Alanine triazole iridium-catalyzed C-N bond formation through borrowing hydrogen strategy

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PII: S0040-4039(16)31130-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.08.093
Reference: TETL 48064

To appear in: *Tetrahedron Letters*

Received Date: 24 July 2016
Revised Date: 29 August 2016
Accepted Date: 30 August 2016

Please cite this article as: Yu, X., Zhao, R., Wan, H., Yang, Y., Wang, D., Alanine triazole iridium-catalyzed C-N bond formation through borrowing hydrogen strategy, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.08.093

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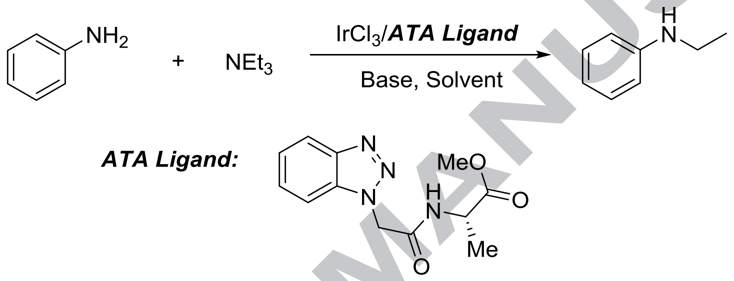

An efficient synthesis of secondary amines has been described through alanine triazole iridium-catalyzed C-N bond formation of an aromatic amine and an alkyl amine by using the borrowing hydrogen strategy. In addition, it was observed that alanine triazole iridium is also an efficient catalyst to promote C-N bond formation of an aromatic amine and alcohols with good to excellent yields.

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Tetrahedron Letters
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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
alanine,
triazole,
iridium,
C-N bond formation,
borrowing hydrogen,

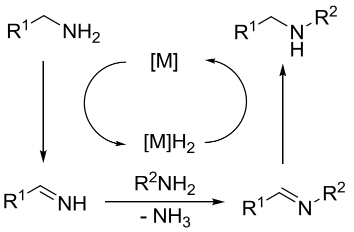
ABSTRACT

An efficient synthesis of secondary amines has been described through alanine triazole iridium-catalyzed C-N bond formation of an aromatic amine and an alkyl amine by using the borrowing hydrogen strategy. In addition, it was observed that alanine triazole iridium is also an efficient catalyst to promote C-N bond formation of an aromatic amine and alcohols with good to excellent yields.

1. Introduction

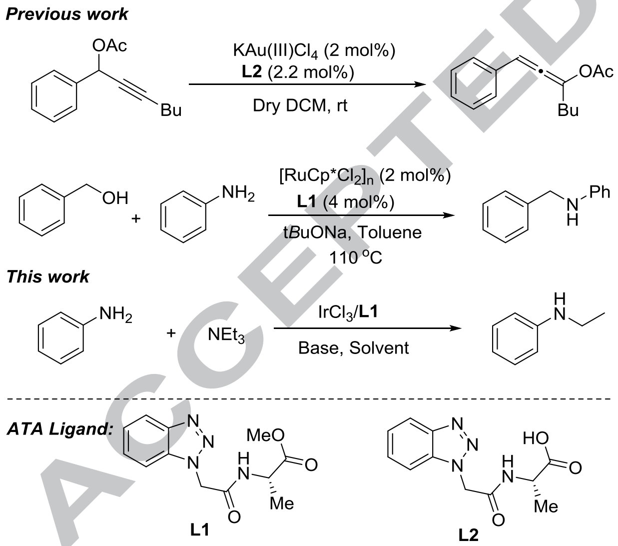
Hydrogen auto-transfer methodology, also called borrowing hydrogen, has recently received considerable attention for providing an economically, environmentally sensible alternative to the conventional alkylation of amines.[1] Under the conditions of the “borrowing hydrogen” methodology, alcohols are easily converted *in situ* into aldehydes or ketones, which are more reactive than alcohols and easily react with amines (Scheme 1).[2] However, the borrowing hydrogen reaction of amines with amines are much difficult. Based on the early amine exchange reactions,[3] Beller *et al.* demonstrated the first ruthenium-catalyzed synthesis of aromatic amines through arylation of aliphatic amines with anilines that proceeds under transfer hydrogenation conditions in 2007.[4] In 2009, Williams group developed iridium-catalyzed coupling of two amines with excellent selectivity in a high temperature, even when both amine components are capable of undergoing oxidation to an imine.[5] Largeron *et al.* reported a facile one-pot oxidation-imine formation-reduction route to secondary amines can be achieved electrolytically from primary amines.[6] Shimizu and Shimura showed Al_2O_3-supported Pd nanoclusters are also effective catalysts for the cross-coupling of amines.[7] In 2012, Shimizu group developed alumina-supported Pt nanoclusters act as an effective heterogeneous catalyst for N-alkylation of amines with other amines.[8] In 2013, Wang *et al.* synthesized iodo-bridged polymeric iridium complexes, which could serve as efficient catalysts in the selective amine cross-coupling reaction.[9] Later, Porcheddu *et al.* reported palladium-catalyzed dehydrogenative generation of imines from amines to synthesis of indoles via cross-couplings of amines with arylhydrazines.[10]

Scheme 1. The borrowing hydrogen reaction of an amine with another amine.



