Asymmetric Catalysis

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Asymmetric Palladium-Catalyzed Allylic Alkylation Using Dialkylzinc Reagents: A Remarkable Ligand Effect**

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Abstract: *A serendipitously discovered palladium-catalyzed asymmetric allylic alkylation reaction with diorganozinc reagents, which displays broad functional group compatibility, is reported. This novel transformation hinges on a remarkable ligand effect which overrides the standard "umpolung" reactivity of allyl–palladium intermediates in the presence of dialkylzincs. Owing to its mild conditions, enantioselective allylic alkylations of racemic allylic electrophiles are possible in the presence of sensitive functional groups.*

The stereoselective introduction of isolated, all-alkyl-substituted stereocenters in cyclic or acyclic frameworks remains a daunting synthetic challenge.[1] In particular, lone ethyl- and methyl-bearing tertiary stereocenters are present in many bioactive substances (Figure 1).[2] Additionally, the methyl or ethyl substitution of methylene groups can lead to enhanced pharmacokinetics by blocking or slowing down typical oxidative metabolic pathways.[3]

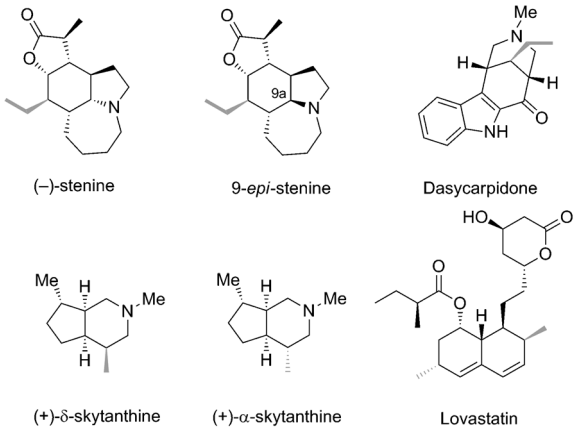

Figure 1. Natural products bearing lone ethyl or methyl stereocenters.

Palladium-catalyzed asymmetric allylic alkylation (AAA) is a powerful bond-forming synthetic method for the formation of C–C and C–X bonds,[4a–c] particularly enabling the quantitative conversion of chiral racemic substrates into single enantiomeric products, through deracemization.[4d–h] The most widely accepted model states that stabilized or "soft" nucleophiles attack the pivotal allyl–Pd intermediate through an outer-sphere substitution reaction with inversion at carbon, thus leading to global retention of configuration. Conversely, nonstabilized or "hard" nucleophiles generally afford overall inversion of configuration, as the nucleophile transmetalates to palladium before reductive elimination to the final product takes place.[4] Pd-catalyzed AAA reactions carried out in conjunction with "soft" nucleophiles are well established in the literature. Unfortunately, most of the work developed for the latter cannot be easily transposed for "hard" nucleophiles. Indeed, the use of main-group organometallic reagents such as Grignard reagents and organolithium derivatives is plagued by β-hydride elimination as a competing mechanistic pathway, leading to reduced products. As a consequence, only few reports describe the use of "hard" nucleophiles in the context of AAA.[5] In particular, dialkylzinc reagents are well known to divert the standard reactivity of Pd–allyl complexes converting them into nucleophilic allyl moieties.[6] This type of "umpolung" chemistry constitutes a successful class of reactions in its own right (Scheme 1a), of which the Marshall–Tamaru propargylation is a prime example that enjoys widespread use in natural product total synthesis.[7]

Highly enantioselective allylic alkylation reactions employing organolithium and Grignard reagents as nucleophiles can be realized with copper catalysis (Scheme 1b).[8] However, the high nucleophilicity and basicity of those reagents is a drawback of these procedures.[9] To the best of our knowledge, deracemizing allylic alkylation of cyclic, racemic electrophiles with "hard" nucleophiles (Scheme 1b) has only been achieved with alkyl lithium or magnesium derivatives thus far. Herein, we report a Pd-catalyzed asymmetric allylic alkylation employing dialkylzinc reagents which relies on a unique ligand effect (Scheme 1c).

