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Highly Selective Intramolecular Carbene Insertion into Primary C−H Bond of α-Diazoacetamides Mediated by a (*p*-Cymene)ruthenium(II) Carboxylate Complex

Vanessa Kar-Yan Lo, Zhen Guo, Matthew Kwok-Wai Choi, Wing-Yiu Yu,† Jie-Sheng Huang, and Chi-Ming Che*

Department of Chemistry, State Key Laboratory of Synthetic Chemistry, and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong (China)

Supporting Information

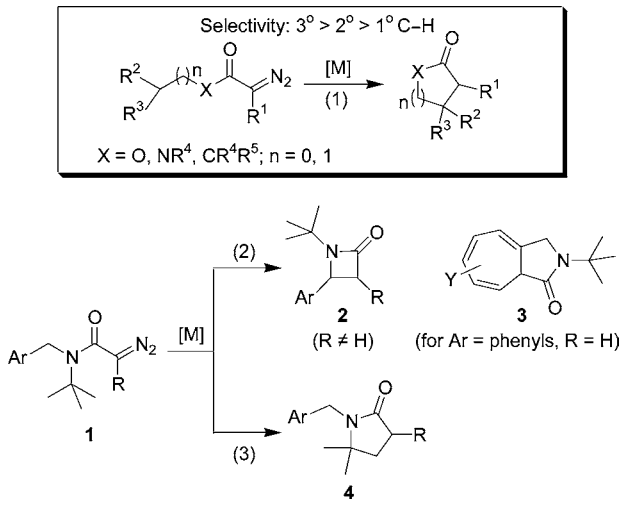
ABSTRACT: Complex [(*p*-cymene)Ru(η^1-O_2CCF_3)$_2$(OH_2)] mediated transformation of α-diazoacetamides $ArCH_2N(C(CH_3)_3)C(O)CHN_2$ to result in carbene insertion into the primary C−H bond exclusively, with the γ-lactam products being isolated in up to 98% yield. This unexpected reaction is striking in view of the presence of usually more reactive sites such as secondary C−H bonds in the substrates. DFT calculations based on proposed Ru-carbene species provide insight into this unique selectivity.

Direct functionalization of sp^3 C−H bonds by metal-catalyzed carbene insertion[1,2] is an attractive and powerful strategy for C−C bond formation. One of the challenges in this area is the functionalization of inert primary (1°) C−H bonds, particularly the selective functionalization of 1° C−H bonds in the presence of more reactive secondary (2°)/tertiary (3°) C−H bonds and/or other functional groups.

Intramolecular C−H bond functionalization by metal-catalyzed carbene insertion has received tremendous attention, predominantly using dirhodium catalysts, with diazo carbonyl compound substrates including diazoesters, diazoketones, and diazoamides (see, for example, reaction 1 in Scheme 1).[2a−c,e,f,h] These reactions usually feature a selectivity order 3° > 2° > 1° C−H bonds. The 1° C−H bonds, when coexisting with reactive 2° or 3° C−H bond(s),[3] remain not efficiently functionalized or in sparse cases[4] are functionalized as major product(s) (up to 80% isolated yield[4e]) along with considerable amounts of 2° or 3° C−H bond functionalization products or other products. For example, the dirhodium-catalyzed reaction of α-diazoacetamides **1** (reaction 2 in Scheme 1)[5] selectively afforded the β-lactams **2** through benzylic 2° C−H bond functionalization and/or the cycloheptatriene **3** through aromatic cycloaddition (Buchner reaction), *without producing 1° C−H bond insertion products such as γ-lactams* **4** (reaction 3 in Scheme 1).

Previously we demonstrated the use of ruthenium complexes as efficient catalysts for intramolecular carbene insertion into 2° or 3° C−H bonds,[6] including the transformation of **1** to **2** in up to 98% yield using catalyst [(*p*-cymene)$RuCl_2$]$_2$ or polymer-supported ruthenium nanoparticles.[6c,d] Similar formation of **2** from **1** was also observed by Maas and co-workers using di- or tetraruthenium carbonyl catalysts, although these ruthenium

Scheme 1



carbonyl complexes can catalyze intramolecular carbene insertion of *N,N*-diethyl-2-diazoacetoacetamide to give a mixture of 1° and 2° C−H bond functionalization products in up to 87% combined yield, with 1° C−H bond functionalization accounting for up to 70% yield.[4g]

Herein we report a (*p*-cymene)ruthenium(II) carboxylate complex that mediated the transformation of **1** (R = H) to **4** (reaction 3 in Scheme 1) in up to 98% isolated yield with neither **3** nor **2** being detected, together with DFT calculation studies on the origin of such selectivity. To the best of our knowledge, this work provides the first example of metal-mediated intramolecular carbene insertion into 1° C−H bonds in virtually quantitative yield in the presence of usually more reactive sites such as 2° C−H bonds.

