Fukutani, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Commun*., 2009, 5141.
11 P. C. Too, S. H. Chua, S. H. Wong and S. Chiba, *J. Org. Chem*., 2011, **76**, 6159.
12 R. K. Chinnagolla, S. Pimparkar and M. Jeganmohan, *Org. Lett*., 2012, **14**, 3032.
13 D. B. Zhao, F. Lied and F. Glorius, *Chem. Sci*., 2014, **5**, 2869.
14 B. Sun, T. Yoshino, M. Kanai and S. Matsunaga, *Angew. Chem., Int. Ed*., 2015, **54**, 12968.
15 Q. Lu, S. Greßies, S. Cembellin, F. Klauck, C. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed*., 2017, **56**, 12778.
16 X.-C. Li, C. Du, H. Zhang, J.-L. Niu and M.-P. Song, *Org. Lett*., 2019, **21**, 2863.
17 S. Kumar, A. M. Nair and C. M. R. Volla, *Org. Lett*., 2020, **22**, 2141.
18 D. S. Deshmukh, N. Gangwar and B. M. Bhanage, *Eur. J. Org. Chem.*, 2019, 2919.
19 S. C. Chuang, P. Gandeepan and C. H. Cheng, *Org. Lett*., 2013, **15**, 5750.
20 W. J. Han, G. Y. Zhang, G. X. Li and H. M. Huang, *Org. Lett*., 2014, **16**, 3532.
21 F. Wang, Q. Wang, M. Bao and X. Li, *Chin. J. Catal*., 2016, **37**, 1423.
22 B. Qi, L. Fang, Q. Wang, S. Guo, P. Shi, B. Chu and J. Zhu, *Tetrahedron Lett*., 2020, **61**, 151771.
23 C. Kornhaaß, C. Kuper and L. Ackermann, *Adv. Synth. Catal*., 2014, **356**, 1619.
24 M. Sen, D. Kalsi and B. Sundararaju, *Chem. – Eur. J*., 2015, **21**, 15529.
25 S. Prakash, R. Kuppusamy and C. Cheng, *ChemCatChem*, 2018, **10**, 683.
26 D. A. Loginov, L. S. Shul’pina, D. V. Muratov and G. B. Shul’pin, *Coord. Chem. Rev*., 2019, **387**, 1.
27 G. Albano, A. Punzi, M. A. M. Capozzi and G. M. Farinola, *Green Chem.*, 2022, **24**, 1809.
28 C. Fischmeister and H. Doucet, *Green Chem*., 2011, **13**, 741.
29 S. Santoro, F. Ferlin, L. Luciani, L. Ackermann and L. Vaccaro, *Green Chem*., 2017, **19**, 1601.
30 P. Gandeepan, N. Kaplaneris, S. Santoro, L. Vaccaro and L. Ackerman, *ACS Sustainable Chem. Eng*., 2019, **7**, 8023.

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