Our investigations in this area stem from a serendipitous observation made during the study of "umpolung"-type reactions of the cyclobutene substrate *rac*-**1** (Scheme 2). When this allylic chloride was exposed to catalytic amounts of [{Pd(allyl)Cl}$_2$], the chiral phosphoramidite L1, and a slight excess of Et_2Zn (2.4 equiv) in the presence of benzaldehyde derivative **2**, the "umpoled" nucleophilic addition product **3** was obtained in good yield.[6] In contrast, when TADDOL-

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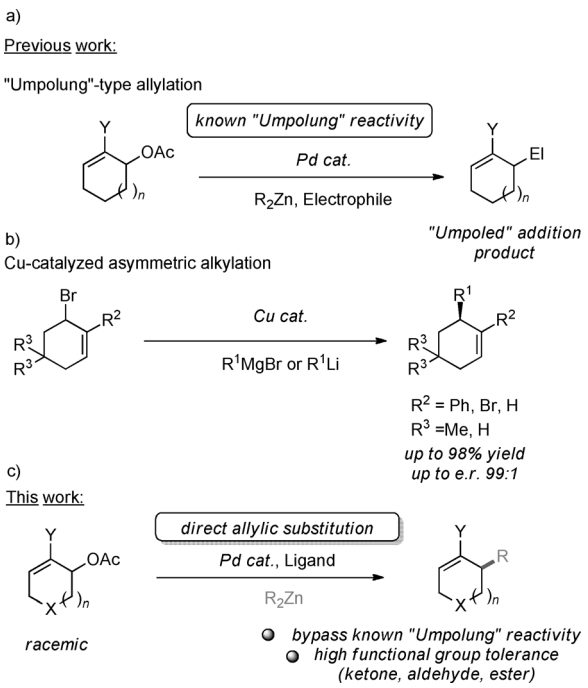
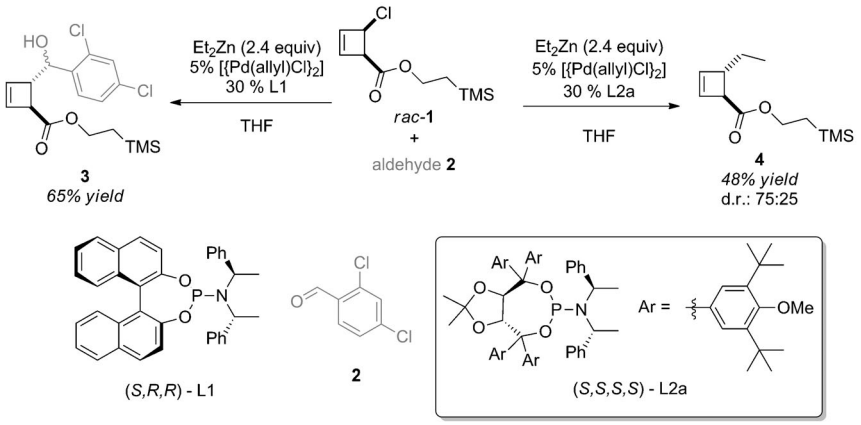


Scheme 1. Pd-catalyzed "umpolung" chemistry and state-of-the-art asymmetric allylic alkylation employing "hard" nucleophiles.



Scheme 2. Serendipitous discovery of an unusual ligand effect. TMS = trimethylsilyl.

derived ligand L2a[4i,10] was employed, we were surprised to observe the ethylated cyclobutene **4** as the only reaction product (Scheme 2).

This unusual ligand effect (particularly given the rather close structural relationship of L1 and L2a) prompted us to investigate the transformation further in the absence of electrophiles. An extensive screening of ligands was conducted and selected examples are depicted in Scheme 3.[11] As shown, chiral phosphoramidites L2/L3, bearing a TADDOL/TARTROL backbone, are uniquely capable of successfully promoting the alkyl transfer reaction. With all other ligands, only the product of halide reduction, cyclobut-2-enoic acid (**7**), was observed.

Further reaction optimization[11] was carried out employing L2a, leading to product **6a** in high diastereo- and enantioselectivity. As portrayed in Scheme 4, both primary and secondary dialkylzinc nucleophiles can be added to the cyclobutenyl framework with moderate to excellent selectivities and yields. Although in our previous studies with cyclobutenyl electrophiles in asymmetric palladium catalysis we observed a very special influence of the small ring size and the carboxylic acid moiety,[4i,12] the early success with ester **1** suggested that this alkyl transfer could be a more general transformation.

