Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Organic & Biomolecular Chemistry

RSCPublishing

COMMUNICATION

An expedient approach to 1,2-dihydroisoquinoline derivatives via Cobalt catalysed *6-endo dig* cyclization followed by Mannich condensation of *o*-alkynylarylaldimines

Cite this: DOI: 10.1039/x0xx00000x

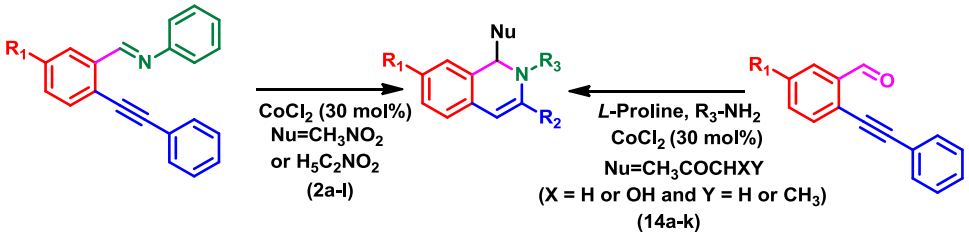
Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Urvashi,[a] *Gaurav K. Rastogi,*[a] *Sandeep K. Ginotra* [b,] *Alka Agarwal* [c] *and Vibha Tandon*[a,d]

A highly effective *6-endo dig* cyclisation of *o*-alkynylaldimines to 1,2-dihydroisoquinolines has been described via direct and nitro Mannich condensation using inexpensive and readily available cobalt chloride as catalyst. This strategy provides an effective procedure for the synthesis of substituted 1,2-dihydroisoquinolines derivatives in moderate to high yields. An addition of pronucleophiles, such as nitromethane, acetone and α-hydroxyacetone to *o*-alkynylarylaldimines have been achieved via isoquinolinium intermediate.

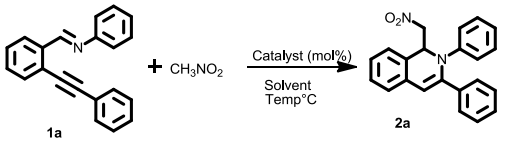


The isoquinoline, dihydro and tetrahydroisoquinoline ring systems are well known and found as core nucleus in wide variety of natural products and pharmaceutical agents,[1] but the fused 1,2-dihydroisoquinoline systems are of paramount significance as they represent biologically active pharmacophores.[2] These privileged scaffolds are versatile intermediates for the synthesis of therapeutic agents such as Lck kinase,[3a] JNK inhibitors,[3b] Rho-kinase,[3c] PTB-1B inhibitor,[4] anti HIV,[5] smooth muscle relaxant (papaverine),[6] antitumor (saframycin-B),[7a] topoisomerase I inhibitor (indenoisoquinoline),[7b] and anticancer agents (cribrostatin).[7c] Over the last few years, many efforts were made to construct these N-heterocyclic scaffolds using different synthetic methodologies.[8,9] Several metal/nonmetal catalyzed reactions emerged as the efficient processes to construct 1,2-dihydroisoquinoline skeleton with broad range of functional moieties.[10-17] Among the various methods, the most common are functionalization of preformed isoquinoline core[10] and *6-endo-dig* ring closure reactions of 2-(1-alkynyl) arene carboxaldehyde imines[11-17] (preformed or generated in situ from *o*-alkynyl benzaldehydes and amines) in the presence of various pronucleophiles, either in the absence of a catalyst or in the presence of bond coordinating Lewis acid catalysts.[12-16] Especially, silver catalyzed ring closure reactions enjoyed more success.[12] However, these reactions, except few examples,[13] are mainly restricted to expensive second and third row transition metals (Ag,[12] Pd,[14] In,[15,16a] Au[16]). Thus the development of inexpensive metal catalyst is expected.

Cobalt salts and complexes are well known to have catalytic abilities in coordinating with the carbon-carbon multi bond for π-complex and to produce many valuable products through enyne-coupling[18] (Pauson-Khand reaction), Alder-Ene[19] and many other reactions. The low cost, ability to activate alkyne and alkene at the low catalyst loading, under mild conditions and our interest to explore the inexpensive metal catalysis[20], prompted us to utilize the relatively inexpensive cobalt catalyst for the construction of the 1,2-dihydroisoquinoline skeleton via *6-endo-dig* ring cyclization.

