DOI: 10.1002/adsc.201100669

Enantioselective α-Arylation of Cyclic Ketones Catalyzed by a Combination of an Unmodified *Cinchona* Alkaloid and a Palladium Complex

Christian Richter,[a] Kalluri V. S. Ranganath,[a] and Frank Glorius[a,*]

[a] Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut, Corrensstraße 40, 48149 Münster, Germany
Fax: (+49) 251-83-33202; e-mail: glorius@uni-muenster.de

Received: August 24, 2011; Revised: October 20, 2011; Published online: January 20, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100669.

Abstract: A palladium/*Cinchona* alkaloid-catalyzed α-arylation between cyclic ketones and aryl halides under phosphine-free conditions is presented. The use of a simple, unmodified *Cinchona* alkaloid results in high levels of activity and selectivity with up to 93% *ee*. These enantioinduction levels are comparable or even higher than the ones reported using palladium/BINAP complexes. To the best of our knowledge, this represents the first use of unmodified *Cinchona* alkaloids as ligands/catalysts in asymmetric transition metal complex-catalyzed cross-coupling reactions.

Keywords: alkaloids; asymmetric catalysis; dual catalysis; enantioselective α-arylation; transition metal catalysis

The metal-catalyzed α-arylation of carbonyl compounds is an important cross-coupling due to the relevance of the resulting carbonyl products for pharmaceutical and biological applications.[1] The intermolecular asymmetric α-arylation is particularly attractive for the preparation of valuable optically active carbonyl compounds, bearing an α-quaternary stereocenter.[2] This reaction has been reported using Pd and Ni salts in the presence of chiral phosphine ligands, which are often expensive, toxic and sensitive.[3] In addition, a chiral heterogeneous catalyst, Pd/Fe_3O_4 nanoparticles modified by a chiral N-heterocyclic carbene (NHC), has been successfully employed in the asymmetric α-arylation.[4]

In the past 30 years, the naturally occurring *Cinchona* alkaloids have been widely applied by themselves or as versatile precursors for organocatalysts in asymmetric synthesis, chromatographic selectors and NMR discriminating agents.[5] Many attractive properties like ready availability, high levels of rigidity, robustness and multifunctional nature render *Cinchona* alkaloids especially valuable.[6] However, whereas unmodified *Cinchona* alkaloids have found prominent applications as chiral modifiers of heterogeneous catalysts,[7,8] only a few studies on *Cinchona* alkaloids and their derivatives used as ligands of transition metal complexes have been reported,[9] except for asymmetric dihydroxylation and amino hydroxylations.[10] Herein, we report the asymmetric α-arylation of ketones using a molecular Pd catalyst in combination with quinine as a ligand. This represents the first formation of quarternary stereocenters by asymmetric C–C bond formation using an unmodified *Cinchona* alkaloid (Figure 1) as chiral ligand.

We commenced our study with the α-arylation of 2-methyl-1-tetralone (**1**) and iodobenzene (**2**) with $Pd(OAc)_2$ and quinine (QN) as the catalyst system. We were pleased to find that running the reaction in PhMe at 100 °C with NaO-*t*-Bu as the base furnished the corresponding α-arylated product **3** in 81% yield

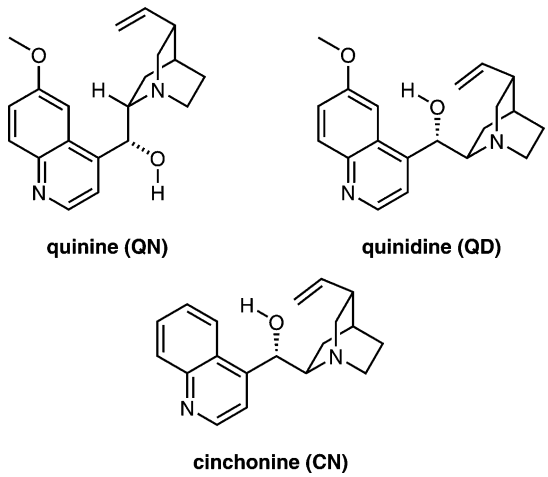
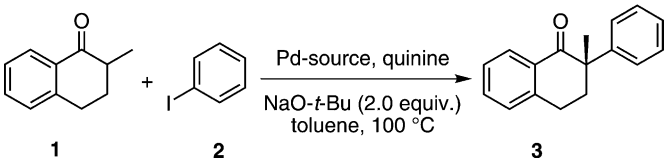


Figure 1. Structures of the applied *Cinchona* alkaloids.

