Asymmetric Catalysis

DOI: 10.1002/anie.201406492

Catalytic Asymmetric Functionalization of Aromatic C–H Bonds by Electrophilic Trapping of Metal-Carbene-Induced Zwitterionic Intermediates**

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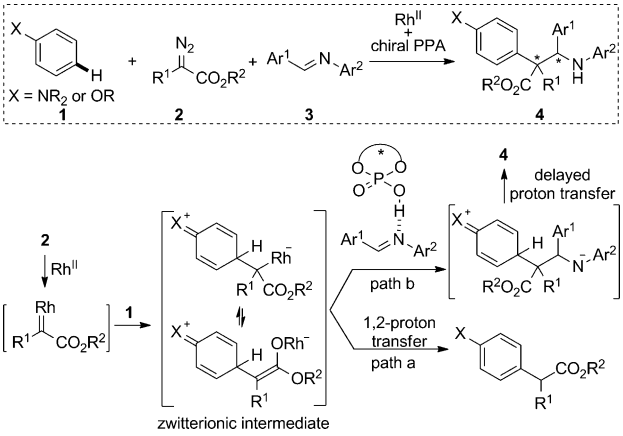
Abstract: *Asymmetric functionalization of aromatic C–H bonds of N,N-disubstituted anilines with diazo compounds and imines is reported for the efficient construction of α,α-diaryl benzylic quaternary stereocenters in good yields with high diastereoselectivities and excellent enantioselectivities. This Rh^{II}/chiral phosphoric acid cocatalyzed transformation is proposed to proceed through a metal-carbene-induced zwitterionic intermediate which undergoes electrophilic trapping. To the best of our knowledge, this is the first asymmetric example of metal carbene-induced intermolecular functionalization of aryl C–H bonds.*

Carbene-induced C–H functionalization by transition-metal-catalyzed decomposition of diazo compounds is among the most efficient and reliable synthetic tools for the construction of C–C bonds.[1] Within this context, by taking advantage of a broad selection of transition-metal catalysts, both non-asymmetric and asymmetric functionalizations of C(sp^3)–H bonds have been extensively studied over the past several decades.[1b–e] However, while non-asymmetric functionalization of aromatic C(sp^2)–H bonds have also been developed to some extent,[2–5] the asymmetric version of metal-carbene-induced functionalization of aromatic C(sp^2)–H bonds remains unexplored except for intramolecular examples[6] or those starting from heteroarenes.[7]

Unlike the carbene-induced C(sp^3)–H functionalization in which efficient asymmetric control could be achieved by chiral transition-metal catalysts via a concerted nonsynchronous transition state,[1b,d,8] the functionalization of aromatic C–H bonds is generally considered to proceed through the formation of a zwitterionic intermediate from electrophilic addition of a metal carbene to the aromatic ring and a subsequent rapid proton transfer (Scheme 1, path a).[1b] This stepwise mechanism makes it very challenging to achieve efficient enantioselective control by means of chiral transition-metal catalysts,[9] probably owing to the difficulty in controlling enantioselectivity during the asymmetric proto-



Scheme 1. Catalytic asymmetric aromatic C–H functionalization by trapping of a metal-carbene-induced intermedaite.

nation step.[10] As part of our continuous research efforts in exploring new transformations based on asymmetric electrophilic trapping of active intermediates generated from metal carbenes,[11,12] we became interested in developing catalytic asymmetric functionalization of aromatic C–H bonds with a similar strategy. We envisioned that the proposed metal-carbene-induced zwitterionic intermediate could be intercepted by electrophiles such as active imines prior to 1,2-proton transfer to give formal C–H insertion products (Scheme 1, path b). With such a strategy, asymmetric control could be realized during the trapping process by introducing chiral cocatalyst such as chiral phosphoric acid (PPA; Scheme 1, path b).[13] Herein, we report the successful development of a catalytic asymmetric functionalization of aromatic C–H bonds from a novel three-component reaction of arenes, diazo compounds, and imines in the presence of a rhodium(II)/chiral PPA catalyst system.[14] This transformation is proposed to proceed through electrophilic trapping of metal-carbene-induced zwitterionic intermediates, and provides an efficient way to access chiral α,α-diaryl all-carbon benzylic quaternary stereocenters, which are common structural scaffolds in medicinal products such as disopyramide (Norpace),[15a] loperamide (Imodium),[15b] methadone (Dolophine),[15c] and proadifen (SKF525A).[15d]