We thus directed our attention to cyclohexenyl electrophiles. In the event, the use of ligand L2b enabled deracemizing, asymmetric allylic alkylation with Et_2Zn to take place on chlorocyclohexenes *rac*-**8** with excellent diastereo- and enantioselectivity. Importantly, the use of *cis*-**8a** and *trans*-**8b** led to *trans*-**9a** and *cis*-**9b** alkylation products, respectively (Scheme 5). This confirmed that this process takes place with clean inversion of configuration at the reactive center.

At this juncture, we evaluated the influence of the leaving group in this alkyl-transfer reaction, and chose 4-phenylcyclohex-1-ene derivatives as substrates (Table 1). Since a vast majority of the known catalytic asymmetric alkylation reactions employ allylic halides as electrophiles, we were enticed by the possibility of using ester leaving groups.[13] Our results are compiled in Table 1.

Excellent diastereocontrol was observed, with *cis* substrates **10a/c–e** converting into the *trans* epimer of the product. The temperature values listed for each substrate represent the lowest temperature at which reactivity was observed, and conveys reactivity differences qualitatively. The acetate substrate (Table 1, entry 1), along with the methyl- and phenylcarbonate derivatives (Table 1, entries 3 and 4) displayed similar efficiency at −20 °C, delivering *trans*-**11a** in good to excellent yield and enantioselectivity. The use of a more hindered pivaloyl ester (Table 1, entry 2) led to no reaction observed even at ambient temperature. The substrate with a tailor-made (2-methylthio)acetyl leaving group (Table 1, entry 5), which was developed in the Ni-catalyzed leaving-group-directed, enantiospecific substitution reported by Jarvo et al.,[1a] also led to a successful reaction, even at lower temperature. It is accepted that coordination of the organozinc reagent to the leaving group accelerates oxidative addition of the substrate to the nickel catalyst. Such an accelerating effect may also be responsible for the qualitatively higher reactivity observed here.

We then further investigated the scope of the reaction. Results are compiled in Table 2. As depicted in entries 1–5, racemic acetates and carbonates undergo deracemizing alkylation by dialkylzinc reagents in good to excellent yields and very good enantioselectivities. Table 2, entries 6–8 showcase the excellent functional group tolerance of dialkylzinc

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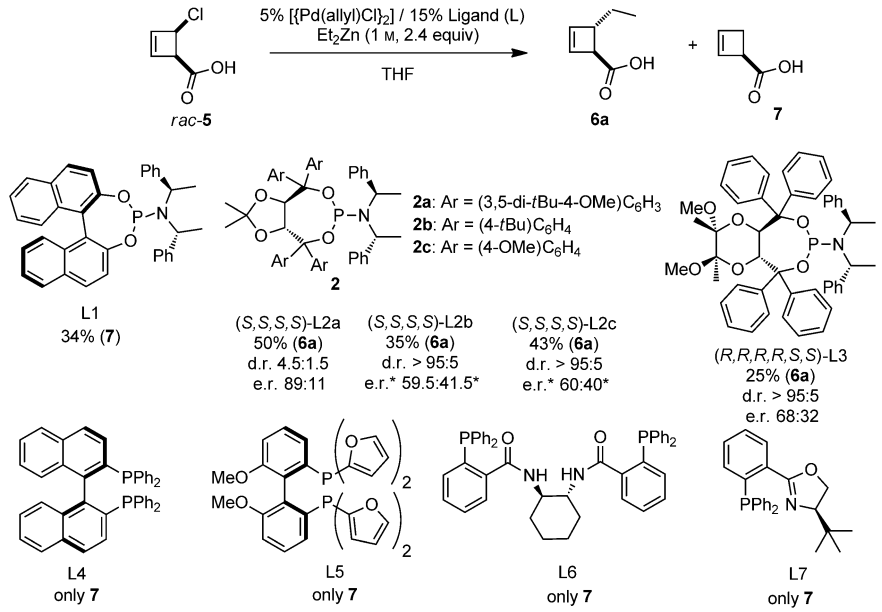
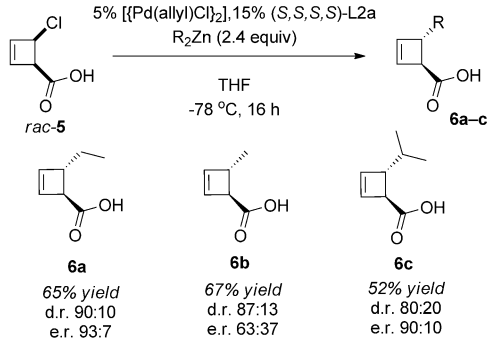
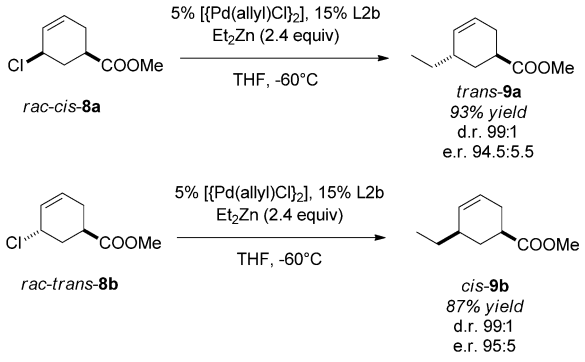


