RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

COMMUNICATION

Ethanol Promoted Titanocene Lewis Acid Catalyzed Synthesis of Quinazoline Derivatives

Received 00th January 20xx,
Accepted 00th January 20xx

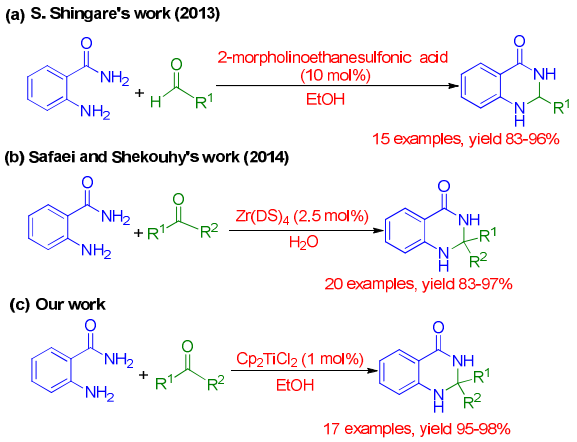
DOI: 10.1039/x0xx00000x

www.rsc.org/

Yanlong Luo, Ya Wu, Yunyun Wang, Huaming Sun, Zunyuan Xie, Weiqiang Zhang* and Ziwei Gao*

An efficient catalytic system by *in-situ* activation of kinetically inert titanocene dichloride with alcoholic solvent for synthesis of quinazoline derivatives was developed. 1 mol% Cp_2TiCl_2 at 30 ℃ afforded 17 examples of quinazoline derivatives with 95-98% yields in 7-12 minutes. The mechanistic experiments using *in-situ* NMR and HRMS elucidated that the coordination of ethanol to titanocene moiety released the catalytic species [$Cp_2Ti(OCH_2CH_3)_2$].

Quinazoline derivatives are an important class of heterocycles with a wide range of pharmacological and biological activities.[1] The catalytic condensation of anthranilamide with aldehydes/ketones provides a direct synthetic methodology of the quinazolinones derivatives. 10 mol% of 2-morpholinoethanesulfonic acid (Scheme 1, a) can promoted the condensation reaction with 83-96% yields.[2-4] Lewis acids of simple metal salts, such as $Zn(PFO)_2$ was more

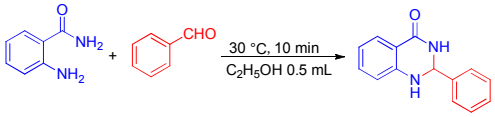


Scheme 1. Approaches for the quinazoline derivatives

active,[5-8] by which 2.5 mol% catalyst loading gave 80-91% yields. Notably, group IVB transition metal Lewis acids are efficient for this transformation. 2 mol% $ZrCl_4$ catalyzed anthranilamide with aldehydes/ketones in 80-97% yield.[9] Dodecylsulfate radical was employed to stabilize Zr^{4+} in aqueous system, 2.5 mol% $Zr(DS)_4$ successfully catalyzed the condensation reaction in water with 83-97% yield (Scheme 1, b).[10] Therefore, developing an efficient and robust Lewis acid catalyst is highly desirable for the synthesis of quinazoline derivatives.

Group IVB metallocene are promising Lewis acid catalyst precursors[11] due to their kinetic stability, electronic tunable metal center and intrinsic metallic Lewis acidity.[12-15] Our previous research found that *O*-donor ligands of salicylic acids, methanol and phenol derivatives enhanced the Lewis acidity of titanoncene centre, which showed the cooperative catalytic activity in various organic condensation reactions, such as Mannich reactions[16-18] and Friedel-Crafts reactions.[19] Herein, we report the direct activation of Cp_2TiCl_2 by alcoholic solvents for rapid synthesis of quinazoline derivatives.

Table 1 Catalyst and concentration screening in the reaction of anthranilamide with benzaldehyde[a]



Entry	Catalyst	Catalyst (mol%)	Yield (%)[b]
1	$ZrCl_4$	5	56
2	$TiCl_4$	5	63
3	Cp_2ZrCl_2	5	89
4	Cp^*TiCl_3	5	71
5	Cp_2TiCl_2	5	98
6	Cp_2TiCl_2	4	98
7	Cp_2TiCl_2	3	98
8	Cp_2TiCl_2	2	97
9	**Cp_2TiCl_2**	**1**	**97**
10	Cp_2TiCl_2	0.5	83
11	$CuCl_2$	5	30
12	$MgCl_2$	5	20
13	$ZnCl_2$	5	42
14	$SrCl_2$	5	55
15	HCl	5	30

