C–H Activation

DOI: 10.1002/ange.201105766

Enantioselective Rhodium(I)-Catalyzed [3+2] Annulations of Aromatic Ketimines Induced by Directed C–H Activations**

*Duc N. Tran and Nicolai Cramer**

Directed functionalizations of unactivated arene C–H bonds with transition-metal catalysts[1] have evolved to be a highly prosperous field in organic chemistry, and enable a complementary and highly efficient access to a broad variety of building blocks.[2] Most often, the directing group itself remains intact during the reaction and needs to be cleaved or modified accordingly in follow-up steps. In this respect, a modification or direct incorporation of this group in the C–H functionalization reaction is an attractive strategy that induces additional complexity. For instance, important directing groups such as imines and carbonyl groups could be transformed into amino or hydroxyl groups by an addition reaction across the C=N[3] or C=O bonds,[4] or, more often, participate in the formation of C–O[5] or C–N bonds.[6] Our continuous interest in C–H functionalization for selective carbocylizations[7] prompted us to explore enantioselective reactions of ketimines with alkynes for formal [3+2] cycloadditions.[8] Such processes lead to densely functionalized indenylamines, which are key substructures in targets, as well as building blocks for various biologically active molecules,[9] and there are only few known strategies to access this class of compounds.[10] In contrast, the envisioned process represents a very efficient and direct route, although several synthetic challenges need to be addressed. Besides the requirement to establish selectivity-determining rules to differentiate between the two aryl substituents of the ketimine, a selective incorporation of unsymmetrically substituted alkynes is desirable. Whereas regioselective migratory insertions are observed for alkyl aryl substituted alkynes, the differentiation between two different alkyl groups is significantly more challenging.[11] Most importantly, the enantioselective addition that leads to free and unsubstituted chiral amines remains challenging. Although catalytic enantioselective methods for the direct preparation of free primary amines are very desirable and the products are highly valuable synthetic intermediates, examples of enantioselective processes in the context of stereoselective C–H functionalizations are very scarce.[12,13] In the case of rhenium-catalyzed [3+2] annulations reported by Kuninobu, Yu, and Takai, only the unligated complex [{$HRe(CO)_4$}$_n$] was employed.[3f] In related rhodium-catalyzed processes of ketones and alkynes to form indenols, Glorius,[4c] Cheng,[4d] and their respective co-workers employed rhodium(III) complexes that contain only a Cp* ligand (Cp* = pentamethylcyclopentadienyl). In all of these cases, the development of a catalytic enantioselective version is a difficult task because of the lack of a steering ligand. In stark contrast, the rhodium(I)-promoted reactions proceed best with complexes ligated by phosphines, thus representing a potential handle for asymmetric catalysis. Only two individual examples of the targeted directed activation/enantioselective readdition to the imine directing group have been reported. One example, which was reported by Zhao and co-workers, involved an alkyne acceptor,[8] and the other, which was reported by our research group, used a terminal allene.[3e] However, both reactions proceed with only modest enantioselectivities and are not general. Herein, we report a robust enantioselective process and illustrate its additional potential for positional activation and regioselective migratory insertion.