Herein, we wish to report that inexpensive cobalt (II) chloride catalyzes the intramolecular cycloaddition of non-activated *o*-alkynylarylaldimines followed by addition of pronucleophile (nitromethane, acetone and α-hydroxyacetone) to afford the substituted 1,2-dihydroisoquinolines in good yields. To find out the optimal reaction condition, we optimized the coupling of (*E*)-N-phenyl-1-(2-(phenylethynyl)phenyl)methanimine

Table 1. Catalyst and conditions screened for the *6-endo-dig* cyclization nitro Mannich reaction[a]

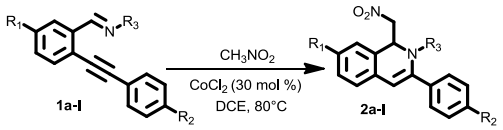


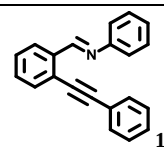
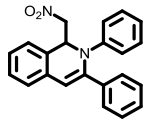
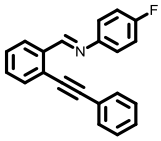
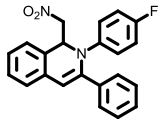
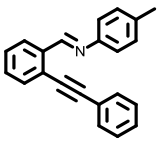
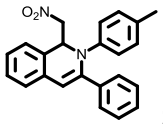
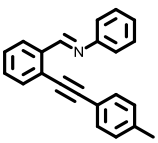
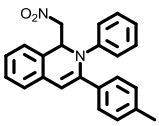
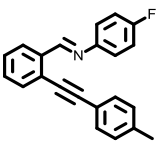
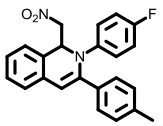
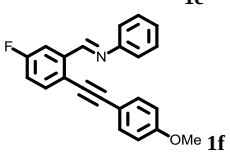
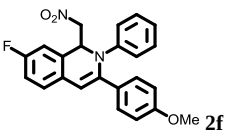
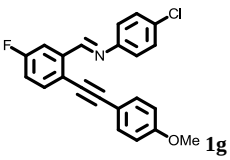
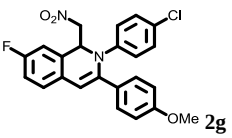
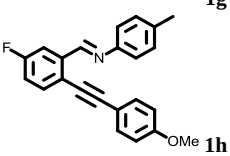
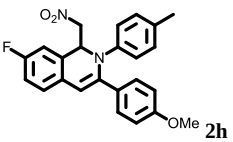
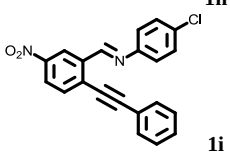
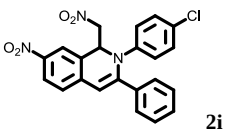
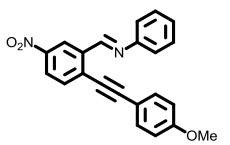
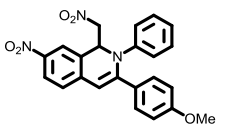
Entry	Lewis acids	Solvent	Time (h)	Temp (°C)	Yield (%)[b]
1	$CoCl_2$ [c]	DCE	24	80	70
2	$CoCl_2$ [d]	DCE	08	80	79
3	$CoCl_2$ [e]	DCE	06	80	90
4	$CoCl_2$ [e]	DCE	NR	RT	NR
5	$CoCl_2$ [e]	DCE	08	50	56
6	$CoCl_2$ [e]	EtOH	08	80	52
7	$CoCl_2$ [e]	DCM	26	40	67
8	$CoCl_2$ [e]	ACN	10	80	54
9	$CoCl_2$ [e]	THF	25	80	57
10	$CoCl_2$ [e]	DMSO	06	80	65
11	$(NEt_3)_4CoCl_4$ [c]	DCE	44	80	63
12	$Co(ac)_2$ [c]	DCE	48	80	45
13	AgOTf [c]	DCE	06	80	75
14	$AgNO_3$ [c]	DCE	04	80	60
15	$PdCl_2$ [c]	DCE	20	80	55
16	$PdCl_2(PPh_3)_2$ [c]	DCE	06	80	48
17	$CoCl_2$ [e] +CuI [c]	DCE	08	80	52

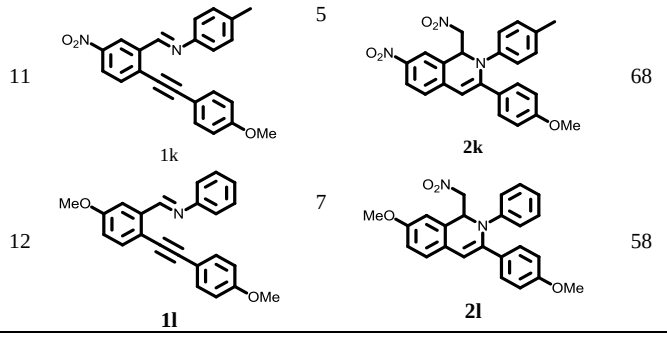
a)The reaction was carried out using **1a** (1 equiv.) and nitromethane (2 equiv.) in the presence of different Lewis acids in different solvents at indicated temperatures; b) Isolated yield; c) 10mol%; d) 20 mol%; e) 30 mol%; NR= no reaction; RT= room temperature.