Ruthenium carboxylate complexes such as [CpRu(η^2-O_2CR')(PPh_3)] (Cp = cyclopentadienyl) were previously reported to react with diazo compounds (such as Ph_2CN_2 and EtO_2CCHN_2) to give five-membered cyclometalated complexes[7] (inset in Scheme 2), a reaction that can be considered as carbene insertion into the M−O bond via attack of carboxylate oxygen by a coordinated carbene group.[8] In this

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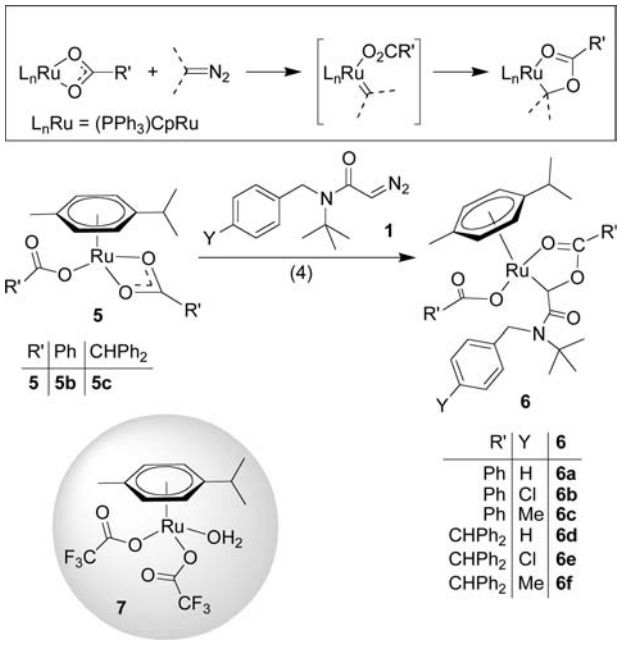
Scheme 2



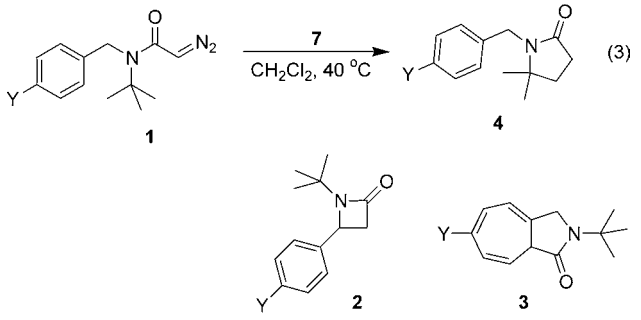
work, we prepared [(*p*-cymene)Ru(η^2-O_2CR')(η^1-O_2CR')] (R′ = Me **5a**, Ph **5b**, $CHPh_2$ **5c**) according to reported procedures[9] and determined the crystal structure of **5b** by X-ray analysis (Figure S1, Supporting Information). Treatment of **5b,c** with 1 equiv of **1** gave the five-membered cyclometalated complexes **6a–f** (reaction 4 in Scheme 2) in 97–99% isolated yields; **2–4** were not detected by ^{1}H NMR analysis of the reaction mixture. Complex **6e** has been structurally characterized by X-ray crystallography (Figure S2).

In efforts to prepare [(*p*-cymene)Ru(η^2-O_2CCF_3)(η^1-O_2CCF_3)] according to the literature procedure,[9] we obtained [(*p*-cymene)Ru(η^1-O_2CCF_3)$_2$(OH_2)] (**7**, Scheme 2), as revealed by its X-ray crystal structure (Figure S3) and ^{1}H NMR analysis at −50 to 50 °C (Figure S4). The ^{1}H NMR analysis also revealed a nonfluxional behavior of **7** in solution, unlike the fluxional behavior of **5b** (Figure S5) attributable to interconversion of η^2- and η^1-coordination modes of its benzoate ligand.[10] Upon treating **7** with **1** (Y = H, Cl, Me; Scheme 2), the corresponding five-membered cyclometalated complexes (**6** in Scheme 2 with R′ = CF_3 and Y = H, Cl, Me) were not obtained.