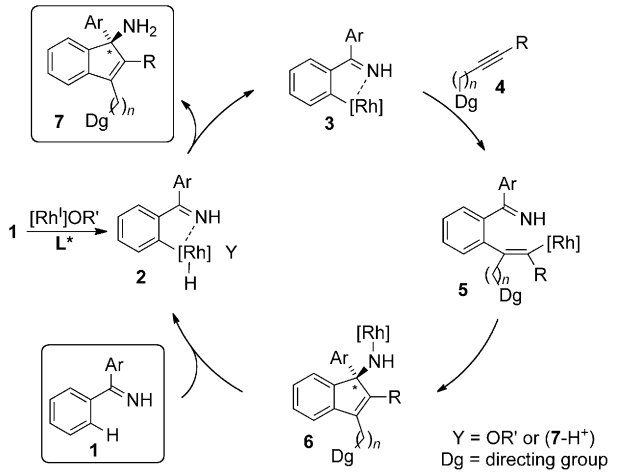
The envisioned reaction is initiated by a cyclometalation of imine **1** with a rhodium(I) complex (Scheme 1).[14] To avoid undesired hydroarylation reactivity and obtain compound **3**, it is essential to remove the hydrogen atom from the metal center, for example, by reductive elimination of either water or amine, respectively. A subsequent carborhodation of the internal alkyne **4** provides a vinyl rhodium species **5**. We speculated that the regioselectivity of this addition step could be controlled with suitable coordinating groups of an unsymmetrically substituted alkyne.[15] In turn, species **5** adds in an enantioselective manner across the ketimine moiety to give **6**. Coordination of another imine substrate, C–H activation, reductive elimination, and release of free indenyl amine **7** would then close the catalytic cycle.

As the rhodium catalyst needs to accommodate several different steps, namely metalation, and alkyne and imine addition, a careful tuning of the conditions and the ligand properties was required. The reaction was initially examined with phenyl(4-nitrophenyl)methanimine (**1a**) and 1,4-dimethoxybut-2-yne as the prototype substrate combination (Table 1).

[*] D. N. Tran, Prof. Dr. N. Cramer
Laboratory of Asymmetric Catalysis and Synthesis
EPFL SB ISIC LCSA, BCH 4305
1015 Lausanne (Switzerland)
E-mail: Nicolai.cramer@epfl.ch
Homepage: http://isic.epfl.ch/lcsa
D. N. Tran
Laboratory of Organic Chemistry, ETH Zurich
Wolfgang-Pauli-Strasse 10
8093 Zurich (Switzerland)

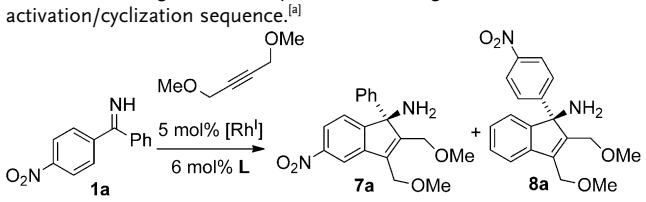
[**] We thank Dr. R. Scopelliti for X-ray crystallographic analysis of compound **7m**. This work was supported by the EPFL, ETH Zurich (ETH-16 08-3), and a starting grant from the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement no. 257891. We thank Solvias AG for MeOBiphep ligands and Takasago International Corporation for Segphos ligands.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201105766.



Scheme 1. Mechanistic model for the rhodium(I)-catalyzed C–H functionalization/cyclization of aryl ketimines with internal alkynes.

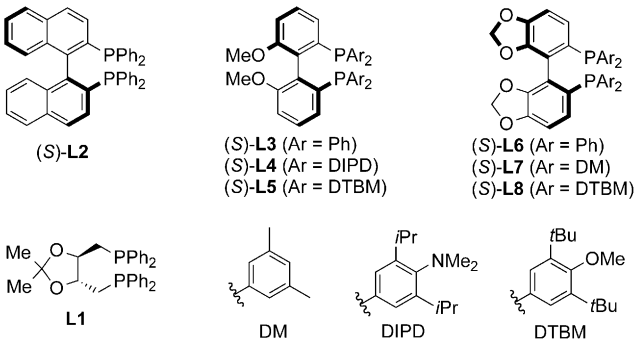
Table 1: Screening of rhodium precursors and ligands in the C–H activation/cyclization sequence.[a]