1a (generated in situ from 2-(phenylethynyl)benzaldehyde and amines) with nitromethane to generate 1-(nitromethyl)-2,3-diphenyl 1,2-dihydroisoquinoline **2a** via *6-endo-dig* ring cyclization (Table 1). The optimization of reaction condition was carried out with respect to different Lewis acids, reaction temperatures and solvents. First, we screened different Lewis acids in 1,2-dichloroethane as solvent for nitro-Mannich reaction imine **1a** at 80 °C (Table 1, entries 1, 11-17). In the current transformation, the results showed that $CoCl_2$ and AgOTf, in contrast to the reaction timing, were competent catalysts to give good yields (Table 1, entries 1 & 13), whereas other Lewis acids ($AgNO_3$, $PdCl_2$, $PdCl_2(PPh_3)_2$) were somewhat inferior (Table 1, entries14-16). Cobalt is an inexpensive metal and known to activate alkynes[18-19], prompted us to explore different cobalt catalysts, but $(NEt_3)_4CoCl_4$ and $Co(ac)_2$ were found to be inferior than $CoCl_2$ in 1,2-dichloroethane at 80ºC (Table 1, entries 11-12). The catalyst loading was found to have significant effect on the conversion (Table 1, entries 1-3) of the reaction. Lowering the catalyst loading decreases the reaction rate and yield as well. Thus 30 mol% $CoCl_2$ was found to be optimum for highest conversion of **1a** to **2a** in 1,2-dichloroethane at 80°C. Efficiency of the catalyst diminished in other solvents such as ethanol, dichloromethane, acetonitrile, tetrahydrofuran, and dimethylsulfoxide (Table 1; entries 6-10). Reduction in the reaction temperature results in a lower yield (56%) whereas, reaction did not proceed at all at r t (Table 1, entries 4 & 5). The presence of Cu as co-catalyst (10 mol% CuI) afforded low conversion of substrate (Table 1, entry 17).

Table 2. Substrate scope of different aldimines (**1a-l**), with nitromethane in the presence of $CoCl_2$.[a]



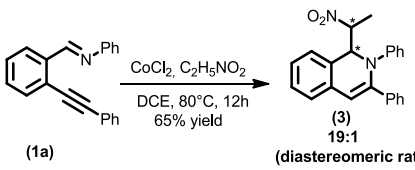
Entry	Substrate	Time(h)	Product	Yield (%)[b]
1	 **1a**	6	 **2a**	90
2	 **1b**	5	 **2b**	65
3	 **1c**	7	 **2c**	80
4	 **1d**	7	 **2d**	62
5	 **1e**	6	 **2e**	78
6	 **1f**	5.5	 **2f**	66
7	 **1g**	5	 **2g**	72
8	 **1h**	6	 **2h**	66
9	 **1i**	7	 **2i**	70
10	 **1j**	5	 **2j**	62



a) The reaction was carried out using **1a-l** (1 equiv.) and nitromethane (2 equiv.) in the presence of 30 mol% $CoCl_2$ in 1,2-dichloroethane at 80 °C, b) Isolated yield.

The scope of the reaction, determined with respect to variety of imines (generated in situ from ortho-arylalkynyl-3-carbaldehydes and amines) under the optimized condition (Table 1, entry 3) is illustrated in Table **2**. Electron poor as well as electron rich imines underwent *6-endo-dig* cyclization to provide structurally diverse 1,2-dihydroisoquinoline derivatives in moderate to excellent yields (Table 2, entries 6-12). A number of functionalities such as fluorine, nitro and methoxy moieties, on *o*-arylalkynyl-3-carbaldehydes as well as on amine part, are compatible with the reaction condition. Unsubstituted or unactivated aldimine **1a** provided product **2a** in 90% yield (Table 2, entry 1). However, imine **1b, 1e** having electron withdrawing *p*-fluorophenyl substituent at R_3 afforded the required product **2b** and **2e** in 65 to 78% yields, respectively (Table 2, entries 2 & 5).The imines **1f-k** having electron withdrawing group at R_1 afforded required products in moderate yields (62 to 72%, Table 2, entries 6-11). Electron donating methoxy group at R_1 afforded desired product **2l** comparatively in lower yield (58%, Table 2, entry 12). Electron donating, - CH_3 group at R_3 gave better yield than electron withdrawing F group at R_3 (Table 2, entry 2 vs 3). The presence of *p*-methoxyphenyl group at alkyne (R_2) does not have much effect on conversion of **1** to the desired product **2**, thus giving almost similar yields (Table 2, entries 7,8,10,11,12). Under the optimized condition, the reaction of **1a** with nitroethane in the presence of 30 mol% $CoCl_2$ afforded the desired product **3** in 65% yield, as mixture of diastereomers with excellent diastereomeric ratio (19:1) (Scheme 1).

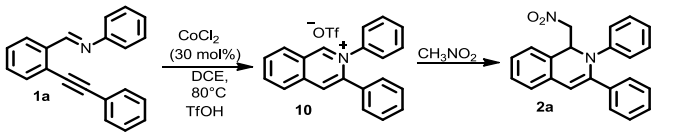
Scheme 1. Addition of nitroethane to (*E*)-N-phenyl-1-(2-(phenylethynyl)phenyl)methanimine (**1a**) in the presence of $CoCl_2$.[a]



a)The reaction was carried out using **1a** (1 equiv.) and nitroethane (2 equiv.) in the presence of 30 mol% $CoCl_2$ in 1,2-dichloroethane at 80°C.