The catalytic behavior of **7** toward intramolecular carbene insertion was initially examined using substrate **1a** (Table 1) under various conditions (Table S1). Previously reported reaction of **1a** catalyzed by dirhodium complexes[5a,b] afforded a mixture of cycloheptatriene **3a** and the benzylic 2° C–H bond insertion product **2a** in 96–99% combined yields (**3a**/**2a** ratio = 98:2 to 30:70) or in the case of catalyst [$Rh_2(O_2CMe)_4$] gave **3a** exclusively.

To our surprise, complex **7** (5 mol %) catalyzed the reaction of **1a** in CH_2Cl_2 at 40 °C for 1 h to predominantly give the 1° C–H bond insertion product **4a** in a **4a**/**3a**/**2a** ratio of 84:7:9 with a 96% combined yield based on consumed substrate (65% conversion, entry 1 in Table S1). At a higher loading of **7** (15 mol %), the selectivity of **4a** increased to a **4a**/**3a** ratio of 96:4 (95% combined yield with 100% substrate conversion; no **2a** was detected by ^{1}H NMR). Complexes **5a–c** at 5 mol % loading catalyzed transformation of **1a** to a mixture of **4a**, **3a**, and **2a** in up to 87% combined yield (reaction time: 24 h) with poor selectivity of **4a**. Other ruthenium complexes, including [(*p*-cymene)$RuCl_2$]$_2$, $Ru_3(CO)_{12}$, [$Ru(CO)_3Cl_2$], and [Ru(TPP)(CO)], were also inferior to **7** in terms of **4a** selectivity (Table S1). Under optimized conditions (25 mol % of catalyst, in CH_2Cl_2 at 40 °C for 1 h), using **7** as a catalyst resulted in the transformation of **1a** to **4a** exclusively, with **4a** isolated in 98% yield (entry 1, Table 1).

Table 1. Intramolecular Carbene C–H Insertion of α-Diazoacetamides 1 Mediated by 7[a]



Y	H	F	Cl	Br	Me	OMe		o-Y	o-Cl
1	1a	1b	1c	1e	1f	1g		1	1d
4	4a	4b	4c	4e	4f	4g		4	4d
3	3a	3b	3c	3e	3f	3g		3	3d
2	2a	2b	2c	2e	2f	2g		2	2d

		product ratio (%)[b]			
entry	substrate **1**	**4**	**3**	**2**	total yield[c] (%)
1	**1a**	**4a**, 100	–[d]	–[d]	98
2	**1b**	**4b**, 100	–	–	98
3	**1c**	**4c**, 100	–	–	98
4	**1d**	**4d**, 100	–	–	97
5	**1e**	**4e**, 100	–	–	96
6	**1f**	**4f**, 82	–	**2f**, 18	95[b]
7	**1g**	**4g**, 39	**3g**, 43	**2g**, 18	95[b]

[a]Reaction conditions: **1** (1.0 mmol), **7** (25 mol %), CH_2Cl_2 (4 mL), 40 °C, 1 h. [b]Determined by ^{1}H NMR analysis of crude reaction mixture using 1,1-diphenylethene as internal standard. [c]Isolated yield. [d]Not detected.

Exclusive formation of 1° C–H bond insertion product **4** from α-diazoacetamides **1** catalyzed by **7** was also found using substrates **1b,c,e** bearing *p*-Y (Y = F, Cl, Br) substituents or **1d** bearing *o*-Cl substituent; the isolated yields of **4b–e** were 96–98% (entries 2–5, Table 1). For α-diazoacetamides **1f,g** bearing *p*-Me and *p*-OMe substituents, respectively, the selectivity for the formation of **4** decreased, with a **4f**/**2f** ratio of 82:18 and a **4g**/**3g**/**2g** ratio of 39:43:18 (entries 6 and 7, Table 1), though the combined yield still reached 95%.