Table 1. Effect of various Pd salts on asymmetric α-arylation between 2-methyl-1-tetralone and iodobenzene.[a]

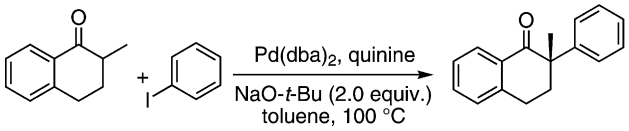


1 2 3

Entry	Pd source	Time [h]	Yield [%][b]	*ee* [%][c]
1	$Pd(OAc)_2$	3	81	87
2	$Pd(dba)_2$	3	85	92
3[d]	$Pd(dba)_2$	72	80	90
4	$[Pd(allyl)Cl]_2$	3	60	3
5	$PdCl_2$	24	38	77
6	$Pd_2(dba)_3$	3	75	90
7	$Pd(TFA)_2$	16	68	91
8	$Pd(acac)_2$	16	76	93

[a] Ketone (0.3 mmol), PhI (0.6 mmol), Pd salt (1.4 mol%), quinine (7.5 mol%), NaO-*t*-Bu (2.0 equiv.), toluene (2.0 mL), 100 °C. The absolute configuration was assigned in analogy to entry 9 of Table 3.
[b] Isolated yields.
[c] The *ee* was measured using an chiral AD-H column (98:2 hexane:*i*-PrOH).
[d] Heated at 60 °C.

Table 2. Effect of amount of ligand on asymmetric α-arylation between 2-methyl-1-tetralone and iodobenzene.[a]



Entry	Quinine [mol%]	Time [h]	Yield [%][b]	*ee* [%][c]
1	0	24	44	0
2	1.4	3	79	65
3	2.5	3	85	85
4	5.0	3	86	88
5	7.5	3	85	92
6[d]	7.5	3	78	90
7	10.0	3	82	87
8	50.0	3	85	90
9[e]	7.5	3	87	-89
10[f]	7.5	3	80	-86

[a] Ketone (0.3 mmol), PhI (0.6 mmol), $Pd(dba)_2$ (1.4 mol%), quinine, NaO-*t*-Bu (2.0 equiv.), toluene (2.0 mL), 100 °C. The absolute configuration was assigned in analogy to entry 9 of Table 3. Negative *ee* values indicate the predominant formation of an *R*-configured product.
[b] Isolated yields.
[c] The *ee* was measured using a chiral AD-H column (98:2 hexane:*i*-PrOH).
[d] Heated at 150 °C.
[e] Quinidine was used instead of quinine.
[f] Cinchonine was used instead of quinine.

and a pronounced *ee* of 87% (Table 1, entry 1). Although screening of different Pd sources resulted in up to 93% *ee*, $Pd(dba)_2$ gave the best combination of activity and selectivity with 92% *ee* and 85% yield after 3 h. Naturally, no reaction was observed in the absence of palladium.

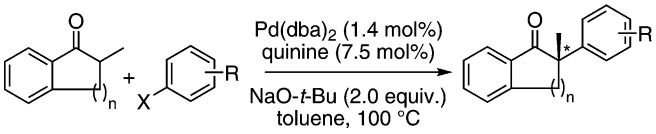
In order to better understand the role of the *Cinchona* ligand, the reaction was also carried out without any chiral ligand [$Pd(dba)_2$ only]; this reaction furnished the expected α-arylated product in 42% yield (obviously, in racemic form) along with a significant number of by-products like 2-methylnaphthol, homocoupling products of both starting materials and aldol-type products (Table 2). The 7.5 mol% of quinine used initially in our study were found to be optimal in terms of selectivity and reactivity. Increasing the amount of alkaloid to 50 mol% did not improve the enantioselectivity and lowering it to 2.5 mol% resulted in a significantly lower *ee* (Table 2). The effect of temperature on the enantioselectivity of the reaction was also investigated. Interestingly, the *ee* only slightly decreased as the temperature was raised to 150 °C, showing the remarkable thermal robustness of the enantioinduction. Using twice as much catalyst (2.8 mol% of Pd and 15.0% alkaloid) also did not increase the enantioselectivity of the α-arylated product. Finally, when applying the pseudoenantiomeric *Cinchona* alkaloid quinidine, as expected the opposite enantiomer of the α-arylation product was formed with only slightly lower *ee* (entry 9). A similar result was obtained with cinchonine (entry 10).