[a]Reaction conditions: anthranilamide (1 mmol), benzaldehyde (1 mmol)
[b]Yield of the isolated product

Key Laboratory of Applied Surface and Colloid Chemistry, MOE, School of Chemistry and Chemical Engineering,Shaanxi Normal University Xi'an 710062 (China) Fax: +86-29-81530727. E-mail: zwq@snnu.edu.cn, zwgao@snnu.edu.cn

† *Footnotes relating to the title and/or authors should appear here.*
Electronic Supplementary Information (ESI) available: See
DOI: 10.1039/x0xx00000x

In ethanol, as low as 1 mol% Cp_2TiCl_2 catalyzed the condensation reaction of anthranilamide and aldehydes up to 98% yield in 7 min. The catalytic system of Cp_2TiCl_2 in ethanol showed the wide range of functional group tolerance in 17 examples with 95-98% yields. The mechanistic experiments unveiled $Cp_2Ti(OCH_2CH_3)_2$ was catalytic species, illuminated the superior activity of Cp_2TiCl_2 in ethanol for the condensation reaction.

Initially, we chose anthranilamide and benzaldehyde as the model substrates to optimize the reaction conditions. As shown in Table 1, $ZrCl_4$ and $TiCl_4$ catalyzed the reaction with 56% and 63% yields, respectively (entries 1 and 2). Organometallic Lewis acid precursors significantly accelerated the condensation reaction, Cp_2ZrCl_2 afforded the desired product quinazoline in 89% yield, and Cp_2TiCl_2 gave 98% yield of quinazoline (entries 3 and 5). Half sandwhich Cp^*TiCl_3 showed 71% yield of desired product (entry 4). Further experiments showed that 1 mol% of Cp_2TiCl_2 still afforded 97% yield, and 0.5 mol% of Cp_2TiCl_2 gave 83% yields (entries 5-10). This solvent activation method was applied for other Lewis acids such as $CuCl_2$, $MgCl_2$, $ZnCl_2$, $SrCl_2$ gave 30%, 20%, 42% and 55% yield, respectively (entries 11-14). The control experiments using 5 mol% HCl afforded 30% yield, which eliminated the possibility that the alcoholysis of titanocene chlorides released HCl as catalytic species (entry 15). The solvent and temperature effect was also screened (see the supporting information).

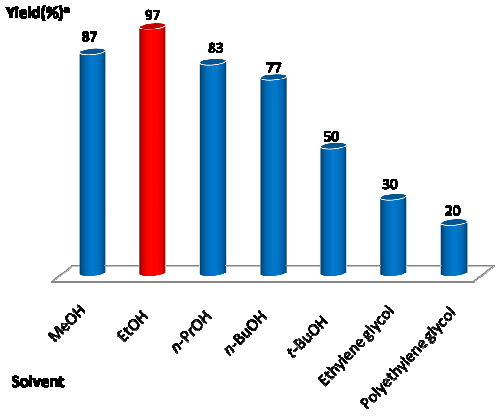
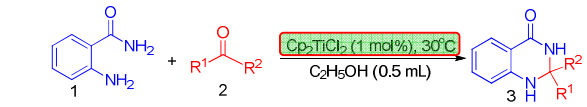
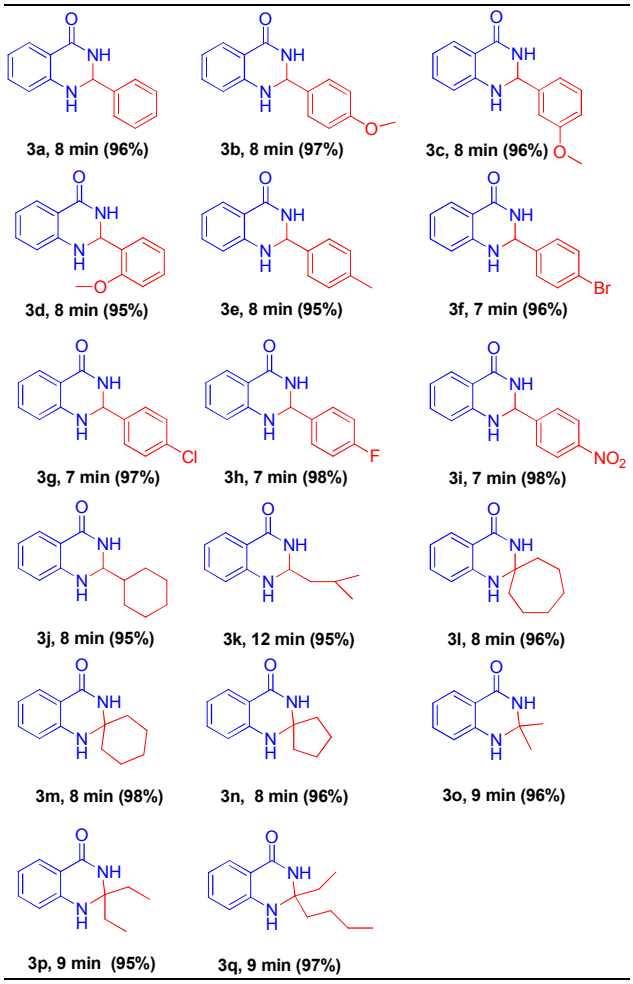