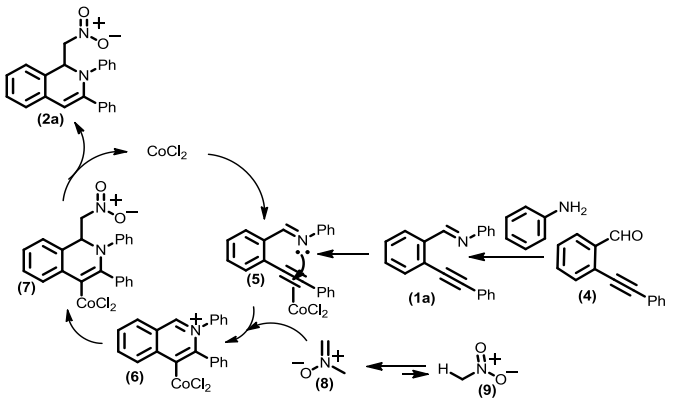
A plausible mechanism for the cobalt (II) chloride catalysed nitromethane addition via *6-endo dig* cyclisation of *o*-alkynylaldimines is proposed in the Scheme **3**. To gain the insight of the proposed catalytic system, we examined the reaction of **1a** with $CoCl_2$ (1equiv.) in the presence of TfOH in DCE at 80°C to get the isoquinolinium triflate salt (**10**) in 98% yield which was then treated with nitromethane (Scheme 2).

Scheme 2. Isoquinolinium salt[a]



a) The reaction was carried out using **1a** in the presence of 30 mol% $CoCl_2$ in 1,2-dichloroethane at 80°C for 4h. **10** was treated with nitromethane for 2h.

Delightfully, the anticipated 1,2-dihydroisoquinoline product **2a** was obtained in 60% yield. This result indicates that catalytic cycle begins with the activation of carbon-carbon triple bond of o-alkynylaldimines (**1a**) by the π-coordination of the Cobalt salt to form a complex **5**, followed by cyclisation to produce cobalt isoquinolinium intermediate **6**. Cobalt complex **6** generates intermediate **7** upon reacting with pronucleophile, aci-nitro methane **8** formed by tautomerisation of nitromethane **9.** Cobalt (II) salt was then regenerated and obtained 1,2-dihydro-isoquinoline product **2a**.

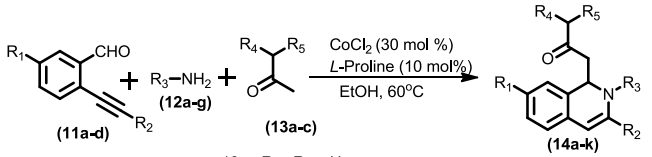


Scheme 3: Plausible mechanism for $CoCl_2$ catalysed nitromethane addition to **1a**.

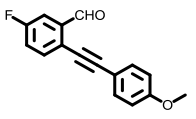
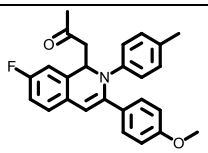
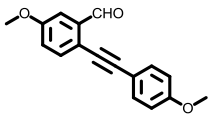
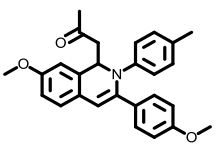
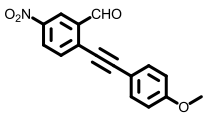
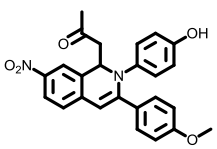
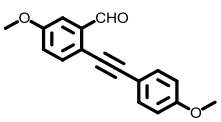
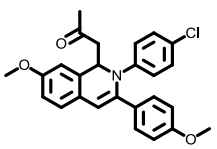
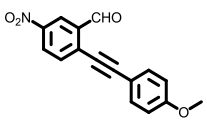
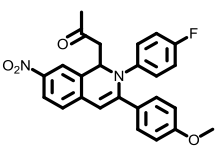
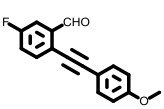
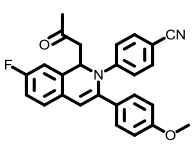
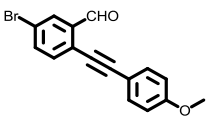
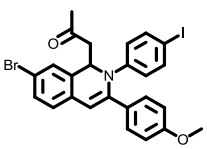
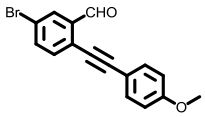
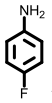
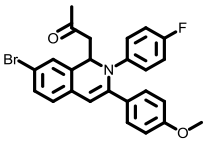
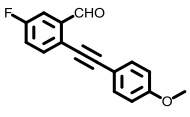
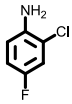
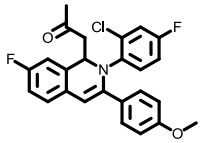
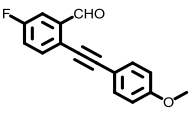
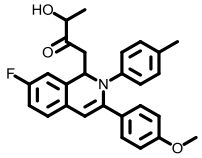
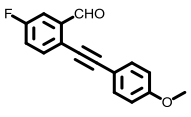
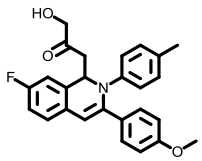
To further extend the scope of $CoCl_2$ catalysed 6-*endo-dig* cyclization. We screened other pronucleophiles such as acetone, hydroxy acetone and 3-hydroxy-2-butanone for the reaction. Gratifyingly, the one pot tandem transformation of *ortho*-arylalkynyl-3-carbaldehydes, anilines and ketone with anhydrous cobalt chloride (30 mol%) in the combination with catalytic amount of *L*-Proline (10 mol%) in ethanol at 60 °C gave good yields of 1,2 dihydroisoquinoline derivatives (**14a-k**) and reactions were completed in 4-16 h. The reaction scope is summarized in Table **3**. In this multicomponent reaction, activated and non-activated (Table 3, entries 1-8) imines (generated in situ from 2-alkynylbenzaldehydes **11** and anilines **12**) that bearing the electron withdrawing and electron donating group at imine nitrogen atom leads to 1,2 dihydroisoquinoline derivatives in good to excellent yields (64-89%). For example, *p*-toluidine **12a** reacted with 2-alkynylbenzaldehyde **11a** or **11b** and acetone to give the corresponding product **14a** or **14b** in excellent yields (88-89%, Table 3, entries 1 & 2). However, *p*-hydroxy aniline **12b** gave 64% yield