We began our initial studies by examining an array of substituted anilines or phenols in a reaction with methyl phenyldiazoacetate (**2a**) and *N*-benzylideneaniline (**3a**) in the presence of both [$Rh_2(OAc)_4$] (1 mol%) and 3,3′-bis-(phenyl)-binol phosphoric acid (*rac*-**5a**, 10 mol%).[16] Among different arenes tested, the formal C–H insertion products

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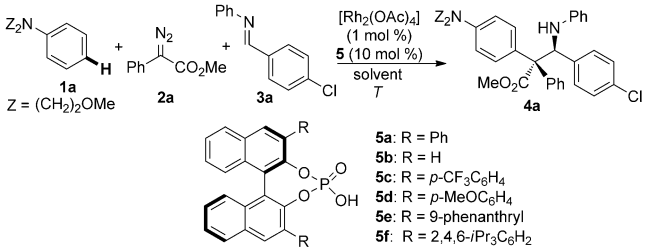
[**] We are grateful for financial support from NSF of China (20932003 and 21125209), the MOST of China (2011CB808600) and STCSM (12JC1403800).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201406492.

were generally observed as the major products, and only *N*,*N*-bis(2-methoxyethyl)aniline (**1a**) was found to produce the desired three-component product in low yield.[17] Albeit in a very low yield, this result demonstrated the feasibility of our designed electrophilic trapping pathway and encouraged us to choose **1a** as the model substrate for further optimization of the reaction conditions. To fulfil catalytic asymmetric control of this transformation, different chiral PPAs were first evaluated. As shown in Table 1, both the efficiency and

Table 1: Optimization of reaction conditions.[a]



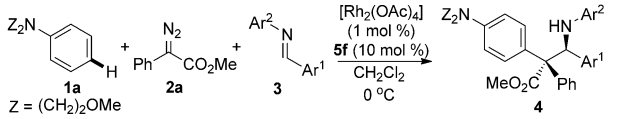
Entry	5	Solvent	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**5a**	CH_2Cl_2	0	19	60:40	16
2	**5b**	CH_2Cl_2	0	9	60:40	7
3	**5c**	CH_2Cl_2	0	<5	–	–
4	**5d**	CH_2Cl_2	0	19	80:20	23
5	**5e**	CH_2Cl_2	0	12	62:38	89
6	**5f**	CH_2Cl_2	0	74	91:9	99
7	**5f**	PhMe	0	56	89:11	96
8	**5f**	DCE	0	58	90:10	99
9	**5f**	$CHCl_3$	0	47	89:11	99
10	**5f**	CH_2Cl_2	25	31	86:14	97
11	**5f**	CH_2Cl_2	−20	48	90:10	99
12	–	CH_2Cl_2	0	<5	–	–

[a] Unless otherwise noted, all reactions were conducted in 0.2 mmol scale of **3a**, **1a**:**2a**:**3a** = 1.5/2.5/1. See the Supporting Information for experimental details. [b] Yield of isolated product after column chromatography. [c] Determined by ^{1}H NMR analysis of crude reaction mixture. [d] Determined by HPLC analysis of the major diastereomer using a chiral stationary phase. DCE = 1,2-dichloroethane.

enantioselectivity of this three-component reaction were dramatically affected by the structure of the chiral phosphoric acid catalysts. The highest diastereo- and enantioselectivity were obtained when (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-binol phosphoric acid (**5f**) was used, thus affording the desired three-component product **4a** in 74% yield with 91:9 d.r. and 99% *ee* (entries 1–6). With 1 mol% $[Rh_2(OAc)_4]$ and 10 mol% **5f**, the effects of solvent and temperature were further investigated. When toluene, 1,2-dichloroethane (DCE), or $CHCl_3$ was used as the solvent instead of CH_2Cl_2, the yield of the desired product **4a** decreased, and the d.r. and *ee* values remained unaffected (entries 7–9). Increasing the reaction temperature to 25°C or decreasing it to −20°C also caused reduced yields of **4a**, but still resulted in high stereoselectivities (entries 10 and 11). The desired product **4a** was not afforded in the absence of phosphoric acid and the corresponding C–H insertion product was observed as the major product (entry 12). This result indicated that the use of phosphoric acid as the co-catalyst can not only provide efficient stereoselective control but is also crucial in increasing the reactivity of imine toward the Mannich-type electrophilic trapping process. In contrast, the C–H insertion product **6a** was reacted with the imine **3a** under the optimal reaction conditions, and the formation of **4a** was not observed.[17] This control experiment excluded the possibility that this three-component reaction proceeded through a stepwise C–H insertion/Mannich addition pathway. Finally, the absolute configuration of the major isomer, *anti*-**4a**, was unambiguously determined to be 2*R*,3*S* by X-ray analysis.[17]