We have undertaken hybrid DFT studies, at the B3LYP/6-31G(d) (LANL2DZ for Ru) level of theory, to gain insight into the origin of the unique selectivity in the **7**-mediated carbene insertion reaction. On the basis of previous DFT studies of dirhodium-catalyzed inter-[11a] and intramolecular[11b] carbene insertion into C–H bonds via Rh-carbene intermediates, we propose the generation of Ru-carbene intermediate **A** (Figure 1) from reaction of complex **7** with **1a**. Given the isolation of **6a–f** for complexes **5b,c** (Scheme 2), the possible transformation of **A** to **6** in Scheme 2 with R′ = CF_3 and Y = H (species **B**) was considered in initial calculations. This transformation is exothermic by 16.3 kcal/mol (Scheme S1), and attempts to locate its transition state were unsuccessful; the

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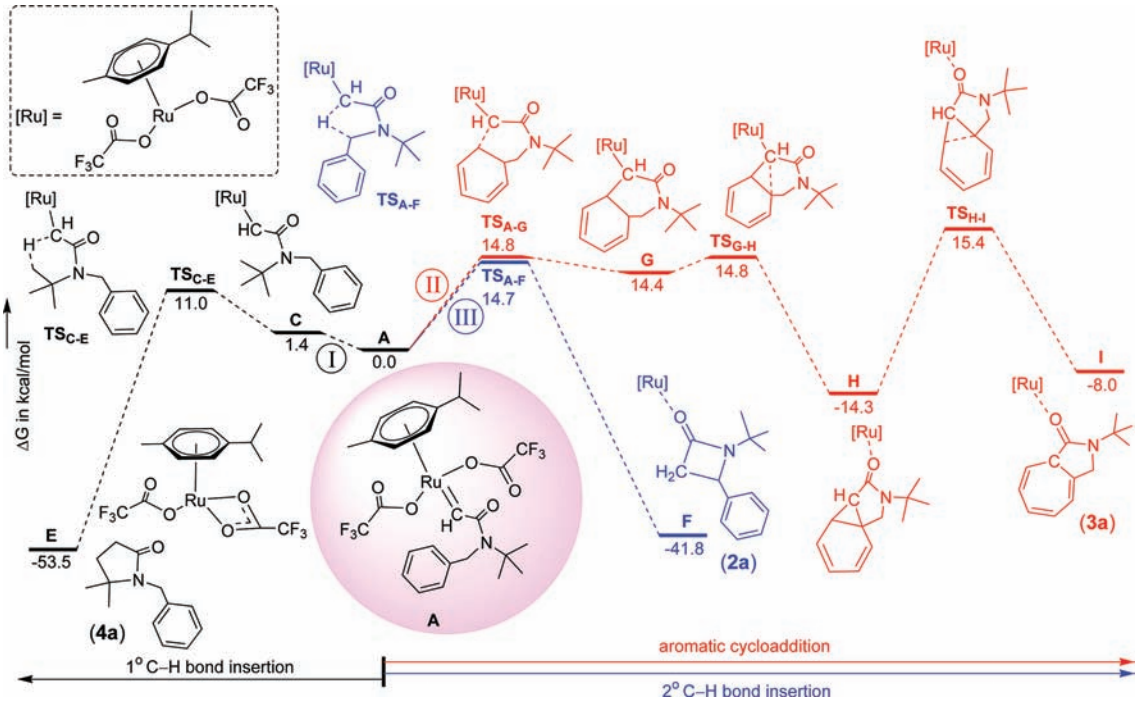

Figure 1. Calculated potential energy surfaces for the formation of (pathway I, black) γ-lactam **4a** by carbene insertion into the 1° C−H bond of ^{t}Bu group, route A to E, (pathway II, red) cycloheptatriene **3a** by aromatic cycloaddition, route A to I, and (pathway III, blue) β-lactam **2a** by carbene insertion into benzylic 2° C−H bond, route A to F, from complex **A** at the B3LYP/6-31G(d):LANL2DZ level.

process might be barrierless (as further supported by the potential energy surface of relaxed scan calculation on C−O bond distance of **B**). However, formation of product **4a** from **B** is less favored, as its transition state $\mathbf{TS_{D\text{-}E}}$ (Scheme S1) is higher in energy by 2.6 kcal/mol than that ($\mathbf{TS_{C\text{-}E}}$, Figure 2) from **A** (pathway I in Figure 1). Therefore, only species **A** was considered in subsequent calculations.

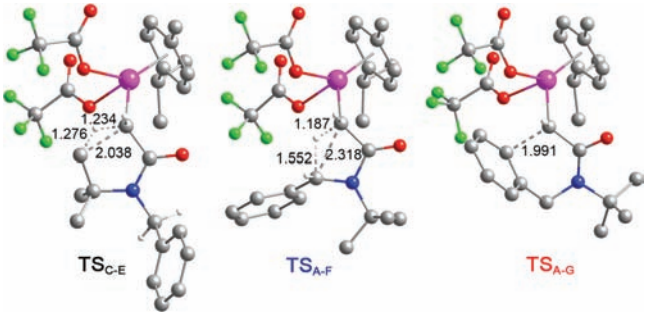

Figure 2. Computed structures of transition states $\mathbf{TS_{C\text{-}E}}$, $\mathbf{TS_{A\text{-}G}}$, and $\mathbf{TS_{A\text{-}F}}$. Key C···H and C···C distances (Å) are shown.