(Table 3, entry 3). On the other hand, all the other anilines mono/di-substituted with electron withdrawing groups gave almost similar yields (68-82%, Table 3, entries 4-9). It was observed that substitution (F and OMe) at R_1 in 2-alkynylbenzaldehyde **11** have no effect on the outcome of the reaction and gave similar yields (Table 3, entries 1 vs 2). Whereas on replacing the acetone with non-symmetric ketone such as hydroxyl acetone (**13b)** and 3-hydroxy-2-butanone (**13c**), the reaction of 2-alkynylbenzaldehyde **11a** with *p*-toluidine (**12a)** proceeded in a highly regioselective manner and afforded only one isomer of corresponding 1,2-dihydroisoquinoline **14j** & **14k** in 51% & 56% yields, respectively (Table 3, entries 9 & 10). The structure of 1-(2-(2-chloro-4-fluorophenyl)-7-fluoro-3-(4-methoxyphenyl)-1,2-dihydroisoquinolin -1-yl)propan-2-one (**14i)** was unambigously confirmed by X-ray diffraction analysis of single crystal (Fig. 1).

Table 3. Reaction of different substituted 2-arylalkynyl-benzaldehyde (**11a-g)**, aniline (**12a-g)** and proneucleophile (**13a)** in presence of $CoCl_2$ and *L*-Proline.[a,b]



13a : R_4 , R_5 = H
13b : R_4 = H , R_5 = OH
13c : R_4 = CH_3 , R_5 = OH

Entry	Substrate **11**	Substrate **12**	Product **14**	Yield (%)[c]
1	 **11a**	 **12a**	 **14a**	88
2	 **11b**	 **12a**	 **14b**	89
3	 **11c**	 **12b**	 **14c**	64
4	 **11b**	 **12c**	 **14d**	78
5	 **11c**	 **12d**	 **14e**	79
6	 **11a**	 **12e**	 **14f**	68
7	 **11d**	 **12f**	 **14g**	82
8	 **11d**	 **12d**	 **14h**	81
9	 **11a**	 **12g**	 **14i**	77
10	 **11a**	 **12a**	 **14j**	51
11	 **11a**	 **12a**	 **14k**	56

a) The reaction was carried out using 2-aryl-(1-alkynyl)benzaldehyde (1 equiv.) and aniline (1 equiv.), ketone (5 equiv.) in the presence of 30 mol% $CoCl_2$ and 10% *L*-proline in ethanol at 60°C, b) *L*-Proline-catalysed reactions gave racemic products, c) Isolated yields based on 2-aryl-(1-alkynyl)benzaldehyde.