With the optimized reaction conditions in hand, the scope with respect to the imines for this Rh^{II}/chiral PPA-catalyzed aromatic C–H functionalization was first examined. A series of substituted *N*-benzylideneanilines was found to undergo the desired transformation to give the corresponding product in good yields with high diastereoselectivities and excellent enantioselectivities (Table 2). Generally, imines derived from

Table 2: Substrate scope of imines.[a]

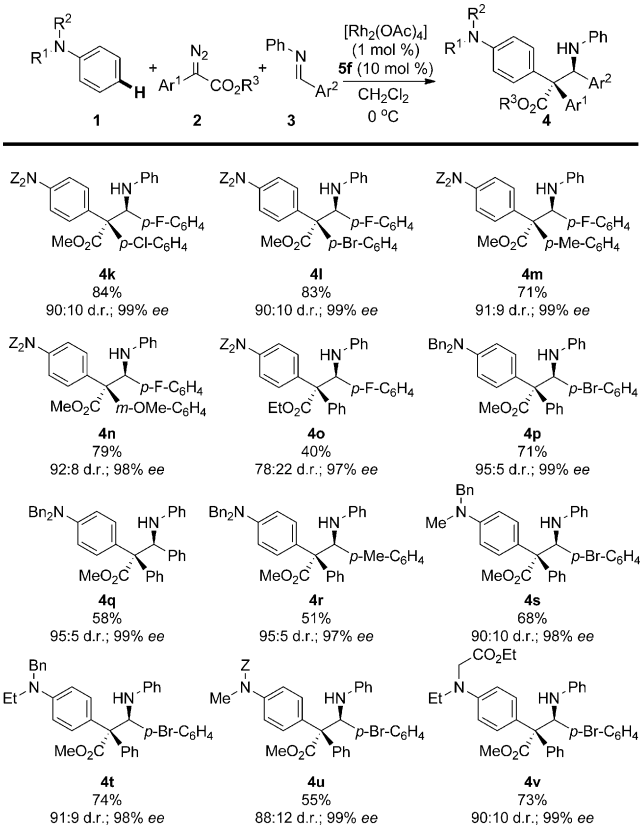


Entry	3	Ar^1/Ar^2	4	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**3a**	*p*-ClC_6H_4/Ph	**4a**	74	91:9	99
2	**3b**	*p*-BrC_6H_4/Ph	**4b**	68	92:8	98
3	**3c**	*p*-FC_6H_4/Ph	**4c**	67	91:9	99
4	**3d**	*p*-$CF_3C_6H_4$/Ph	**4d**	68	87:13	98
5	**3e**	3,4-$Cl_2C_6H_3$/Ph	**4e**	73	95:5	90
6	**3f**	Ph/Ph	**4f**	57	88:12	96
7	**3g**	*p*-MeC_6H_4/Ph	**4g**	43	82:18	98
8	**3h**	*p*-FC_6H_4/*p*-ClC_6H_4	**4h**	68	86:14	99
9	**3i**	*p*-ClC_6H_4/*p*-BrC_6H_4	**4i**	57	85:15	99
10	**3j**	Ph/*m*-BrC_6H_4	**4j**	56	80:20	97

[a] Unless otherwise noted, all reactions were conducted in 0.2 mmol scale of **3**, **1a**/**2a**/**3** = 1.5:2.5:1. [b] Yield of product isolated after column chromatography. [c] Determined by ^{1}H NMR analysis of crude reaction mixture. [d] Determined by HPLC analysis of the major diastereomer using a chiral stationary phase.

electron-deficient benzaldehydes gave the desired products in higher yields with higher diastereoselectivities than those derived from electron-rich benzaldehydes, whereas the enantioselectivities remained excellent for almost all cases (entries 1–3 and 5, 7 versus entries 4 and 6). In contrast, imines derived from electron-deficient anilines afforded the desired products with slightly lower diastereoselectivites while the yields and enantioselectivities remained almost unaffected (entry 8 versus entry 3; entry 9 versus entry 1; and entry 10 versus entry 4).