* 2.5% Pd, 7.5% Ligand were used

Scheme 3. Ligand screening for the ethyl-transfer reaction. e.r. values were determined on the *N*-benzylamide derivative of **6a**.[11] Yields determined by ^{1}H NMR analysis (internal standard).



Scheme 4. Catalytic asymmetric alkylation of cyclobutenyl electrophiles.[11]

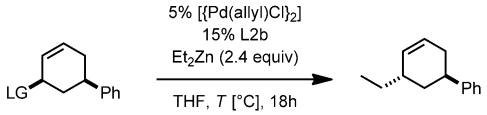


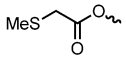
Scheme 5. Inversion of configuration in the catalytic asymmetric alkylation of cyclohexenyl electrophiles. Yields are for isolated products.[11]

nucleophiles, as Weinreb amides, ketones, and even free aldehydes (Table 2, entry 7) are tolerated in this transformation. Allylic piperidine acetates are also suitable electrophiles for this transformation, which is not limited to substrates with six-membered rings (Table 2, entries 9 and 10).

The complementarity of the transformations reported herein relative to state-of-the-art, copper-catalyzed allylic alkylation methodologies is best expressed by the experiments depicted in Scheme 6. As shown, a standard copper-catalyzed asymmetric allylic alkylation[8d] employing EtMgBr as the nucleophile with the free ketone **19a** leads to extensive 1,2-addition to the carbonyl group,[11] generating a complex mixture (Scheme 6a). Additionally, attempted Cu-catalyzed preparation of a racemic sample of **22b** for the determination of the enantioselectivity by chromatography (HPLC) led to the product (**26a**) of reduction of a putative ring-opened intermediate **25** (Scheme 6b).[8g–i]

Table 1: Leaving-group effect. The d.r. value of product **11a** was > 95:5 in all entries (^{1}H NMR analysis of the crude product). Yields refer to isolated product.[11]



Entry	Leaving group	Substrate	*T* [°C]	Yield [%]	e.r.
1	OAc	**10a**	−20	89	98:2
2	OPiv	**10b**	RT	–	–
3	OCO_2Me	**10c**	−20	76	98:2
4	OCO_2Ph	**10d**	−20	85	98:2
5		**10e**	−40	79	97:3

Interestingly, exposure of linear acetate **27a** to similar reaction conditions cleanly led to the reduced product **28** in high yield (Scheme 7). A deuterium-labeling experiment delivered **28d** and identified this as the result of "umpolung"-type transmetalation towards a nucleophilic allyl–metal intermediate, quenching of which likely leads to the observed product.

The alkylated products obtained offer additional opportunities for synthetic modification (Scheme 8). Regio- and stereoselective halohydrin formation affords **29** in 68% yield,

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Table 2: Scope of the deracemizing alkyl-transfer reaction. Reaction conditions are the same as those in Scheme 5 and yields are for isolated compounds.