Entry	[Rh^I]	L	Yield[b] [%]	**7a**:**8a**[c]	e.r.[d]
1	[{Rh(coe)$_2$(OMs)}$_2$]	**L5**	0	–	–
2	[Rh(coe)$_2$(acac)]	**L5**	0	–	–
3	[{Rh(cod)(OMe)}$_2$]	**L5**	83	>20:1	96:4
4	[{Rh(cod)(OH)}$_2$]	**L5**	88	>20:1	96.5:3.5
5	[{Rh(cod)(NH*t*Bu)}$_2$]	**L5**	80	>20:1	96:4
6[e]	[{Rh(coe)$_2$(OH)}$_2$]	**L5**	<5	–	–
7	[{Rh(coe)$_2$(OH)}$_2$]	**L5**	89	>20:1	96.5:3.5
8[f]	[{Rh(cod)(OH)}$_2$]	**L5**	32	>20:1	96:4
9[g]	[{Rh(cod)(OH)}$_2$]	**L5**	73	>20:1	96:4
10[h]	[{Rh(cod)(OH)}$_2$]	**L5**	0	–	–
11[i]	[{Rh(cod)(OH)}$_2$]	**L5**	58	>20:1	96:4
12	[{Rh(cod)(OH)}$_2$]	**L1**	57	15:1	58:42
13	[{Rh(cod)(OH)}$_2$]	**L2**	34	9:1	77:23
14	[{Rh(cod)(OH)}$_2$]	**L3**	64	7:1	80:20
15	[{Rh(cod)(OH)}$_2$]	**L4**	78	>20:1	69:31
16	[{Rh(cod)(OH)}$_2$]	**L6**	50	6:1	76:24
17	[{Rh(cod)(OH)}$_2$]	**L7**	69	15:1	71:29
18	[{Rh(cod)(OH)}$_2$]	**L8**	92	>20:1	93.5:6.5
19[j]	[{Rh(cod)(OH)}$_2$]	**L8**	69	>20:1	90.5:9.5

[a] Reaction conditions: **1a** (0.1 mmol, 0.5 M in toluene), dimethoxybutyne (0.3 mmol), [Rh^I] (5 mol%), **L** (6 mol%), 80°C, 16 h. [b] Yield of isolated product **7a**. [c] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] With 1.5 equiv of *tert*-butylamine. [f] In octane. [g] In DMF. [h] In dioxane. [i] In *tert*-amyl alcohol. [j] At 120°C. DMF = dimethylformamide.