Starting from species **A**, products **3a** and **2a** were formed through pathways II and III, via transition states $\mathbf{TS_{A\text{-}G}}$ and $\mathbf{TS_{A\text{-}F}}$ (Figure 2), respectively, as depicted in Figure 1. Compared with pathways II and III, pathway I has the following features: (i) lower potential energy surface of the transition state (11.0 ($\mathbf{TS_{C\text{-}E}}$) vs 14.8 ($\mathbf{TS_{A\text{-}G}}$) and 14.7 ($\mathbf{TS_{A\text{-}F}}$) kcal/mol); (ii) more exothermic (−53.5 vs −8.0 and −41.8 kcal/mol); (iii) significantly less elongated C−H bond in the transition state (C···H distance 1.276 ($\mathbf{TS_{C\text{-}E}}$) vs 1.552 ($\mathbf{TS_{A\text{-}F}}$) Å, Figure 2). Evidently, pathway I features an early transition state with a lower energy barrier than pathways II and III. Therefore, the transformation of species **A** to **4a** via carbene insertion into 1° C−H bond is kinetically and thermodynamically favorable, in agreement with selective formation of **4a** in the reaction of **1a** catalyzed by **7**. This preferential 1° C−H insertion selectivity is likely to be attributed to the combined steric effect of auxiliary $CF_3CO_2^-$ ligand and conformation of coordinated carbene ligand generated in situ from the diazo compound, directing the 1° C−H bond to the proximity of the reactive Ru-carbene unit.

A closer approach of the *N*-^{t}Bu 1° C−H bond to the carbene ligand for cyclization is suggested by Thorpe−Ingold effect, or in more general terms the *gem*-dialkyl effect and *gem*-disubstituent effect;[12] such effects also include the reactive rotamer effect (i.e., higher population of the rotamers properly oriented for the cyclization). We examined the selectivity of **7** for substrates $PhCH_2N(^{i}Pr)C(O)CHN_2$ (**1′**) and $^{i}PrN(^{i}Pr)C(O)CHN_2$ (**1″**) bearing *N*-^{i}Pr group(s), which would benefit from *gem*-dialkyl effect in the 3° instead of 1° C−H bond insertion. In these reactions, **1′** was converted into aromatic cycloaddition product in ∼80% yield, with the 1° and 3° C−H insertion products each in ∼5% yield for **1′** and ∼21% yield for **1″** (Scheme S2). Note that changing the *N*-^{t}Bu group in **1a** to *N*-^{i}Pr somewhat reduces the nucleophilicity of the 1° C−H bonds, thus decreasing their reactivity toward electrophilic carbene ligand. Superior reactivity of the ^{t}Bu group has been reported in selective intermolecular 1° C−H functionalization reactions catalyzed by palladium complexes[13,14] via, for example, five-membered palladacycle intermediates.[13a,b] However, the absence of product **4a** in the dirhodium-catalyzed reaction of **1a**,[5a,b] and the low selectivity of **4a**,**g** in the reaction of **1a**,**g** catalyzed by **5** and **7**, respectively, indicate insignificant or minor impact of the *N*-^{t}Bu group in these cases, possibly due to steric hindrance and/or unfavorable electronic factors (such as decreased electrophilicity of the carbene group due to lack of strongly electron-withdrawing CF_3 groups in **5**, or increased nucleophilicity of the phenyl group or benzylic 2° C−H bonds

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in the substrate caused by electron-donating *p*-MeO substituent). Thus, the selective formation of **4a**−**e** from the **7**-catalyzed reaction of **1a**−**e** should stem from both electronic effects and steric effects or kinetic factors, including favorable distance and shape of the transition state for the 1° C−H insertion. Manipulation of steric and electronic effects is among the strategies employed for selective functionalization of the least hindered 1° C−H bonds of linear alkanes by metal-catalyzed intermolecular reactions.[15]