Fig. 1 Alcohols accelerated Cp_2TiCl_2 catalyzed the condensation reaction of anthranilamide with benzaldehyde. [a]Yield of the isolated product.

The activation effects of various alcohols were investigated to demonstrate the pronounced accelerating effect on titanocene dichloride catalyzed condensation reaction of anthranilamide with benzaldehyde (Fig. 1). It was found that ethanol was the best solvent, in which the yield was 97%. Methanol, *n*-propanol and *n*-butanol showed less accelerating effect and gave the yields from 77-87%. Based on the facile substitution reactions of alkoxy groups with titanocene dichloride in alcohols, [20] it is probably because that the coordination between alcohols and titanocene species results in enhancing Lewis acidity of Ti centre and thus improving the catalytic efficiency. This hypothesis was further supported by the condensation reactions catalyzed by titanocene dichloride in sterically hindered *t*-butanol, the yields of the condensation reaction dramatically decreased to 50%. Furthermore, it was also found that polylol suppressed the activity of titanocene dichloride, ethylene glycol only obtained 30% yield. This because titanocene dichloride in polylol, which readily formed a stable complex, was not an effective catalyst, indicating the chelation might be an unfavourable coordination mode for unleashing Lewis acidity of titanocene dichloride. Owing to the fact that the sterical hindrance is disadvantageous to alcohols coordinating to organometallic centre, the yields of the condensation reaction dramatically decreased with the use of polyethylene glycol, only afforded 20% yields. These findings led us to establish a new protocol for activation of inert Cp_2TiCl_2 by a solvent strategy accelerating the condensation reaction.

Table 2 Substrate scope for the synthesis of quinazolinones derivatives[a,b]





[a]All the reaction were carried out in the presence of 1 mmol 1, 1.0 equiv 2. [b]Yields of the isolated product.

The scope and limitation of the new catalyst system were evaluated with anthranilamide and a range of aldehydes/ketones under the optimized conditions as show in Table 2. Initially, we investigated the reaction using several electron-donating and electron-withdrawing substituted benzaldehydes (**3a–3i**) with anthranilamide under optimized conditions. The electronic effects have no significant impact on reaction rate, which result in 96-99% yield. Nevertheless *o*-methoxy substituted benzaldehyde was used as a substrate for this reaction, the yield of desired product was 95%, lower than *p*- and *m*- substituted benzaldehyde, which directly reflects steric hindrance is disadvantages for this reaction. Aliphatic aldehyde such as cyclohexanecarbaldehyde (**3j**) was also readily introduced into this reaction, the desired product was formed with yield of 95%. The reaction of anthranilamide and isovaleraldehyde (**3k**) proceeded slightly slowly and afforded 95% yield as long as 12 min. Subsequently, these optimized conditions were applied for the conversion of various kinds of aliphatic ketones and anthranilamide into the corresponding quinazoline derivatives. Among the three kinds of cyclic ketones, the yield of cyclohexanone (**3m**) was 98% higher than cycloheptanone's (**3l**) and cyclopentanone's (**3n**) which were 96%. When the ketones were chain ketones, such as acetone (**3o**), 3-pentanone (**3p**) and 3-heptanone (**3q**), the reactions also proceeded smoothly and resulted in 96%, 95% and 97%.