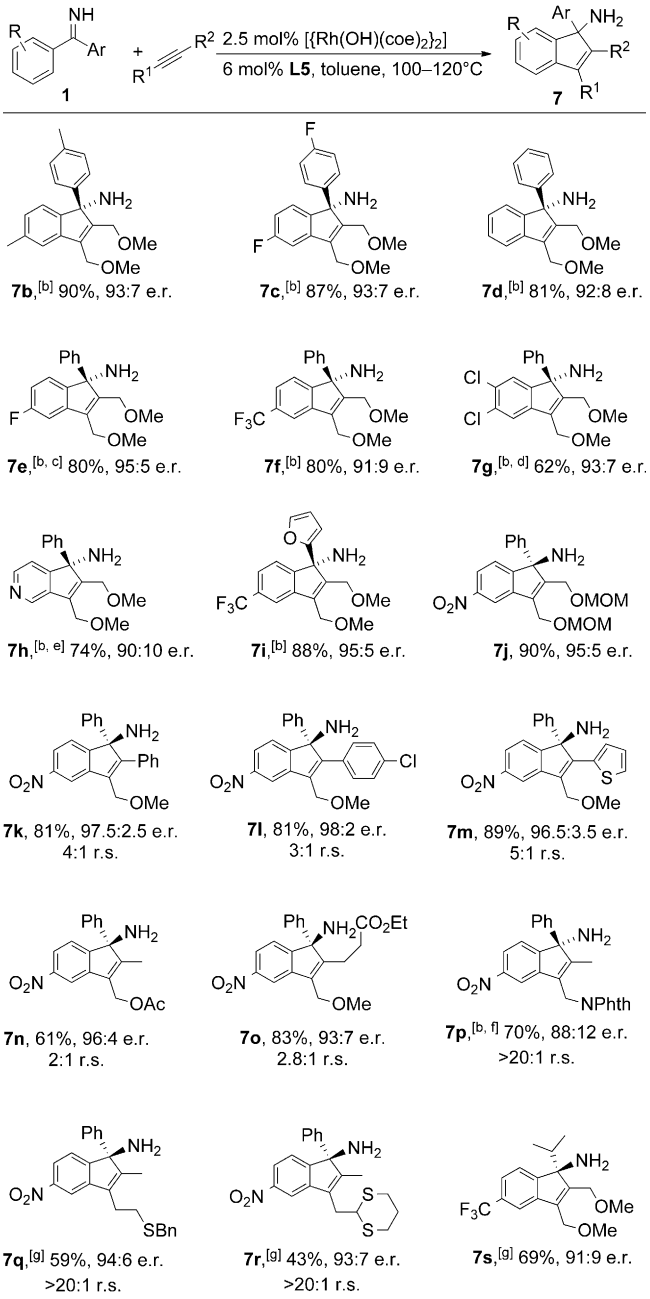
As cationic rhodium(I) or halide-counterion-containing complexes are not reactive (data not shown), we screened different oxygen-based counterions. Hydroxide ions provide superior results than other anionic oxygen-based counterions with respect to conversion and enantioselectivity (Table 1, entries 1–4). We believe that the coordinating nature of the counterion OR′ plays a pivotal role in the initial catalytic cycle by converting the rhodium complex into the catalytically active species (Scheme 1). Hence, by using [{Rh(cod)(*t*BuNH)}$_2$] as an approximation of the hypothesized species **6**, a comparable result was obtained (Table 1, entry 5). However, the addition of 1.5 equivalents of *tert*-butylamine to the reaction mixture dramatically reduced the conversion and yield (Table 1, entry 6), which is indicative for a product inhibition. Premixing of the metal complex and the phosphine ligand prior to addition of both substrates is essential to ensure high conversions. Whilst [{Rh(cod)(OH)}$_2$] requires a preincubation at at least 60°C for 10 min, the complex [{Rh(coe)$_2$(OH)}$_2$] with a more labile cyclooctene ligand allows a more convenient premixing for a few minutes at ambient temperature (Table 1, entry 7).[16] Several different solvent categories were evaluated and the conversion and yield are highest in aromatic solvents. However, the selectivity of the reaction is similar in octane, DMF, and *tert*-amyl alcohol (Table 1, entries 8–11). A screening of different chiral phosphine ligands (Scheme 2) showed that biaryl phosphines



Scheme 2. Chiral phosphine ligands utilized in this study.

are best suited (Table 1, entries 12–18). Both the yield and the enantioselectivity are sensitive to the steric bulk of the ligands. DTBM-MeOBiphep (**L5**) and DTBM-Segphos (**L8**) showed the best performance and gave enantiomeric ratios of 96.5:3.5 and 93.5:6.5, respectively (Table 1, entries 4 and 18). The use of **L4**, which has isopropyl instead of *tert*-butyl groups, resulted in a significantly reduced enantioselectivity (Table 1, entry 15). An increase of the reaction temperature by 40° to 120°C caused a decrease in enantioselectivity (90.5:9.5; Table 1, entry 19). Besides control of the enantioselectivity, the increasing steric bulk of the ligand is also beneficial for the chemoselectivity of the initial cyclometalation step. The ratio between **7a** and **8a** ranges from 6:1 to 15:1 when **L1**–**L3**, **L6**, and **L7** are used, however, product **8a** is not detected when **L4**, **L5**, and **L8** are used (**7a**:**8a** > 20:1).