In summary, the (*p*-cymene)ruthenium(II) carboxylate complex **7** unexpectedly exhibited a strikingly high selectivity toward intramolecular carbene insertion into 1° C−H bonds in the presence of usually more reactive benzylic 2° C−H bonds. Using **7** as catalyst, a number of α-diazoacetamides **1** (R = H) were converted to γ-lactams **4** exclusively, with isolated yields of 96−98% (entries 1−5, Table 1). *To the best of our knowledge, an effective transformation of* ***1*** *to* ***4*** *has not been documented previously.* The present work provides a unique example of sp^3 C−H bond functionalization and points to the feasibility of developing ruthenium catalysts for selective functionalization of 1° C−H bonds via carbene insertion by judicious choice of ligands and substrates. Studies are under way to extend the reaction to other types of substrates; for example, reaction of $PhCH_2CH_2N(C(CH_3)_3)C(O)CHN_2$ mediated by **7** also exclusively afforded the 1° C−H bond insertion product (Scheme S3).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization of compounds (including NMR spectra and CIF files), Table S1, Figures S1−S5, Schemes S1−S3, and coordinates of computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

cmche@hku.hk

Present Address

[†]State Key Laboratory of Chiralsciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Handbook of C−H Transformations: Applications in Organic Synthesis*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005. (b) *C−H Activation*; Yu, J.-Q., Shi, Z., Eds.; Topics in Current Chemistry *292*; Springer-Verlag: Berlin, 2010.

(2) Selected recent reviews: (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (d) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (e) Hansen, J.; Davies, H. M. L. *Coord. Chem. Rev.* **2008**, *252*, 545. (f) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061. (g) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (h) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (i) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950.

(3) For diazoester $(CH_3)_3COC(O)CHN_2$ containing neither 3° nor 2° sp^3 C−H bond, a copper-catalyzed intramolecular carbene insertion into the 1° C−H bond in up to 99% isolated yield has been reported. See: Martín, C.; Belderraín, T. R.; Pérez, P. J. *Org. Biomol. Chem.* **2009**, *7*, 4777.

(4) For examples, see: (a) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (b) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8991. (c) Doyle, M. P.; Zhou, Q.-L.; Raab, C. E.; Roos, G. H. P. *Tetrahedron Lett.* **1995**, *36*, 4745. (d) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837. (e) Padwa, A.; Straub, C. S. *J. Org. Chem.* **2003**, *68*, 227. (f) Grohmann, M.; Buck, S.; Schäffler, L.; Maas, G. *Adv. Synth. Catal.* **2006**, *348*, 2203. (g) Grohmann, M.; Maas, G. *Tetrahedron* **2007**, *63*, 12172.

(5) Selected examples: (a) Doyle, M. P.; Shanklin, M. S.; Oon, S.-M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384. (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (c) Snyder, J. P.; Padwa, A.; Stengel, T.; Arduengo, A. J., III; Jockisch, A.; Kim, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 11318.

(6) (a) Cheung, W.-H.; Zheng, S.-L.; Yu, W.-Y.; Zhou, G.-C.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2535. (b) Zheng, S.-L.; Yu, W.-Y.; Xu, M.-X.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 1445. (c) Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081. (d) Choi, M. K.-W.; Yu, W.-Y.; So, M.-H.; Zhou, C.-Y.; Deng, Q.-H.; Che, C.-M. *Chem. Asian J.* **2008**, *3*, 1256.

(7) (a) Werner, H.; Braun, T.; Daniel, T.; Gevert, O.; Schulz, M. *J. Organomet. Chem.* **1997**, *541*, 127. (b) Baratta, W.; Del Zotto, A.; Rigo, P. *Organometallics* **1999**, *18*, 5091.

(8) (a) Daniel, T.; Mahr, N.; Braun, T.; Werner, H. *Organometallics* **1993**, *12*, 1475. (b) Rodríguez-García, C.; Oliva, A.; Ortuño, R. M.; Branchadell, V. *J. Am. Chem. Soc.* **2001**, *123*, 6157.

(9) Tocher, D. A.; Gould, R. O.; Stephenson, T. A.; Bennett, M. A.; Ennett, J. P.; Matheson, T. W.; Sawyer, L.; Shah, V. K. *J. Chem. Soc., Dalton Trans.* **1983**, 1571.

(10) Kavanagh, B.; Steed, J. W.; Tocher, D. A. *J. Chem. Soc., Dalton Trans.* **1993**, 327.

(11) Selected examples: (a) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181. (b) Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2003**, *345*, 1159.

(12) A recent review: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

(13) Selected examples: (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (b) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (c) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680.

(14) Selected recent reviews involving palladium-catalyzed 1° C−H functionalization: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902.

(15) (a) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (b) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992 and references therein.