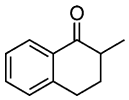
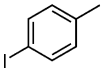
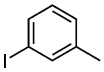
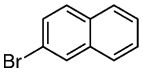
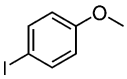
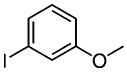
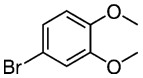
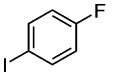
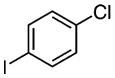
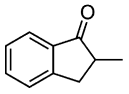
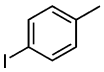
A survey of different solvents and bases revealed that toluene and NaO-*t*-Bu are a superior combination. Employing weaker inorganic bases such as K_3PO_4 resulted in no product formation. The yield and *ee* decreased in other solvents like THF and 1,4-dioxane (see the Supporting Information).

In order to test the effectiveness of the Pd/quinine-catalyzed arylation reaction, various aryl iodides and bromides were examined under the optimized conditions in the presence of quinine. The *meta*- and *para*-substituted aryl iodides showed good yields and good to very good *ee*s. However, reactivity was lower with bromides compared to aryl iodides in the arylation of 2-methyl-1-tetralone in combination with $Pd(dba)_2$ and quinine (Table 3, entry 2). There was no reaction with unactivated chloroarenes under the optimized reaction conditions. Unfortunately, ester and cyano groups on the aryl halide were not tolerated.

The absolute stereochemistry of 2-methyl-2-(3,4-dimethoxyphenyl)-tetralone (Table 3 entry 9) could be determined as (*S*) by comparison of the optical rotation with literature data.[3d] It is reasonable to assume that all products are formed with the same sense of enantioinduction.

Table 3. Asymmetric α-arylation of ketones with aryl halides.[a]



Entry	Ketone	Aryl halide	Yield [%][b]	*ee* [%][c]
1			85	92
2			70	77
3			79	87
4			76	89
5			37	63
6			72	77
7			86	83
8			91	83
9			57	70 (*S*)[d]
10			86	85
11			83	77
12			76	74
13			72	58
14			77	72

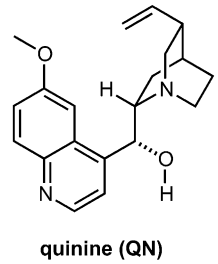
[a] Ketone (0.3 mmol), aryl halide (0.6 mmol), $Pd(dba)_2$ (1.4 mol%), quinine (7.5 mol%), NaO-*t*-Bu (2.0 equiv.), toluene (2.0 mL), 100 °C; reaction time: aryl iodides 3–8 h, aryl bromides 16–30 h.

[b] Isolated yields.

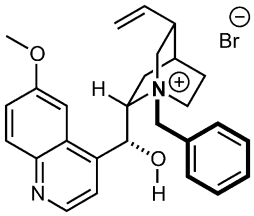
[c] The *ee* value was measured using a chiral AD-H column (98:2 hexane:*i*-PrOH).

[d] Comparison of the negative sign of optical rotation of the product of entry 9 with literature data for the same compound indicates the *S*-configuration of the product formed.

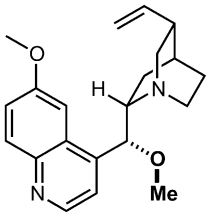
In order to better understand the role of quinine, two derivatives of this alkaloid were prepared: in one the quinuclidine nitrogen was benzylated (**4**), in the other the hydroxy group was methylated (**5**) (Figure 2). Then, these modified quinine ligands were



quinine (QN)



4



5

Figure 2. Quinine and its *N*-benzylated (**4**) and *O*-methylated (**5**) derivatives.

tested in the arylation reaction between 2-methyl-1-tetralone and iodobenzene at 100 °C in the presence of base. Interestingly, under standard conditions, the α-arylated product was formed in 42 and 44% yield, respectively, and each time only in racemic form. A similar result was observed when no quinine was added to the reaction mixture. This clearly indicates that both functional groups (tertiary quinuclidine N and hydroxy group) are essential for the proper mode of action of the quinine in this asymmetric transformation, and are needed for both activity and selectivity.