Scheme 3 shows the scope of the reaction under the optimized conditions. Besides symmetrical diaryl ketimines (**1b**–**1d**), a variety of electronically different unsymmetrical diaryl ketimines (**1e**–**1g**) were employed. Generally, imine substrates that possess electron-withdrawing substituents on one of the aromatic substituents show a higher reactivity and provide a good differentiation in preference of the more



Scheme 3. Scope of C–H activation/cyclization sequence.[a] [a] Reaction conditions: **1** (0.1 mmol, 0.2–1.0 M in toluene), alkyne (1.5–3 equiv), $[\{Rh(coe)_2(OH)\}_2]$ (2.5 mol%), (*S*)-**L5** (6.0 mol%), 100–120 °C, 16 h; **7**:**8** = 20:1; r.s. = regioselectivity respective to the alkyne; e.r. values were determined by HPLC analysis on a chiral stationary phase, and isomeric ratios were determined from the ^{1}H NMR spectra of the crude reaction mixtures. [b] (*R*)-**L5** was used. [c] **7**:**8** = 15:1. [d] **7**:**8** = 11:1. [e] **7**:**8** = 5:1. [f] Chlorobenzene was used instead of toluene. [g] With 5 mol% $[\{Rh(cod)(OH)\}_2]$ and 12 mol% **L5**. Bn = benzyl, cod = cyclooctadiene, coe = cyclooctene, MOM = methoxymethyl, Phth = phthaloyl.

electron-poor ring when **L5** is used. These characteristics are maintained with heteroaromatic substituents. For instance, pyridine-containing imine **1h** reacts selectively at the pyridyl moiety to give **7h**, whereas for **1i**, the electron-rich furyl group remains untouched and **7i** is formed exclusively. Aryl alkyl substituted ketimines can be employed in the reaction (**7s**), although a slightly lower enantiomeric ratio, which is caused by a higher reaction temperature of 120 °C, is observed. When evaluating the reactivity of the internal alkyne,[17] we were particularly interested in unsymmetrically substituted compounds, which not only broaden the scope of the reaction, but also introduce an additional element of selectivity to control. Besides high enantiomeric ratios, alkyl aryl substituted alkynes also provide synthetically useful regioselectivity and gave products **7k**–**7m**. Addressing regioselectivity in alkynes, especially with two different alkyl substituents, remains a largely unsolved problem for transition-metal-catalyzed carbometalations.[11] To address this issue, we examined different potentially coordinating functional groups such as alkyl ethers, esters, phthalimides, and sulfur-containing functional groups at different distances from the alkyne.[15] In all cases, the migratory insertion occurred preferentially at the carbon atom proximal to the directing group. As already observed for the cyclometalation step, **L5** showed higher regioselectivities for the carborhodation step than propane-1,3-diylbis(diphenylphosphane) (dppp), which was utilized to prepare the corresponding racemic samples. Depending on the nature of the coordinating group on the alkyne, moderate regioselectivities were obtained with ether and ester groups (**7o** and **7n**). However, it is particularly noteworthy that even a sensitive propargyl ester can be utilized without side reactions to give **7n**. In contrast, phthalimide-, thioether-, or thioacetal-bearing alkynes reacted highly regioselective and formed only one single regioisomer (**7p**, **7q**, and **7r**, respectively).

The absolute configuration as well as the constitution of the products was established by X-ray crystallographic analysis of product **7m** (Figure 1).[18] *R*-Configured amine **7m** is obtained when the reaction is performed with (*S*)-DTBM MeOBiphep ((*S*)-**L5**) as ligand.