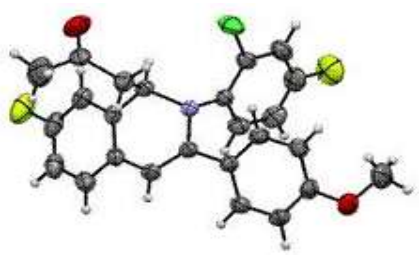
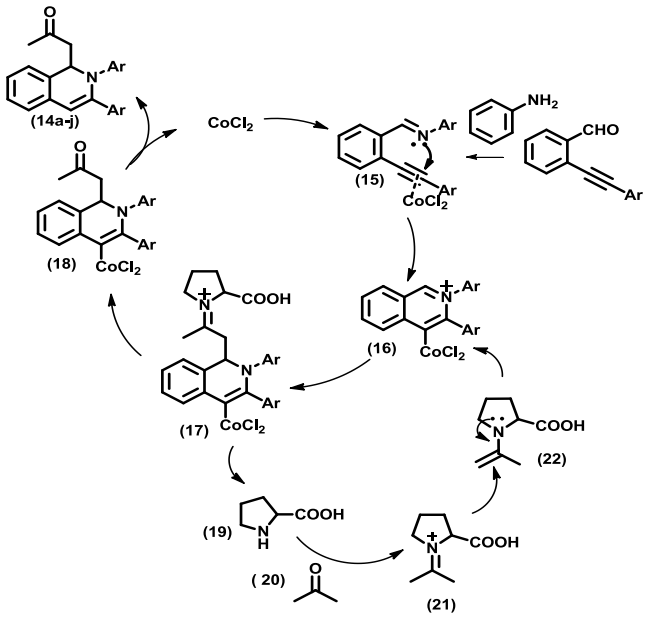


Fig.1. X-Ray crystallographic ORTEP illustration of 1,2-dihydroisoquinoline **14i.**

The plausible mechanism of the cobalt chloride catalysed cyclization and tandem addition via three component reaction is

shown in Scheme **4**. It is proposed that the current transformation is proceeded via dual activation of electrophile and nucleophile by a metal and enamine catalyst respectively. The imine **15 (**generated in situ from 2-alkynylbenzadehyde and aniline) formed cyclised isoquinolinium intermediate **16** by intramolecular attack of the nitrogen atom on the electron deficient alkyne (activated via the coordination of the triple bond with cobalt chloride). Subsequently isoquinolinium intermediate **16** attacked by the enamine **22** (generated by the reaction of *L*-proline and acetone) to generate **17** which upon hydrolysis results in regeneration of *L*-proline and intermediate **18,** releasing 1,2-dihydroisoquinoline and cobalt chloride at the final stage.



Scheme 4. The possible mechanism of the cobalt chloride catalysed tandem addition and cyclisation of 2-aryl-(1-alkynyl) benzaldehyde.

Conclusions

In summary, we have developed a cost effective $CoCl_2$ based reaction system for direct addition of nitromethane to imine to synthesize highly functionalized 1,2-dihydroisoquinoline derivatives in good to excellent yields. We have also shown that one pot combination of $CoCl_2$ and *L*-proline is highly effective for the synthesis of 1,2-dihydroisoquinolines via multicomponent reactions of 2-alkynylbenzal-dehyde, amines and different ketones. A plausible mechanism for both reactions, based on direct addition and/or the dual activation concept, with/without *L*-proline as co-catalyst is proposed. The investigation to uncover the related transformations and application to natural products synthesis are in progress in our laboratory.

Acknowledgements

The authors are grateful to the Department of Science and Technology for financial support and USIC, University of Delhi for providing Instrumentation.

Supplementary data

Copies of ^{1}H NMR, ^{13}C NMR of all new compounds and CIF for compound **14** i are provided. This material is available free of charge in the online version.

Notes and References

[a]*Chemical Biology Research Laboratory, Department of Chemistry, University of Delhi, Delhi-110007, India.*
[b]*Syngene International Ltd, Biocon Park,Plot # 2 & 3, Phase IV, Bommasandra, Jigani Link Road,Bengaluru, Karnataka- 560099, India.*
[c]*Department of Medicinal Chemistry, Banaras Hindu University, Varanasi-221005, Utter Pradesh, India.*
[d]*Special Centre for Molecular Medicine, Jawaharlal Nehru University, Delhi–110067, India.*