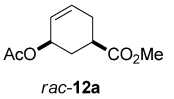
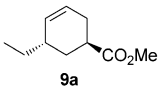
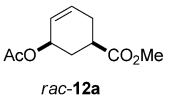
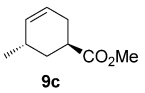
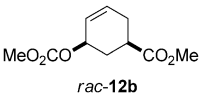
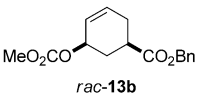
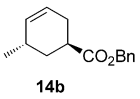
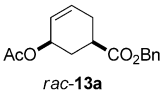
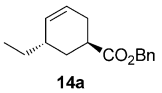
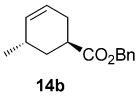
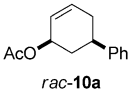
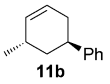
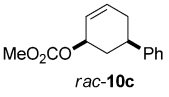
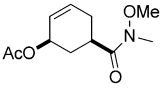
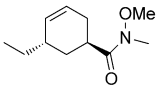
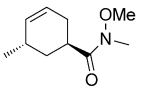
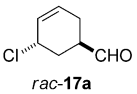
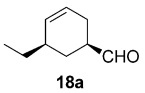
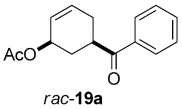
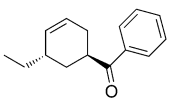
Entry	Substrate	Product	d.r.	Yield [%]	e.r.
1	 *rac*-**12a**	 **9a**	99:1	78	94:6
2	 *rac*-**12a**	 **9c**	99:1	87	85:15
	 *rac*-**12b**		99:1	60	87:13
3	 *rac*-**13b**	 **14b**	99:1	55	84:16
4	 *rac*-**13a**	 **14a**	99:1	78	95:5
		 **14b**	99:1	85	84:16
5	 *rac*-**10a**	 **11b**	97:3	92	89:11
	 *rac*-**10c**		97:3	72	90:10
6	 *rac*-**15a**	 **16a**	99:1	86	93:7
		 **16b**	99:1	90	93:7
7	 *rac*-**17a**	 **18a**	82:18[a]	72[b]	90:10
8	 *rac*-**19a**	 **20a**	99:1	75	87:13

Table 2: (Continued)

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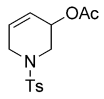
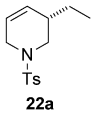
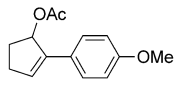
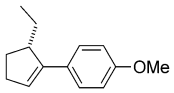
9	 *rac*-**21a**	 **22a**	–	82[c]	90:10
		 **22b**		81	85:15
10	 *rac*-**23a**	 **24a**	–	80	88:12

[a] d.r. starting material = 90:10. [b] Yield of isolated alcohol (DIBALH reduction). [c] Ratio of **22a** to reduced compound 1:1.[11]

while dihydroxylation leads to highly functionalized cyclohexane **30** in short order.[14] The lone tertiary stereocenter apparently exerts notable sterecontrol over functionalization of the neighboring alkene. Furthermore, the cyclobutene analogue **6a** enables a short synthesis of isopilopic acid benzyl amide **31**.[15] Upon ozonolysis and oxidation, the desired natural product derivative is obtained in 56% yield.

In summary, we have developed the first enantioselective Pd-catalyzed alkylation employing dialkylzinc reagents as nucleophiles. This unusual transformation, which thwarts the standard "umpolung" reactivity of allyl–palladium intermediates in the presence of diorganozinc reagents, hinges on a remarkable ligand effect of TADDOL-derived phosphoramidites as privileged ligand scaffolds. The broad functional group tolerance of dialkylzinc reagents renders them potentially complementary alternatives to the commonly employed alkyl lithium and magnesium analogues. Further studies on the mechanism and scope of this reaction are in progress.

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Keywords: alkylation · deracemization · diethylzinc · enantioselectivity · palladium

[1] For selected methods for the construction of tertiary, benzylic stereocenters, see: a) H. M. Wisniewska, E. C. Swift, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, *135*, 9083–9090; b) Y. Hatanaka, T. Hiyama, *J. Am. Chem. Soc.* **1990**, *112*, 7793–7794; c) J. F. Paquin, C. Defieber, C. R. J. Stephenson, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 10850–10851; d) S. Nave, R. P. Sonawane, T. G. Elford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 17096–17098.