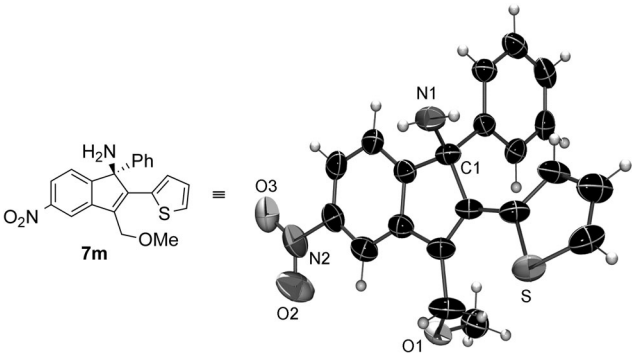
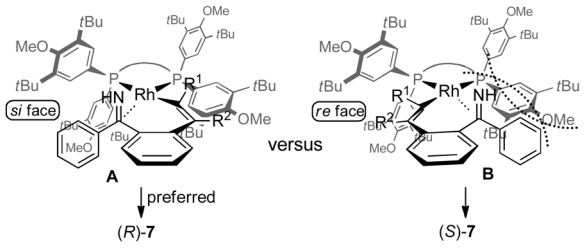


Figure 1. ORTEP representation of **7m** (thermal ellipsoids drawn at 50% probability).

The absolute configuration can be rationalized by the stereochemical pathway illustrated in Scheme 4, which shows that the imine moiety is attacked preferentially on its *si* face. Intermediate **A** is preferred to **B** as it avoids an unfavorable interaction of the ketimine portion and a DTBM residue of ligand (*S*)-**L5**.



Scheme 4. Stereochemical pathway with (*S*)-DTBM-MeOBiphep (**L5**; gray).

In conclusion, we have developed enantioselective rhodium(I)-catalyzed C–H functionalizations of unsubstituted ketimines with internal alkynes. With this protocol, a control of the stereogenic center of the amino group, a positional selectivity of the C–H activation site, as well as a regioselective addition across unsymmetrically substituted dialkyl alkynes are achievable. For the latter feature, a range of common functional groups can direct the reaction. The reaction is applicable to an attractive substrate range and is tolerant to various functional groups and heterocycles. Future studies are aimed at a deeper mechanistic understanding of the individual steps to develop more efficient catalytic systems and further improve the selectivity and generality of related rhodium(I)-catalyzed functionalizations.

Experimental Section

$[\{Rh(coe)_2(OH)\}_2]$ (1.70 mg, 2.50 μmol) and **L5** (6.91 mg, 6.00 μmol) were weighed into a vial equipped with a magnetic stirrer bar. The vial was sealed with a rubber septum and flushed with nitrogen. Dry toluene (0.1 mL) was added, the mixture was degassed by three freeze-pump-thaw cycles and stirred for 15 min at 23 °C. This solution of the preformed complex was transferred to another vial that contained a degassed and preheated (80 °C) solution of ketimine **1a** (22.6 mg, 0.10 mmol) and 1,4-dimethoxybut-2-yne (36 μL, 0.30 mmol) in toluene (0.1 mL). After 16 h, the reaction mixture was cooled to 23 °C and directly purified by column chromatography on silica gel (EtOAc/pentane = 2:1, R_f = 0.36) to give **7a** (30.3 mg, 89 %, e.r. = 96.5:3.5) as a colorless oil.

Received: August 15, 2011
Published online: October 4, 2011

Keywords: alkynes · annulation · asymmetric catalysis · C–H activation · rhodium

[1] For reviews on directed C–H functionalizations, see: a) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834; b) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35–60; c) D. Kalyani, M. S. Sanford, *Top. Organomet. Chem.* **2007**, *24*, 85–116; d) C.-H. Jun, E.-A. Jo, J.-W. Park, *Eur. J. Org. Chem.* **2007**, 1869–1881; e) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222–234; f) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655.

[2] For representative reviews on C–H functionalizations, see: a) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1769; b) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; c) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; d) F. Kakiuchi, *Top. Organomet. Chem.* **2007**, *24*, 1–33; e) T. Satoh, M. Miura, *Top. Organomet. Chem.* **2007**, *24*, 61–84; f) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; g) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; h) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013–3039; i) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; j) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; k) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087–4109; l) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; m) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874–5883; n) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725–748; o) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; p) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677–685; q) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; r) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; s) "C–H Activation ": *Topics in Current Chemistry*, *Vol. 292* (Eds.: J.-Q. Yu, Z. Shi), Springer, Heidelberg, **2010**.