1. (a) J. D. Phillipson, M. F. Roberts and M. H. Zenk, The Chemistry and Biology of Isoquinoline, Alkaloids, Springer-Verlag: New York, 1985; (b) K. W. Bentley, The Isoquinoline Alkaloids, Harwood Academic: Australia, 1998, Vol 1; (c) P. Ramesh, N. S. Reddy, and Y. Venkateswarlu, *J. Nat. Prod.*, 1999, ***62***, 780; (d) S. Oi, K. Ikedou, K. Takeuchi, M. Ogino, Y. Banno, H. Tawada, and T. Yamane, PCT Int. Appl.2002, *600* pp (WO 2002062764 A1); (e) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, ***102***, 1669; (f) M. Chrzanowska, and M. D. Rozwadowska, *Chem. Rev.*, 2004, ***104***, 3341; (g) K. Inoue, U. Kulsum, S. A. Chowdhury, S. I. Fujisawa, M. Ishihara, I. Yokoe and H. Sakagami, *Anticancer Res.*, 2005, ***25***, 4053; (h) S. Su,and J. A. Jr. Porco, *Org. Lett.*, 2007, ***9***, 4983; (i) J. F. Gonzales, E.de la Cuesta and C. Avendano, *Bioorg. Med. Chem.*, 2007, ***15***, 112.
2. (a) D. A. Handley, R. G. V. Valen, M. K. Melden, W. J. Houlihan, and R. N. Saunders, *J. Pharmacol. Exp. Ther.*, 1988, ***247***, 617; (b) W. J. Houlihan, S. H. Cheon, V. A. Parrino, D. A. Handley, and D. A. Larson, *J. Med. Chem.*, 1993, ***36***, 3098; (c) W. J. Houlihan, P. G. Munder, D. A. Handley, S. H. Cheon, and V. A. Parrino, *J. Med. Chem.*, 1995, ***38***, 234; (d) D. Scholz, H. Schmidt, E. E. Prieschl, R. Csonga, W. Scheirer, V. Weber, A. Lembachner, G. Seidl, G. Werner, P. Mayer, and T. Baumruker, *J. Med. Chem.*, 1998, ***41***, 1050; (e) S. Zheng, C. Chan, T. Furuuchi, B. J. D. Wright, B. Zhou, J. Guo and S. D. Danishefsky, *Angew. Chem., Int. Ed.*, 2006, ***45***, 1754; (f) J. Chen, X. Chen, B.C. Michele and J. Zhu, *J. Am. Chem. Soc.*, 2006, ***128***, 87; (g) G. Vincent and R. M. Williams, *Angew. Chem., Int. Ed.*, 2007, ***46***, 1517.
3. (a) R. J. Snow, M. G. Cardozo, T. M. Morwick, C. A. Busacca, Y. Dong, R. J. Echner, S. Jakes, S. Kapadia, S. Lukas, N. Moss, M. Panzenbeck, G. W. Peet, J. D. Peterson, A. P. Prokopowiez, R. Sellati and M. A. Tschantz, *J. Med. Chem.*, 2002, ***45***, 3394; (b) Y. Asano, S. Kitamura, T. Ohra, F. Itoh, M. Kajino, T. Tamura, M. Kaneko, S. Ikeda, H. Igata, T. Kawamoto, S. Sogabe, S. Matsumoto, T. Tanaka, M. Yamaguchi, H. Kimura and S. Fukumoto, *Bioorg. Med. Chem.*, 2008, ***16***, 4699; (c) T. Bosanac, E. R. Hickey, J. Ginn, M. Kashem, S. Kerr, S. Kugler, X. Li, A. Olague, S. Schlyer and E. R. R. Young, *Bioorg. Med. Chem. Lett.*, 2010, ***20***, 3746.
4. Z. Chen and J. Wu, *Org Lett.*, 2010, ***12***, 4856.
5. (a) M. V. Reddy, M. R. Rao, D. Rhodes, M. S. Hansen, K. Rubins, F. D. Bushman, Y. Venkateswarlu and D. J. Faulkner, *J. Med. Chem.*, 1999, ***42***, 1901; (b) K. Iwasa, M. Moriyasu, Y. Tachibana, H. S. Kim, Y. Wataya, W. Wiegrebe, K. F. Bastow, L. M. Cosentino, M. Kozuka and K. H. Lee, *Bioorg. Med. Chem.*, 2001, ***9***, 2871.
6. T. Kaneda, Y. Takeuchi, H. Matsui, K. Shimizu, N. Urakawa and S. Nakajyo, *J. Pharmacol. Sci.*, 2005, ***98***, 275.