According to the observation that both functional groups are essential, we envision three fundamentally different modes of enantioinduction (Figure 3). (**A**) The formation of a catalytically active Pd/quinine complex, where quinine acts as a bidentate ligand. Such a kind of binding mode, although not in the context of catalysis, was reported by Beck et al.[11] (**B**) Quinine acts as a bridge between the Pd complex and the substrate. A well studied example for the ability of quinine to bring together two reactants is the Michael addition of aromatic thiols to cyclohexenones.[12] Also Pd complexes are known where only the quinuclidine nitrogen is binding to the metal.[11] (**C**) Quinine acts as an organocatalyst, binding non-covalently to the substrate by formation of H-bonds, π interactions or other weak forces. These interactions could activate the substrate and shield one side of the car-

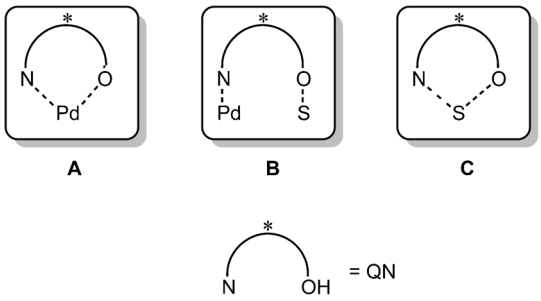
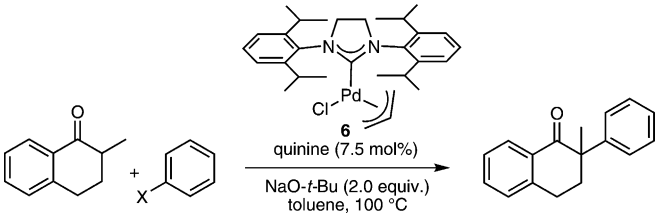


Figure 3. Possible modes of activation and enantioinduction by quinine (QN); (S = substrate).

bonyl moiety. This kind of enantioinduction is known for *Cinchona*-derived phase-transfer organocatalysts.[13]

Considering the different modes from **A** to **C** the number of free coordination sites on the Pd atom is increasing. In mode **A** after oxidative addition there are no free coordination sites available. Therefore a strongly binding additional ligand on the Pd complex should suppress or decrease the reactivity, if the reaction is processing *via* mode **A**. Mode **B** should be affected less by blocking a coordination site and mode **C** should not be affected at all. Besides their interesting electronic and steric properties, NHCs are known to form stable metal-NHC complexes with many metals, among them Pd.[14] Thus, in order to block active sites on the Pd, the (SIPr)Pd(allyl)Cl complex (**6**) was prepared, which liberates an active NHC-Pd(0) species under basic conditions.[15] This complex was subjected as Pd source to our standard conditions (Table 4). Without any addition of quinine the reaction proceeded quickly within 90 min and a yield of 48% was obtained. In the presence of quinine full conversion was observed after 4 h. The slower reaction rate could be caused by the binding of quinine to Pd blocking active sites at the metal complex. Interestingly, the yield increased to 92% and an *ee* of 80% was observed, which clearly shows that the addition of quinine forms a more chemoselective and enantioselective catalytically active species. The observation that the presence of quinine is lowering the reaction rate while still providing good levels of enantioinduction could be aligned with mode **B**. The lower *ee* obtained with complex **6** than with $Pd(dba)_2$ could be explained by a faster racemic background reaction of small amounts of the free NHC-Pd(0) species, as the reaction rate without quinine is much faster for the NHC-Pd complex than for $Pd(dba)_2$ (Table 4, entry 1 *vs.* Table 2, entry 1). It must be pointed out that these experiments are more a hint than proof for mode **B**. Since NHC-Pd complexes are known to oxidatively add to C–Cl bonds,[14,6] we also investigated the use of aryl chlorides using (SIPr)Pd(allyl)Cl complex (**6**). Unfortunately the reactivity with and without quinine was quite low – no full conversion was observed after three days and reaction seemed to stop after 3 days – and the enantioinduction was minimal at best (Table 4).