[3] a) Y. Kuninobu, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2005**, *127*, 13498–13499; b) Y. Kuninobu, Y. Tokunaga, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2006**, *128*, 202–209; c) Y. Kuninobu, Y. Nishina, M. Shouho, K. Takai, *Angew. Chem.* **2006**, *118*, 2832–2834; *Angew. Chem. Int. Ed.* **2006**, *45*, 2766–2768; d) T. Fukutani, N. Umeda, K Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141–5143; e) D. N. Tran, N. Cramer, *Angew. Chem.* **2010**, *122*, 8357–8360; *Angew. Chem. Int. Ed.* **2010**, *49*, 8181–8184; f) Y. Kuninobu, P. Yu, K. Takai, *Org. Lett.* **2010**, *12*, 4274–4276; g) D. N. Tran, N. Cramer, *Chimia* **2011**, *65*, 271–273.

[4] a) P. W. R. Harris, C. E. F. Rickard, P. D. Woodgate, *J. Organomet. Chem.* **1999**, *589*, 168–179; b) K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Synlett* **2010**, 97–100; c) F. W. Patureau, T. Besset, N. Kuhl, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2154–2156; d) K. Muralirajan, K. Parthasarathy, C.-H. Cheng, *Angew. Chem.* **2011**, *123*, 4255–4258; *Angew. Chem. Int. Ed.* **2011**, *50*, 4169–4172.

[5] a) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407–1409; b) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362–5367; c) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212–11222.

[6] a) S.-G. Lim, J. Hee Lee, C. W. Moon, J.-B. Hong, C.-H. Jun, *Org. Lett.* **2003**, *5*, 2759–2761; b) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475; c) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051; d) Y. Su, M. Zhao, K. Han, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5462–5465; e) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585–9587; f) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326–18339; g) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353; h) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569; i) T. K. Hyster, T. Rovis, *Chem. Sci.* **2011**, *2*, 1606–1610; j) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem.* **2011**, *123*, 6503–6506; *Angew. Chem. Int. Ed.* **2011**, *50*, 6379–6382; k) L. Ackermann, A. V. Lygin, N. Hofmann, *Org. Lett.* **2011**, *13*, 3278–3281.

[7] a) T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem.* **2009**, *121*, 6438–6441; *Angew. Chem. Int. Ed.* **2009**, *48*, 6320–6323; b) T. Seiser, N. Cramer, *Chem. Eur. J.* **2010**, *16*, 3383–3391; c) M. Albicker, N. Cramer, *Angew. Chem.* **2009**, *121*, 9303–9306; *Angew. Chem. Int. Ed.* **2009**, *48*, 9139–9142; d) T. Seiser, G. Cathomen, N. Cramer, *Synlett* **2010**, 1699–1703; e) M. Waibel, N. Cramer, *Angew. Chem.* **2010**, *122*, 4557–4560; *Angew. Chem. Int. Ed.* **2010**, *49*, 4455–4458; g) T. Seiser, N. Cramer, *Angew. Chem.* **2010**, *122*, 10361–10365; *Angew. Chem. Int. Ed.* **2010**, *49*, 10163–10167; h) M. Waibel, N. Cramer, *Chem. Commun.* **2011**, *47*, 346–348.