7. (a) Y. Mikami, K. Yokoyama, H. Tabeta, K. Nakagaki and T. Arai, *J. Pharm. Dyn.*, 1981, ***4***, 282; (b) C. Marchand, S. Antony, K. W. Kohn, M. Cushman, A. Ioanoviciu, B. L. Staker, A. B. Burgin, L. Stewart and Y. Pommier, *Mol. Cancer Ther.*, 2006, ***5***, 287; (c) J. F. Gonzales, E. de la Cuesta and C. Avendano, *Bioorg. Med. Chem.*, 2007, ***15***, 112.
8. (a) K. R. Roesch and R. C. Larock, *Org.Lett.*, 1999, ***1***, 553; (b) K. R. Roesch, H. Zhang and R. C. Larock, *J. Org. Chem.*, 2001, ***66***, 8042; (c) K. R. Roesch and R. C. Larock, *J. Org. Chem*., 2002, ***67***, 86; (d) Q. Huang, J. A. Hunter and R. C. Larock, *J. Org. Chem*., 2002, ***67***, 3437; (e) G. Dai and R. C. Larock, *J. Org. Chem*., 2002, ***67***, 7042; (f) G. Dai, and R. C. Larock, *J. Org. Chem.*, 2003**,** ***68***, 920; (g) Q. Huang and R. C. Larock, *J. Org. Chem*., 2003, ***68***, 980.
9. a) E. J. Corey, D. Y. Gin and R. S. Kania, *J. Am. Chem. Soc.*, 1996**,** ***118***, 9202; b) G. Vincent and R. M. Williams, *Angew. Chem., Int. Ed.*, 2007, ***46***, 1517; (c) M. Chaumontet, R. Piccardi and O. Baudoin, *Angew. Chem. Int. Ed.*, 2007, ***48***, 179.
10. a) G. E. Lee, H. S. Lee, S. D. Lee, J.-H. Kim, W.-K. Kim and Y.-C. Kim, *Bioorg. Med. Chem. Lett.*, 2009, ***19***, 954; (b) P. Hewavitharanage, E. O. Danilov and D. C. Neckers, *J. Org. Chem.*, 2005, ***70***, 10653.
11. N. Asao, K. Iso and S. S. Yudha, *Org lett*., 2006, ***72***, 1233.
12. (a) N. Asao, S. S. Yudha, T. Nogami and Y. Yamamoto, *Angew. Chem.,Int. Ed.*, 2005, ***44***, 5526; (b) Q. Ding, X. Yu and J. Wu, *Tetrahedron Lett.*, 2008, ***49***, 2752; (c) Z. Chen, X. Yang and J. Wu, *Chem. Commun.*, 2009, 3469; and reference cited therein; (d) H. Waldmann, L. Eberhardt, K. Wittstein and K. Kumar, *Chem. Comm.* 2010, ***46***, 4622; (e) N. A. Markina, R. Mancuso, B. Neuenswander, G. H. Lushington and R. C. Larock, *ACS Comb Sci*, 2011,***13***, 265; (f) A. K. Verma, D. Choudhary, R. K. Saunthwal, V. Rustogi and M. Patel, *J. Org. Chem.*, 2013, ***78***, 4386; (g) A. K. Verma, D. Choudhary, R. K. Saunthwal, V. Rustogi, M. Patel and R. K. Tiwari, *J. Org. Chem*, 2013, ***78***, 6657; (h) B. Jiang, Y. Zhou, Q. Kong, H. Jiang, H. Liu and J. Li, *Molecules*, 2013, ***18***, 814; (i) S. U. Dighe and S. Batra, *Tetrahedron*, 2013, ***69,*** 9875.
13. a) C. Peng, J. Cheng and J. Wang, *Adv. Synth. Catal.*, 2008, ***350***, 2359; (b) Y. Wu, Y. Zhang, Y. Jiang and D. Ma, *Tetrahedron Lett*., 2009, ***50***, 3683; (c) H-C. Ouyang, R-Y. Tang, P. Zhong, X.-G. Zhang, and J.-H. Li, *J. Org. Chem*., 2011, ***76***, 223.
14. a) Q. Ding, B. Wang and J. Wu, *Tetrahedron***,** 2007, ***63***, 12166; (b) M. Yu, Y. Wang, C. -J. Li and X. Yao, *Tetrahedron Lett***.,** 2009, ***50***, 6791; (c) H. Zhou, H. Jin, S. Ye, X. He and J. Wu, *Tetrahedron Lett.*, 2009, ***50,*** 4616.
15. R. Yanada, S. Obika, H. Kono, and Y. Takemoto, *Angew. Chem. Int. Ed*., 2006, ***45***, 3822. 16. (a) S. Obika, H. Kono, Y. Yasui, R. Yanada and Y. Takemoto, *J. Org. Chem.*, 2007, ***72***, 4462; (b) Q. Ding, X. Yu and J. Wu, *Tetrahedron lett.*, 2008**,** ***49***, 2752; (c) N. T. Patil, A. K. Mutyala, G. V. V. Lakshmi, P. V. K. Raju and B. Sridhar, *Eur. J. Org. Chem.*, 2010, 1999; (d) R. R. Jha, R. K. Saunthwal and A. K. Verma, *Org. Biomol. Chem*., 2014, ***12***, 552.
17. (a) Q. Ding, Z. Wang and J. Wu, *J. Org. Chem.*, 2009, ***74***, 921; (b) S. U. Dighe and S. Batra, *Tetrahedron*, 1913, ***69,*** 9875.
18. (a) S. E. Gibson and N. Mainolfi, *Angew. Chem. Int. Ed*., 2005, ***44***, 3022; (b) T. Shibataa, *Adv. Synth. Catal*., 2006, ***348***, 2328; (c) R. Santhoshkumar, S. Mannathan, and C.-H. Cheng, *Org. Lett*., 2014, ***16***, 4208.
19. G. Hilt, and J. Treutwein, *Angew. Chem. Int. Ed.*, 2007, ***46***, 8500.
20. (a) S. K. Ginotra, B. S. Chhikara, M. Singh, R. Chandra and V. Tandon, *Chem. Pharma. Bull.*, 2004**,** ***52***, 989; (b) S. K. Ginotra and V. K. Singh, *Tetrahedron*, 2006**,** ***62***, 3573; (c) M. Raj, Vishnumaya, S. K. Ginotra and V. K. Singh, *Org. Lett.*, 2006, *8*, 4097; (d) S. K. Ginotra and V. K. Singh, *Org. Biomol. Chem.*, 2006**,** ***4***, 4370; (e) S. K. Ginotra and V. K. Singh, *Org. Biomol. Chem.*, 2007**,** ***5***, 3932.