Table 4. Asymmetric α-arylation of 2-methyl-1-tetralone catalyzed by the (SIPr)Pd(allyl)Cl complex.[a]



Entry	Quinine [mol%]	Aryl halide	Time [h]	Yield [%][b]	*ee* [%][c]
1	0	PhI	1.5	48	0
2	7.5	PhI	4	92	80
3	0	PhCl	72	33[d]	0
4	7.5	PhCl	72	28[d]	5

[a] Ketone (0.3 mmol), aryl halide (0.6 mmol), (SIPr)Pd(allyl)Cl (1.4 mol%), quinine (7.5 mol%), NaO-*t*-Bu (2.0 equiv.), toluene (2.0 mL), 100 °C, reaction time: aryl iodides 3–8 h, aryl bromides 16–30 h.

[b] Isolated yields.

[c] The *ee* value was measured using a chiral AD-H column (98:2 hexane:*i*-PrOH).

[d] NMR yield (CH_2Br_2 as internal standard).

Finally, a combination of Pd/Fe_3O_4 nanoparticles (replacing the homogeneous Pd complex) and quinine as modifier was investigated for the described α-arylation, also resulting in an active and selective catalyst system (for example, the reaction between **1** and **2** provided the product in 74% yield and 82% *ee*). However, surprisingly, no heterogeneous system resulted, as mercury poisoning and filtration test indicated a homogeneous nature of the catalytically active species.[4,18]

In conclusion, we have developed a Pd/*Cinchona*-catalyzed α-arylation reaction of cyclic ketones and aryl bromides and iodides under phosphine-free conditions. An unmodified *Cinchona* alkaloid results in high levels of activity and selectivity with up to 93% *ee*. It is important to note that the enantioinduction levels obtained are comparable or even higher than the ones reported using Pd/BINAP complexes.[3a] To the best of our knowledge, this represents the first use of unmodified *Cinchona* alkaloids as ligands in asymmetric transition metal complex-catalyzed cross-coupling reactions.[17]

Experimental Section

General Remarks

For detailed experimental procedures, spectral data and characterization see the Supporting Information.

Typical Experimental Procedure for the α-Arylation of Ketones with Aryl Halides

An oven-dried Schlenk flask was charged with $Pd(dba)_2$ (1.4 mol%), quinine (7.5 mol%) and NaO-*t*-Bu (2.0 equiv.). Toluene (2 mL), the respective aryl halide (2 equiv.) and ketone (1 equiv.) were added and the reaction mixture was heated at 100 °C. After completion of the reaction (monitored by GC-MS), the reaction mixture was poured into saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), the combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash column chromatography provided the respective title compounds.

Acknowledgements

Generous financial support by Alexander von Humboldt Foundation (KVSR) and the Deutsche Forschungsgemeinschaft (SFB 858) is gratefully acknowledged. The research of FG has been supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation. We are grateful to Buchler GmbH for a generous gift of Cinchona alkaloids.

References

[1] For a recent review, see: F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082–1146.

[2] Review on asymmetric α-arylation reactions, see: a) C. C. C. Johansson, T. J. Colacot, *Angew. Chem.* **2010**, *122*, 686–718; *Angew. Chem. Int. Ed.* **2010**, *49*, 676–707; see also: b) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234–245; c) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211–241. For intramolecular asymmetric α-arylations, see: d) S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402–3415; e) E. P. Kündig, T. M. Seidel, Y.-X. Jia, G. Bernadinelli, *Angew. Chem.* **2007**, *119*, 8636–8639; *Angew. Chem. Int. Ed.* **2007**, *46*, 8484–8487; f) S. Würtz, C. Lohre, R. Fröhlich, K. Bergander, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 8344–8345.

[3] a) J. Åhman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 1918–1919; b) T. Hamada, A. Chieffi, J. Åhman, and S. L. Buchwald *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268; c) G. Chen, F. Y. Kwong, H. On Chan, W. Y. Yu, A. S. C. Chan, *Chem. Commun.* **2006**, 1413–1415; d) X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

[4] a) K. V. S. Ranganath, J. Kloesges, A. Schäfer, F. Glorius, *Angew. Chem.* **2010**, *122*, 7952–7956; *Angew. Chem. Int. Ed.* **2010**, *49*, 7786–7789; review: b) K. V. S. Ranganath, F. Glorius, *Catal. Sci. Technol.* **2011**, *1*, 13–22.