[8] For a racemic version, see: Z.-M. Sun, S.-P. Chen, P. Zhao, *Chem. Eur. J.* **2010**, *16*, 2619 – 2627.
[9] a) H. Yu, I. J. Kim, J. E. Folk, X. Tian, R. B. Rothman, M. H. Baumann, C. M. Dersch, J. L. Flippen-Anderson, D. Parrish, A. E. Jacobson, K. C. Rice, *J. Med. Chem.* **2004**, *47*, 2624 – 2634; b) A. Di Stefano, P. Sozio, I. Cacciatore, A. Cocco, G. Giorgioni, B. Costa, M. Montali, A. Lucacchini, C. Martini, G. Spoto, F. Di Pietrantonio, E. Di Matteo, F. Pinnen, *J. Med. Chem.* **2005**, *48*, 2646 – 2654; c) K. R. Kim, J. H. Lee, S. J. Kim, S. D. Rhee, W. H. Jung, S.-D. Yang, S. S. Kim, J. H. Ahn, H. G. Cheon, *Biochem. Pharmacol.* **2006**, *72*, 446 – 454; d) J. H. Ahn, M. S. Shin, S. H. Jung, J. A. Kim, H. M. Kim, S. H. Kim, S. K. Kang, K. R. Kim, S. D. Rhee, S. D. Park, J. M. Lee, J. H. Lee, H. G. Cheon, S. S. Kim, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5239 – 5244.
[10] a) A. R. Katritzky, O. V. Denisko, S. Busont, *J. Org. Chem.* **2000**, *65*, 8066 – 8068; b) C.-C. Liu, R. P. Korivi, C.-H. Cheng, *Chem. Eur. J.* **2008**, *14*, 9503 – 9506; c) Y. Zhu, G. Yin, D. Hong, P. Lu, Y. Wang, *Org. Lett.* **2011**, *13*, 1024 – 1027.
[11] For examples with hydrogenatable vinyl groups as regiocontrolling element, see: M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem.* **2011**, *123*, 1374 – 1377; *Angew. Chem. Int. Ed.* **2011**, *50*, 1338 – 1341.
[12] For a review of stereoselective C–H activation reactions, see: R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242 – 3272.
[13] The enantioselective synthesis of amines by C–H functionalizations has been limited to nitrenoid insertion reactions, for a review, see: F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926 – 1936.
[14] For some mechanistic and theoretical studies, see: a) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820 – 5831; b) L. Li, W. W. Brennessel, W. D. Jones, *Organometallics* **2009**, *28*, 3492 – 3500; c) D. L. Strout, S. Zaric, S. Q. Niu, M. B. Hall, *J. Am. Chem. Soc.* **1996**, *118*, 6068 – 6069; d) M. D. Su, S. Y. Chu, *J. Am. Chem. Soc.* **1997**, *119*, 5373 – 5383; e) S. Q. Niu, M. B. Hall, *J. Am. Chem. Soc.* **1998**, *120*, 6169 – 6170; f) A. J. Toner, S. Grundemann, E. Clot, H. H. Limbach, B. Donnadieu, S. Sabo-Etienne, B. Chaudret, *J. Am. Chem. Soc.* **2000**, *122*, 6777 – 6778.
[15] For an example of substrate-directed rhodium-catalyzed hydroacylation of olefins by using thioethers, see: a) M. M. Coulter, K. G. M. Kou, B. Galligan, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16330 – 16333; for a recent review, see: b) G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498 – 2543; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450 – 2494.
[16] For all reactions, the addition of the catalyst solution directly to a preheated solution of the alkyne and imine proved to be crucial for high conversion and reproducible results.
[17] Terminal and electron-deficient alkynes such as propiolic acid derivatives do not provide the desired product **7**.
[18] Crystallographic data for **7m**: $C_{21}H_{18}N_2O_3S$, $M = 378.43$, tetragonal, space group $P4_3$, $a = 15.424(2)$ Å, $c = 15.361(3)$ Å, $V = 3654.4(10)$ Å^3, $Z = 8$, $D_{calc} = 1.376$ Mg m^{-3}, reflections collected: 12890, independent reflections: 6613 ($R_{int} = 0.0514$), R(all) = 0.0664, wR(gt) = 0.1464. CCDC 837171 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request/cif.