To shed light on the delicate accelerating effect of alcohols, the interaction between Cp_2TiCl_2 and CH_3CH_2OH were investigated by ^1H NMR and HRMS.[21] ^1H NMR experiments were conducted using Cp_2TiCl_2 in CD_3CD_2OD at intervals with addition of aniline as base (Fig. 2). The characteristic cyclopentadienyl (Cp) protons can be regarded as a probe to measure the formation of new titanocene complexes. No coordination occurred and only one Cp singlet of Cp_2TiCl_2 at δ 6.59ppm (●) was detected. When adding 1 equiv aniline, the new titanocene complex species $Cp_2TiCl(OCH_2CH_3)$ (**III**)

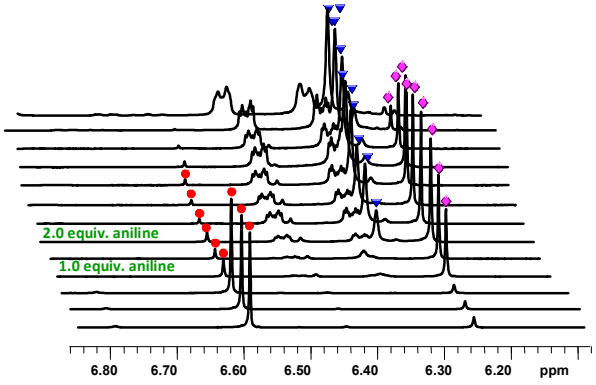
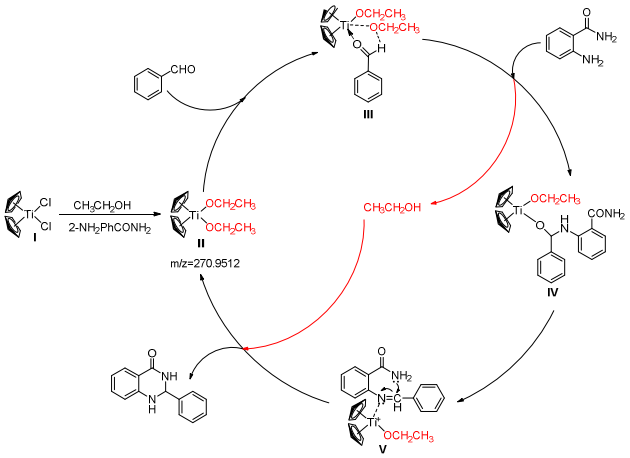


Fig. 2 Partial 400MHz ^1H NMR spectra (CD_3CD_2OD) of a solution containing Cp_2TiCl_2 with addition of aniline. ●6.59 ppm **I** [Cp_2TiCl_2]; ◆6.25 ppm **III** [$Cp_2TiCl(OCH_2CH_3)$]; ▼6.34 ppm **II** [$Cp_2Ti(OCH_2CH_3)_2$]

at δ 6.25 ppm(◆) formed.[22] The resonances of $Cp_2TiCl(OCH_2CH_3)$ increased while the resonance of Cp_2TiCl_2 declined gradually. When adding another 1 equiv aniline, as the singlet at 6.25 ppm increased, one new Cp protons singlet $Cp_2Ti(OCH_2CH_3)_2$ appeared at δ 6.34 ppm(▼)(**II**). $Cp_2TiCl(OCH_2CH_3)$ was consumed gradually in CD_3CD_2OD in the presence of base and formed new titanocene species $Cp_2Ti(OCH_2CH_3)_2$ (**II**). The putative species **II** were further supported by HRMS experiments performed in the positive ion mode (see the supporting information Fig. S2 and Fig. S3). The ion peaks at *m/z* 270.9512 in the CH_3CH_2OH solution of Cp_2TiCl_2 was corresponding to [**II** $+H^+$]. These observations clearly demonstrate the CH_3CH_2OH is not just a medium to dissolve the sandwich complexes but also can be another reactant involved in the process of activating Cp_2TiCl_2 via ethyoxyl groups binding to Cp_2Ti^{IV} moiety. It can be concluded that in the coordination reaction, pre-catalyst titanocene dichloride readily converted into the detectable titanocene species **II**, and presumably it was the organometallic Lewis acid catalyst.[23]



Scheme 2. Proposed mechanism for the synthesis of quinazoline derivatives catalyzed by Cp_2TiCl_2 in ethanol

A plausible mechanism for the formation of quinazoline derivatives catalyzed by titanocene dichloride in ethanol solution is outlined in Scheme 2. Initially, titanocene dichloride **I** pre-catalyst is activated by ethanol and transformed to catalytic active species titanocene diethoxy complexes **II** in the presence of anthranilamide and releases HCl simultaneously. The newly formed complex **II** coordinate with aldehyde as shown in **III**, in which the enolization is accelerated synergistically as the carbonyl coordinate to oxophilic Ti and the ethoxy ligand abstracts the proton. Then the condensation of the activated aldehyde with the amino group of anthranilamide produces an imine intermediate with the H^+ in solution. In the meantime, the part of imine could be activated by cation **V**. Thus, the final product could be formed by intramolecular nucleophilic attack of the amide nitrogen on activated imine carbon, followed by a proton transfer. Once the product is released, catalytic active species **II** is regenerated by the coordination of CH_3CH_2OH and releases H^+ for the next cycle.