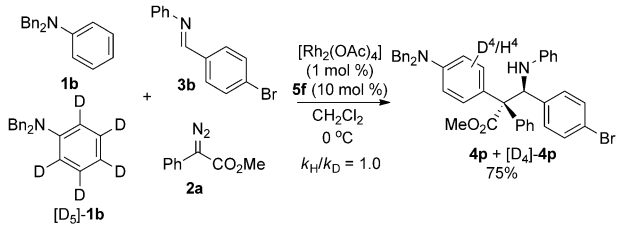
Next, the scope with respect to the diazo compounds and arenes were further investigated. A series of substituted methyl aryldiazoacetates were found to undergo the desired transformation to give the corresponding products in good yields with high diastereoselectivities and excellent enantioselectivities (**4k**–**n**; Scheme 2). When ethyl phenyldiazoace-



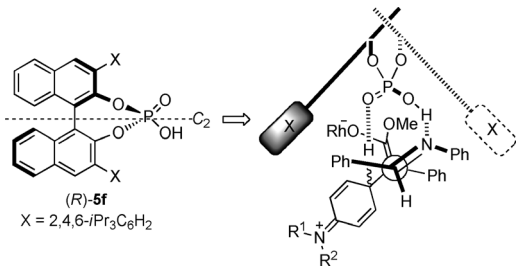
Scheme 2. Substrate scope with respect to diazo compounds and arenes. Reaction conditions: **1** (0.3 mmol), **2** (0.5 mmol), **3** (0.2 mmol). Yield of the isolated product is reported. The d.r. value was determined by ^{1}H NMR analysis of the crude reaction mixture and *ee* value was determined by HPLC of the major diastereomer using a chiral stationary phase. Z = $(CH_2)_2$OMe.

tate was used as the diazo source, both the yield and d.r. value of the desired product were decreased compared with the results obtained from methyl phenyldiazoacetate (**4o** versus **4c** in Table 2). Different *N,N*-disubstituted anilines were then tested. *N,N*-dibenzyl aniline showed superior reactivity compared to that of **1a**, thus yielding the desired products in good yields with much improved d.r. and excellent *ee* values (**4p**, **4q**, and **4r**; compare to **4b**, **4f**, and **4g** in Table 2). Since the *N,N*-dibenzyl substitution could be easily removed by hydrogenation,[18] the current transformation offers an appealing way for introducing a benzylic quaternary stereocenter at the *para* position of free anilines. Different unsymmetrically disubstituted aniline derivatives also afforded the corresponding products in good yields with high diastereoselectivities and excellent enantioselectivities (**4s–v**).

To partially support our proposed pathway involving a zwitterionic intermediate, an intermolecular kinetic isotope effect experiment was conducted. The reaction between **1b** and the deuterated analogue [D_5]-**1b** demonstrated a kinetic isotope effect of $k_H/k_D = 1.0$, which suggests that the C–H bond cleavage is not involved in the rate-limiting step (Scheme 3). This result is consistent with our proposed reaction pathway in which the electrophilic trapping of the zwitterionic intermediate with the imine is the rate-determining as well as the asymmetric-controlling step.



Scheme 3. Intermolecular kinetic isotope effect.



Scheme 4. Proposed transition state.

To rationalize the observed stereochemistry for this aromatic C–H functionalization, an interaction model proposed by Simon and Goodman[19] was used to explain the stereochemical outcome of this Mannich-type addition in the presence of chiral PPAs (Scheme 4). The chiral PPA **5f** initially interacts with the imine substrate through hydrogen bonding between the catalyst proton and the nitrogen atom of the imine. In contrast, a weak hydrogen bond between the Lewis basic phosphoryl oxygen atom and the acidic C–H proton in the zwitterionic intermediate is also formed. These two hydrogen-bonding interactions together cause the nitrogen substituent of the imine to be oriented toward the empty side of the catalyst pocket to avoid steric hindrance with the bulky substituent on the PPA. Followed by proton transfer through chiral PPA, efficient chirality induction is realized.

In summary, we have achieved the first asymmetric functionalization of aryl C–H bonds though a three-component reaction of N,N-disubstituted anilines with diazo compounds and imines in the presence of Rh^{II}/chiral phosphoric acid cocatalysts. This transformation is proposed to proceed via the generation of zwitterionic intermediates by electrophilic addition of metal carbenes to the aromatic ring, and subsequent electrophilic trapping process with imines. This transformation not only offers an efficient way for the construction of α,α-diaryl all-carbon benzylic quaternary stereocenters in good yields with high diastereoselectivities and excellent enantioselectivities, but also provides experimental evidence to support the electrophilic addition pathway via a zwitterionic intermediate for traditional metal-carbene-induced functionalization of aromatic C–H bonds.

Received: June 23, 2014
Published online: September 1, 2014

Keywords: asymmetric catalysis · C–H activation · carbenes · rhodium · zwitterions

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