[5] a) H. M. R. Hoffmann, J. Frackenpohl, *Eur. J. Org. Chem.* **2004**, 4293–4312; b) K. Kacprzak, J. Gawronski, *Synthesis* **2001**, 961–998; c) A SciFinder search on August 12th, 2011 resulted in 149 references where quinine is used as a catalyst.

[6] a) S. Gou, X. Chen, Y. Xiong, X. Feng, *J. Org. Chem.* **2006**, *71*, 5732–5736; b) W. Wang, S. Gou, X. Liu, X. Feng, *Synlett* **2007**, 2875–2878; c) S. K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196; d) T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526–533; e) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; f) D. Petterson, M. Marcolini, L. Bernadi, F. Fini, R. P. Herrera, V. Sgarzani, A. Ricci, *J. Org. Chem.* **2006**, *71*, 6269–6272; g) J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413–415; h) D. H. Paull, C. J. Abraham, M. T. Scerba, E. Alden-Danforth, T. Lectka, *Acc. Chem. Res.* **2008**, *41*, 655–663.

[7] For a lead reference on chiral modifiers in asymmetric catalysis, see: a) T. Mallat, E. Orglmeister, A. Baiker, *Chem. Rev.* **2007**, *107*, 4863–4890. For an overview on asymmetric heterogeneous catalysis, see: b) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850–4881; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732–4762.

[8] For the pioneering report, see: Y. Orito, S. Imai, S. Niwa, G. H. Nguyen, *J. Synth. Org. Chem. Jpn.* **1979**, *37*, 173–174.

[9] a) W. He, P. Liu, B. L. Zhang, X. L. Sun, S. Y. Zhang, *Appl. Organomet. Chem.* **2006**, *20*, 328–334; b) J. Shi, M. Wang, L. He, K. Zheng, X. Liu, L. Lin, X. Feng, *Chem. Commun.* **2009**, 4711–4713; c) T. Kaczorowski, I. Justyniak, T. Lipinska, J. Lipkowski, J. Lewinski, *J. Am. Chem. Soc.* **2009**, *131*, 5393–5395; d) I. Tesarowicz, B. Oleksyn, W. Nitek, *Chirality* **2007**, *19*, 152–161; e) V. Rai, I. N. N. Namboothiri, *Tetrahedron: Asymmetry* **2008**, *19*, 767–772; f) T.-P. Loh, J.-R. Thou, Z. Yin, *Org. Lett.* **1999**, *11*, 1855–1857; for an insighful review on the use of the *Cinchona* alkaloid scaffold in catalysis, see: g) L. Stegbauer, F. Sladojevich, D. J. Dixon, *Chem. Sci.* **2012**, DOI: 10.1039/c1sc00416f.

[10] a) H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; b) D. Nilov, O. Reiser, *Adv. Synth. Catal.* **2002**, *344*, 1169–1173.

[11] R. Hubel, K. Polborn, W. Beck, *Eur. J. Inorg. Chem.* **1999**, 471–482.

[12] H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417–430.

[13] U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446–447.

[14] a) W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342–1363; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309; b) *N-Heterocyclic Carbenes in Synthesis*, (Ed.: S. P. Nolan), Wiley-VCH, Weinheim, Germany, **2006**; c) *N-Heterocyclic Carbenes in Transition Metal Catalysis*, (Ed.: F. Glorius), Springer, Berlin, **2007**; d) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824–2870; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813; e) S. Würtz, F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523–1533; f) S. Dìez-Gonzàlez, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3676; g) for a recent

review on the physico-chemical properties of NHCs, see T. Dröge, F. Glorius, *Angew. Chem.* **2010**, *122*, 7094–7107; *Angew. Chem. Int. Ed.* **2010**, *49*; 6940–6952.
[15] M. S. Viciu, R. F. Germaneau, S. P. Nolan, *Org. Lett.* **2002**, *4*, 4053–4056.
[16] For a review on the activation of aryl chlorides, see: A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350–4386; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.
[17] For the rare use of modified *Cinchona* alkaloids in asymmetric transition metal catalysis, see: a) M. Zielinska-Blajet, R. Siedlecka, J. Skarzewski, *Tetrahedron: Asymmetry* **2007**, *18*, 131–136; b) Q. F. Wang, W. He, X. Y. Liu, H. Chen, X. Y. Qin, S. Y. Zhang, *Tetrahedron: Asymmetry* **2008**, *19*, 2447–2450.
[18] See Supporting Information for further information.