[2] a) H. Fujioka, K. Nakahara, N. Kotoku, Y. Ohba, Y. Nagatomi, T.-L. Wang, Y. Sawama, K. Murai, K. Hirano, T. Oki, S. Wakamatsu, Y. Kita, *Chem. Eur. J.* **2012**, *18*, 13861–13870; b) M. Amat, M. Pérez, N. Llor, C. Escolano, F. J. Luque, E. Molins, J.

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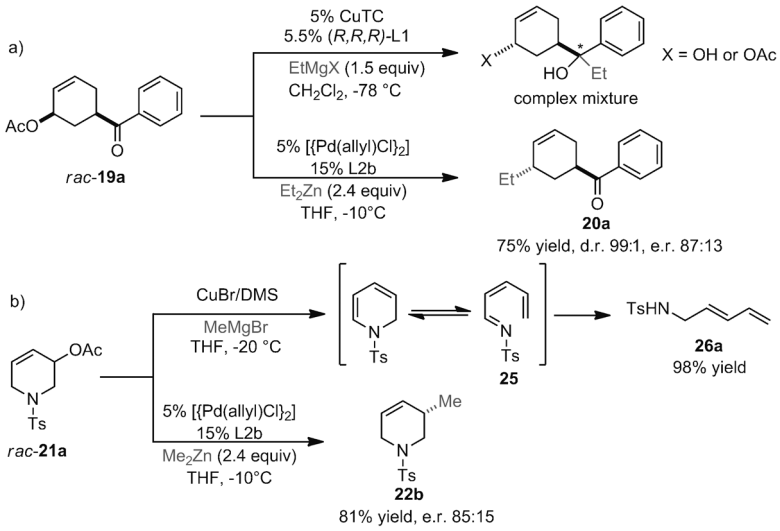
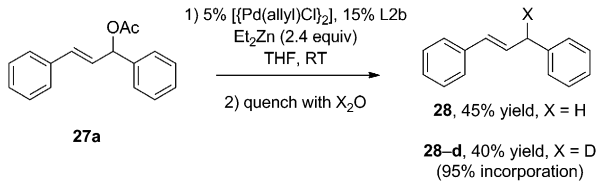
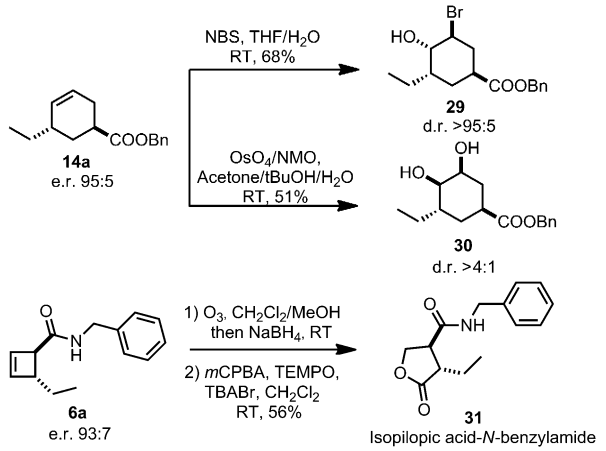


Scheme 6. Complementarity between copper- and palladium-catalyzed alkyl transfer reactions. DMS = dimethyl sulfide, Ts = tosyl.



Scheme 7. Deuterium-labeling experiment on linear substrate **27a**.



Scheme 8. Stereoselective derivatization of alkylation products **14a** and **6a**. Bn = benzyl, *m*CPBA = *meta*-chloroperbenzoic acid, NBS = *N*-bromosuccinimide, NMO = *N*-methylmorpholine *N*-oxide, TBABr = tetrabutylammonium bromide, TEMPO = 2,2,6,6-tetramethylpiperidinyl-oxy.