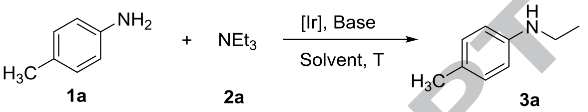
Traditionally, the catalyst plays a crucial role in borrowing hydrogen reactions. Among this, iridium complexe is one of the most effective and promising catalyst for this transformation.[11,12] Zhang group developed a novel iridium/acid co-catalyzed transfer hydrogenative coupling strategy to alkyl chain lengthened N-heteroaromatics from six-membered 2-alkyl cyclic amines and aldehydes.[13] Li *et al.* reported the synthesis of quinazolinones via acceptorless coupling of o-aminobenzamides with methanol catalyzed by metal−ligand bifunctional catalyst [Cp*Ir(2,2’-bpyO)(H_2O)].[14] Xu and co-workers described autocatalyzed dehydrative a-alkylation reactions of ketones with alcohols to selectively afford ketone or alcohol products by C-C bond formation with good yields and excellent chemselectivity.[15] Yu *et al*. reported the synthesis of secondary and tertiary amines from direct N-alkylation of primary and secondary amines with alcohols using a heterogeneous bimetallic Pt-Sn/γ-Al_2O_3 catalyst.[16] Zhao *et al.* reported a nice dynamic kinetic asymmetric amination of α-branched alcohols using borrowing hydrogen methodology through cooperative catalysis of an iridium complex with a chiral phosphoric acid.[17] In 2014, we developed several bisbenzoxazolyl and benzothienyl iridium(III) complexes, which exhibit good catalytic activity in borrowing hydrogen for C-C or C-N bond formation under mild conditions.[18] Recently, we synthesized a new type of ligand alanine triazole (ATA)(Scheme 2), which exhibited the improved stability and high catalytic activities in allene synthesis and hydration reaction.[19] In addition, preliminary studies showed alanine triazole ruthenium could be used borrowing hydrogen reactions. The concept of this research is the reactivity and stability of metal complexes largely depends on ligands coordinating with metal cations, where the reactivity and stability of metal were tuning through the ligands. When the triazole was introduced into amino acid derivatives, the designed new ligands maybe improve the reactivity and stability of metal catalyst through three kinds of functional groups or coordination sites: ester group, amino group and triazole part. Herein, we reported that alanine triazole iridium-catalyzed C-N bond formation reactions through borrowing hydrogen strategy, especially, for the selective transformations of aromatic amines and alkyl amines.

Scheme 2. Alanine triazole ligands (ATA) prompted reactions.



In our previous work, we found the new alanine triazole ligand (ATA) could great adjust reaction activity of gold and ruthenium, but the corresponding crystals are difficult to cultivate. Based on this, we have conducted the survey about the coordination of ATA ligand with iridium. Even we have paid our great efforts to these crystals but still failed. Since many catalysts are often prepared *in situ* and also get great success, we select the simple $IrCl_3$ as a catalyst and alanine triazole as the ligand to test reaction activity. Next, *p*-toluidine was chosen as a substrate to test the reaction. So, the borrowing hydrogen reaction of *p*-toluidine and triethylamine was carried on (Table 1). The experiment showed that $IrCl_3$/ATA showed much better catalytic activity. For a better yield, a series of screening of reaction conditions were explored. The best result was achieved with xylene as the solvent and sodium hydroxide as the base. It should be noted that $RuCl_3$/ATA almost could not catalyze this transformation (Table 1, entries 15-16).

Table 1. Screening of reaction conditions [a]

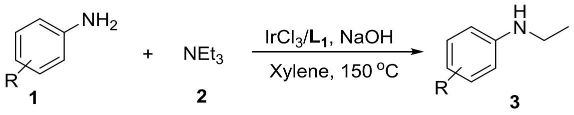


Entry	Catalyst	Base	Solvent	Yield[%][b]
1	$IrCl_3$	Na_2CO_3	Toluene	<5
2	$[Ir(COD)Cl]_2$	Na_2CO_3	Toluene	<5
3	$IrCl_3$/ATA	Na_2CO_3	Toluene	18
4	$[Ir(COD)Cl]_2$/ATA	Na_2CO_3	Toluene	11
5	$IrCl_3$/ATA	-	Toluene	<5
6	-	Na_2CO_3	Toluene	<5
7	$IrCl_3$/ATA	Cs_2CO_3	Toluene	26
8	$IrCl_3$/ATA	K_2CO_3	Toluene	17
9	$IrCl_3$/ATA	NaOH	Toluene	47
10	$IrCl_3$/ATA	NaOH	THF	32
11	$IrCl_3$/ATA	NaOH	DCM	<5
12	$IrCl_3$/ATA	NaOH	MeOH	<5
13	$IrCl_3$/ATA	NaOH	Xylene	65
14	$IrCl_3$/ATA	NaOH	Xylene [c]	83
15	$RuCl_3$/ATA	NaOH	Xylene	<5
16	$[RuCp^*Cl_2]_n$/ATA	NaOH	Xylene	28

[a] Reagents and conditions: **1a** (1 mmol), **2a** (1 mL), [Ir] loading (2 mol%, 0.02 mmol), $\mathbf{L_1}$ (2.4 mol%). Base (1.2 mmol), solvent (3 mL), reflux, 20 h. [b] Isolated yield. [c] $IrCl_3$ (10 mol%), $\mathbf{L_1}$ (12 mol%), 72 h.