Conclusions

In summary, a robust Lewis acid catalytic system was developed by the activation of inert Cp_2TiCl_2 by ethanol for efficient synthesis of quinazoline derivatives. As low as 1 mol% of Cp_2TiCl_2 efficiently catalyzed the condensation reaction of 17 examples with 95-99% yield. The mechanistic studies including ^1H NMR and HRMS analyses suggested that the coordination of CH_3CH_2OH to titanocene dichloride formed catalytic active species $Cp_2Ti(OCH_2CH_3)_2$, which led to superior activity for the condensation reaction. These results

illuminated a new catalytic system, which allows for a most concise, efficient and mild protocol for the synthesis of quinazoline derivatives. Furthermore the moderate reaction conditions, air-stable organometallic Lewis acid catalyst, absence of any cocatalyst and ligand make this an environment friendly methodology amenable for scale-up.

Acknowledgements

This work was supported by the 111 Project (B14041), the grant from National Natural Science Foundation of China (21271124, 21272186, 21371112), the Fundamental Funds Research for the Central Universities (GK201501005, GK201302015, GK201503029), the Project Supported by Natural Science Basic Research Plan in Shaanxi Province of China (Program No. 2015JQ2056), the Program for Changjiang Scholars and Innovative Research Team in University (IRT_14R33).

Notes and references

1 (a) M. J. Hour, L. J. Huang, S. C. Kuo, Y. Xia, K. Bastow, Y. Nakanishi, E. Hamel and K. H. Lee, *J. Med. Chem.,* 2000, **43**, 4479. (b) H. L. Birch, G. M. Buckley, N. Davies, H. J. Dyke, E. J. Frost, P. J. Gilbert, D. R. Hannah, A. F. Haughan, M. J. Madigan, T. Morgan, W. R. Pitt, A. J. Ratcliffe, N. C. Ray, M. D. Richard, A. Sharpe, A. J. Taylor, J. M. Whitworth and S. C. Williams, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 5335. (c) E. Cohen, B. Klarberg and J. R. Vaughan, *J. Am. Chem. Soc.,* 1959, **81**, 5508.

2 Z. Karimi-Jaberi and L. Zarei, *S. Afr. J. Chem.,* 2012, **65**, 36.

3 B. L. Vilas and V. S. Pravin and S. S. Murlidhar, *Tetrahedron Lett*., 2013, **54**, 5778.

4 S. Nagarajan, T. M. Shaikh and E. Kandasamy, *New J. Chem*., 2015, **39**, 9693.

5 L. M. Wang, L. Hu, J. H. Shao, J. J. Yu and L. Zhang, *J. Fluorine Chem*., 2008, **129**, 1139.

6 M. Wang, T. T. Zhang, Y. Liang and J. J. Gao, *Chin. Chem. Lett.,* 2011, **22**, 1423.

7 J. X. Chen, D. Z. Wu, F. He, M. C. Liu and H. Y. Wua, *Tetrahedron Lett*., 2008, **49**, 3814.

8 J. Safari and S. G. Ravandi, *RSC Adv*., 2014, **4**, 11654.

9 M. Abdollahi-Alibeik and E. Shabani, *Chin. Chem. Lett*., 2011, **22**, 1163.

10 H. R. Safaei, M. Shekouhy, S. Khademi, V. Rahmanian and M. Safaei, *J. Ind. Eng. Chem*., 2014, **20**, 3019.

11 (a) A. Gansauer, D. Franke, T. Lauterbach and M. Nieger, *J. Am. Chem. Soc*., 2005, **127**, 11622; (b) G. Erker, G. Kehr and R. Froehlich, *Coord. Chem. Rev*., 2006, **250**, 36; (c) P. J. Chirik, *Organometallics*., 2010, **29**, 1500; (d) T. Saito, H. Nishiyama, H. Tanahashi, K. Kawakita, H. Tsurugi and K. Mashima, *J. Am. Chem. Soc*., 2014, **136**, 5161; (e) D. F. Chen, Z. Y. Han, X. L. Zhou and L. Z. Gong, *Acc. Chem. Res*., 2014, **47**, 2365; (f) M. E. Sloan, A. Staubitz, T. J. Clark, C. A. Russell, G. C. L. Jones and I. Manners, *J. Am. Chem. Soc*., 2010, **132**, 3831; (g) A. Zydor, V. G. Kessler and S. D. Elliott, Phys. *Chem. Chem. Phys*., 2012, **14**, 7954; (h) A. M. Chapman and D. F. Wass, *Dalton Trans*., 2012, **41**, 9067.