Bosch, *J. Org. Chem.* **2004**, *69*, 8681 – 8693; c) M. M. Cid, E. Pombo-Villar, *Helv. Chim. Acta* **1993**, *76*, 1591 – 1607; d) A. Endo, M. Kuroda, K. Tanzawa, *FEBS Lett.* **1976**, *72*, 323 – 326.

[3] For methyl substitution as a strategy to slow down metabolic oxidation, see: a) T. G. Burke, Z. Mi, *J. Med. Chem.* **1993**, *36*, 2580 – 2582; b) A. Palani, S. Shapiro, H. Josien, T. Bara, J. W. Clader, W. J. Greenlee, K. Cox, J. M. Strizki, B. M. Baroudy, *J. Med. Chem.* **2002**, *45*, 3143 – 3160.

[4] a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395 – 422; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921 – 2943; c) F. F. Huerta, A. B. E. Minidis, J. E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321 – 331; d) K. Faber, *Chem. Eur. J,.* **2001**, *7*, 5004 – 5010; e) J. Steinreiber, K. Faber, H. Griengl, *Chem. Eur. J.* **2008**, *14*, 8060 – 8072; f) H. Pellissier, *Tetrahedron* **2011**, *67*, 3769 – 3802; g) M. T. Oliveira, D. Audisio, S. Niyomchon, N. Maulide, *ChemCatChem* **2013**, *5*, 1239 – 1247; h) M. Luparia, M. T. Oliveira, D. Audisio, F. Frébault, R. Goddard, N. Maulide, *Angew. Chem.* **2011**, *123*, 12840 – 12844; *Angew. Chem. Int. Ed.* **2011**, *50*, 12631 – 12635.

[5] a) P. Zhang, L. A. Brozek, J. P. Morken, *J. Am. Chem. Soc.* **2010**, *132*, 10686 – 10688; b) L. A. Brozek, M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2011**, *133*, 16778 – 16781; c) M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2012**, *134*, 8770 – 8773; d) S. Niyomchon, D. Audisio, M. Luparia, N. Maulide, *Org. Lett.* **2013**, *15*, 2318 – 2321. For poorly enantioselective Pd-catalyzed allylic alkylations with organozinc reagents, see: e) J.-C. Fiaud, L. Aribi-Zouioueche, *J. Organomet. Chem.* **1985**, *295*, 383. For a rare non-asymmetric example see: f) I. Stary, P. Kocovsky, *J. Am. Chem. Soc.* **1989**, *111*, 4981 – 4982.

[6] For Pd-catalyzed "umpolung" chemistry, see: a) G. P. Howell, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2006**, *4*, 1278 – 1283; b) Y. Tamaru, A. Tanaka, K. Yasui, S. Goto, S. Tanaka, *Angew. Chem.* **1995**, *107*, 862 – 864; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 787 – 789; c) S. Zhu, X. Quiao, Y. Zhang, L. Wang, Q. Zhou, *Chem. Sci.* **2011**, *2*, 1135 – 1140; d) M. Kimura, M. Shimizu, K. Shibata, M. Tazoe, Y. Tamaru, *Angew. Chem.* **2003**, *115*, 3514 – 3517; *Angew. Chem. Int. Ed.* **2003**, *42*, 3392 – 3395; e) G. Zanoni, S. Gladiali, A. Marchetti, P. Piccinini, I. Tredici, G. Vidari, *Angew. Chem.* **2004**, *116*, 864 – 867; *Angew. Chem. Int. Ed.* **2004**, *43*, 846 – 849.

[7] a) J. A. Marshall, *J. Org. Chem.* **2007**, *72*, 8153 – 8166; b) J. A. Marshall, N. D. Adams, *J. Org. Chem.* **1999**, *64*, 5201 – 5204. For a recent synthetic application, see: c) B. M. Trost, B. M. O'Boyle, D. Hund, *J. Am. Chem. Soc.* **2009**, *131*, 15061.