Having identified suitable reaction conditions, we explored the above methods to other aromatic amines and triethylamine. As shown in Table 2, a wide range of substrates and functional groups are tolerated including methoxy, methyl, chloro, and *tert*-butyl substituents at the different positions of aromatic amines. Notably, 4-(*tert*-butyl)aniline was also a suitable substrate for this transformation, and the corresponding products was achieved in good yield under optimized conditions.

Table 2. Substrate expansion [a,b]



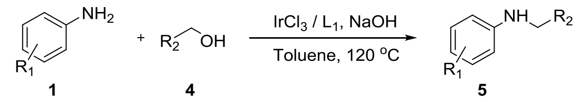
Entry	R	Yield[%][b]
1	*p*-Me	65 **(3a)**
2	H	66 **(3b)**
3	*p*-*t*Bu	79 **(3c)**
4	*p*-MeO	74 **(3d)**
5	*p*-Cl	58 **(3e)**
6	*m*-Cl	53 **(3f)**
7	*p*-F	65 **(3g)**
8	*o*-Br	57 **(3h)**
9	(2-)Py	54 **(3i)**
10	(1-)Np	69 **(3j)**

[a] Reagents and conditions: **1** (1.0 mmol), **2** (1 mL), $IrCl_3$ (2

mol), **L_1** (2.4 mol%), NaOH (1.2 mmol), xylene (3 mL), 150 ^{o}C, 20 h. [b] Isolated yield.

Encouraged by the promising results, we further employed the above methods to other phenyl amines and various alcohols. The obtained results were summarized in Table 3. The results showed different N-alkylated anilines were obtained with good to excellent yields by using this catalyst. The effect of substituents on the aromatic ring of amine has also been explored. It was observed that anilines with electron-donating or electron-withdrawing substituents could react under the optimal reaction conditions with the overall yield in 69% to 90%. Subsequently, the reactions of different alcohols were explored. Clearly, aromatic alcohols, including *p*-methylbenzyl alcohol, *p*-methoxylbenzyl alcohol, *p*-chlorobenzyl alcohol and furfuryl alcohol could react smoothly and give yields ranging from 72% to 93%.

Table 3. Alkylation of amines with alcohols [a, b]



Entry	R_1	R_2	Yield[%][b]
1	H	*n*Pr	74 **(5a)**
2	H	4-Me-Ph	87 **(5b)**
3	H	Ph	90 **(5c)**, 85 [c]
4	H	4-Cl-Ph	76 **(5d)**
5	4-Cl	Ph	73 **(5e)**
6	H	4-OMe-Ph	87 **(5f)**
7	4-OMe	Ph	82 **(5g)**
8	4-F	Ph	76 **(5h)**
9	3-Cl	4-Cl-Ph	74 **(5i)**
10	4-Cl	4-OMe-Ph	86 **(5j)**
11	2-Cl	Ph	69 **(5k)**
12	(2-)Py	Ph	85 **(5l)**
13	Ph	(2-)furyl	78 **(5m)**
14	(1-)Naph	Ph	84 **(5n)**

[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.1 mmol), $IrCl_3$ (2 mol%), **L_1** (2.4 mol%). NaOH (1.2 mmol), toluene (3 mL), 120 ^{o}C, 20 h. [b] Isolated yield. [c] $[RuCp^*Cl_2]_n$ /ATA (2 mol%), ref 19.

Conclusions

In summary, an efficient method for secondary amines synthesis has been developed through alanine triazole iridium-catalyzed cross-coupling of an aromatic amine and an alkyl amine by using the borrowing hydrogen strategy. In addition, it was observed that alanine triazole is also an effective ligand to promote Ir-catalyzed C-N bond formation reactions of an aromatic amine and alcohols with good to excellent yields. This provides an alternative methodology to synthesis of substituted amine derivatives.

Supporting Information

Supplementary data related to this paper is available free of charge via the Internet.

Acknowledgements

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (21401080), the Natural Science Foundation of Jiangsu Province of China (BK20130125), Jiangsu Talents Project (2013-JNHB-027), China Postdoctoral Science Foundation (2014M550262, 2015T80495) and MOE & SAFEA for the 111 Project (B13025).

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Highlights

- Borrowing hydrogen reaction of an aromatic amine and an alkyl amine
- C-N bond formation of an aromatic amine and alcohols
- Alanine triazole iridium-catalyzed secondary amines synthesis