12 A. Gansaeuer, I. Winkler, D. Worgull, D. Franke, T. Lauterbach, A. Okkel and M. Nieger, *Organometallics.*, 2008, **27**, 5699.

13 R. Qiu, X. Xu, L. Peng, Y. Zhao, N. Li and S. Yin, *Chem.–Eur.J*., 2012, **18**, 6172.

14 A. Gansäuer, M. Behlendorf, A. Cangonul, C. Kube, J. M. Cuerva,
J. Friedrich, and M. V. Gastel, Angew. Chem. Int. Ed., 2012, **51**, 3266.

15 A. Gansäuer, S. Hildebrandt, A. Michelmann, T. Dahmen, D. v. Laufenberg, C. Kube, G. D. Fianu, and R. A. Flowers II, Angew. Chem. Int. Ed., 2015, **54**, 7003.

16 Y. Wu, C. Chen, G. Jia, X. Y. Zhu, H. M. Sun, G. F. Zhang, W. Q. Zhang and Z. W. Gao, *Chem.–Eur.J*., 2014, **20**, 1.

17 X. Y. Zhu, C. Chen, B. X. Yu, G. F. Zhang, W. Q. Zhang and Z. W. Gao, *Chem. Lett*., 2014, **43**, 1832.

18 Y. Wu, X. Wang, Y. L. Luo, J. Wang, Y. J. Jian, H.M. Sun, G. F Zhang, W. Q. Zhang and Z. W Gao, *RSC Adv*., 2016, **6**, 15298.

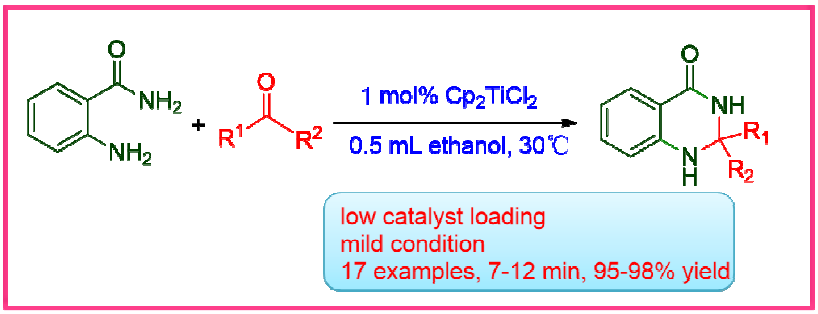
19 X. Wang, Z. H. Wang, G. F. Zhang, W. Q. Zhang, Y. Wu and Z. W. Gao, *Eur. J. Org. Chem*., 2016, **3**, 502.

20 (a) J. H. Toney and T. J. Marks, *J. Am. Chem. Soc.*, 1985, **107**, 947; (b) R. Fandos, B. Gallego, A. Otero, A. Rodriguez, M. J. Ruiz, P. Terreros and C. Pastor, *Organometallics.*, 2007, **26**, 2896.

21 (a) A. F. A. Peacock, A. Habtemariam, R. Fern´andez, V. Walland, F. P. A. Fabbiani, S. Parsons, R. E. Aird, D. I. Jodrell and P. J. Sadler, *J. Am. Chem. Soc.*, 2006, **128**,1739; (b) D. Schroder, *Acc. Chem. Res.*, 2012, **45**, 1521.

22 J. C. Huffman, K. G. Moloy, J. A. Marsella and K. G. Caulton, *J. Am. Chem. Soc.*,1980, **80**, 3009.

23 J. L. Li, Z. W. Gao, P. Sun, L. X. Gao and W. Tikkanen, *Inorg. Chim. Acta*., 2011, **368**, 231.



An efficient strategy to activated air-stable Lewis acid precursor, Cp_2TiCl_2 by alcoholic solvent for rapid synthesis of quinazoline derivatives