[8] a) M. Pérez, M. Fañanás-Mastral, P. H. Bos, A. Rudolph, S. R. Harutyunyan, B. L. Feringa, *Nat. Chem.* **2011**, *3*, 377 – 381; b) J.-B. Langlois, A. Alexakis, *Chem. Commun.* **2009**, 3868 – 3870; c) D. Grassi, C. Dolka, O. Jackowski, A. Alexakis, *Chem. Eur. J.* **2013**, *19*, 1466 – 1475; d) J.-B. Langlois, D. Emery, J. Mareda, A. Alexakis, *Chem. Sci.* **2012**, *3*, 1062 – 1069; e) M. Pérez, M. Fañanás-Mastral, V. Hornillos, A. Rudolph, P. H. Bos, S. R. Harutyunyan, B. L. Feringa, *Chem. Eur. J.* **2012**, *18*, 11880 – 11883; f) M. Fañanás-Mastral, M. Pérez, P. H. Bos, A. Rudolph, S. R. Harutyunyan, B. L. Feringa, *Angew. Chem.* **2012**, *124*, 1958 – 1961; *Angew. Chem. Int. Ed.* **2012**, *51*, 1922 – 1925; g) J. F. Teichert, S. Zhang, A. W. v. Zijl, J. W. Slaa, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2010**, *12*, 4658 – 4660; h) D. J. Hyett, J. B. Sweeney, A. Tavassoli, *Tetrahedron Lett.* **1997**, *38*, 8283 – 8286. For authoritative reviews on Cu-catalysis, see: i) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796 – 2823; j) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824 – 2852.

[9] For Cu-catalyzed procedures employing other nucleophiles, see: a) R. Shintani, K. Takatsu, M. Takeda, T. Hayashi, *Angew. Chem.* **2011**, *123*, 8815 – 8818; *Angew. Chem. Int. Ed.* **2011**, *50*, 8656 – 8659; b) Y. Shido, M. Yoshida, M. Tanabe, H. Ohmiya, M.

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Sawamura, *J. Am. Chem. Soc.* **2012**, *134*, 18573 – 18576; c) M. A. Kacprzynski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 10676 – 10681; d) N. Yoshikai, K. Miura, E. Nakamura, *Adv. Synth. Catal.* **2009**, *351*, 1014 – 1018.

[10] a) H. Teller, S. Flügge, R. Goddard, A. Fürstner, *Angew. Chem.* **2010**, *122*, 1993 – 1997; *Angew. Chem. Int. Ed.* **2010**, *49*, 1949 – 1953; b) H. W. Lam, *Synthesis* **2011**, 2011 – 2043.

[11] See the Supporting Information for further experimental details.

[12] a) D. Audisio, M. Luparia, M. T. Oliveira, D. Klütt, N. Maulide, *Angew. Chem.* **2012**, *124*, 7426 – 7429; *Angew. Chem. Int. Ed.* **2012**, *51*, 7314 – 7317; b) D. Audisio, G. Gopakumar, L. Xie, L. G. Alves, C. Wirtz, A. M. Martins, W. Thiel, C. Farès, N. Maulide, *Angew. Chem.* **2013**, *125*, 6434 – 6438; *Angew. Chem. Int. Ed.* **2013**, *52*, 6313 – 6316.

[13] For general analyses of leaving-group effects in Pd catalysis, see: a) L. A. Evans, N. Fey, J. N. Harvey, D. Hose, G. C. Lloyd-Jones, P. Murray, A. G. Orpen, R. Osborne, G. J. J. Owen-Smith, M. Purdie, *J. Am. Chem. Soc.* **2008**, *130*, 14471 – 14473; b) C. Johansson, G. Lloyd-Jones, P. Norrby, *Tetrahedron: Asymmetry* **2010**, *21*, 1585 – 1592; c) P. Fristrup, T. Jensen, J. Hoppe, P. Norrby, *Chem. Eur. J.* **2006**, *12*, 5352 – 5360; d) C. Amatore, A. Jutand, L. Mensah, G. Meyer, J. Fiaud, J. Legros, *Eur. J. Org. Chem.* **2006**, 1185 – 1192.

[14] a) G. A. Molander, B. Czakó, D. J. St. Jean, *J. Org. Chem.* **2006**, *71*, 1172 – 1180; b) P. Gupta, P. J. Pal, Y. S. Reddy, D. Yashwant, D. H. Vankar, *Eur. J. Org. Chem.* **2011**, 1166 – 1175.

[15] L. Reichel, G. Schreiber, *Pharmazie* **1968**, *23*, 594.

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