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Highly Efficient Three-Component Synthesis of β-Lactams from *N*-methylhydroxylamine, Aldehydes, and Phenylacetylene

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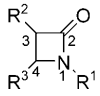
Abstract: The three-component reaction of *N*-substituted hydroxylamines, aldehydes, and phenylacetylene catalyzed by CuCl/2,2′-bipyridine in the presence of NaOAc under neat conditions afforded the corresponding β-lactams in good to excellent yields. Aromatic, heteroaromatic, and aliphatic aldehydes are tolerated in this reaction. The electronic effects of the aldehydes were studied for the reaction with *N*-methylhydroxylamine and *N*-benzylhydroxylamine. For *N*-methylhydroxylamine, electron-rich aldehydes provided higher yields than electron-deficient aldehydes, whereas for *N*-benzylhydroxylamine, no significant electronic effect was observed for the aldehydes.

Keywords: aldehydes · copper · hydroxylamines · lactams · multicomponent reactions

Introduction

β-Lactams are among the best known and most extensively investigated heterocyclic ring systems as a result of both their biological activities, such as antibiotic properties,[1] and their wide use as synthetic intermediates.[1d][2] General methods for the construction of β-lactams include:[3] 1) formation of the N1–C2 bond, for example, by cyclization of a ketene and an imine[4] and cyclization of a β-amino acid;[5] 2) formation of the C2–C3, for example, through trialkylstannane-mediated closure of the C2–C3 bond;[6] 3) formation of the C3–C4 bond, for example through intramolecular nucleophilic displacement[7] and oxidative coupling of dianions of acyclic amides;[8] and 4) formation of the C4–N1 bond, for instance, by S_N2-type displacement of primary halogen atoms by an amide nitrogen atom under basic conditions.[9] Among the different approaches for the synthesis of β-lactams,[1–9] the Kinugasa reaction[10] is an efficient method to construct the four-membered β-lactam ring by means of a [3+2] cycloaddition/rearrangement of nitrones and copper phenylacetylide complexes.



Since the initial report by Kinugasa and Hashimoto,[10a] significant advances have been made on this subject. In 1995, Miura et al. found that the reaction could be carried out by the reaction of terminal alkynes and nitrones in the presence of a substoichiometric amount of CuI.[11] Furthermore, it was also possible to perform the reaction asymmetrically to give the desired product with 57% *ee* and 68:32 d.r. by using the CuI–pybox system. Recently, Fu and co-workers[12] found that bis(azaferrocenes)–CuCl could catalyze the Kinugasa reaction to afford the desired products with good to excellent diastereo- and enantioselectivity. More recently, Tang and co-workers reported[13] that chiral tris(oxazoline) in the presence of $Cu(ClO_4)_2{\cdot}6H_2O$ also catalyzes the Kinugasa reaction between terminal alkynes and nitrones, giving high *cis* diastereoselectivities and good enantioselectivities (55–85% *ee*). The mechanism of the Kinugasa reaction is still not clear. The proposed mechanism (Scheme 1) involves a formal [3+2] cycloaddition of a nitrone and a copper acetylide (generated in situ) to form an isoxazoline intermediate. Protonation, formation of an oxaziridine species, and subsequent rearrangement of the oxaziridine ring provides the β-lactam. Furthermore, the *cis* isomer (initially formed) can be equilibrated to the *trans* isomer at C3 under basic conditions.[14]

Unfortunately, there is no reported synthesis of *N*-alkyl β-lactams, which are more prevalent in natural products and biological compounds, by using the Kinugasa reaction. Furthermore, nitrones have to be presynthesized in these reactions. Recently, we developed various aldehyde–alkyne–amine couplings (A^3-coupling)[15] (Scheme 2, route a) and asymmetric aldehyde–alkyne–amine couplings (AA^3-cou-

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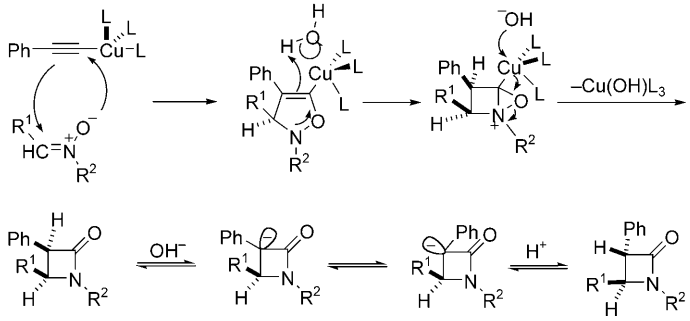
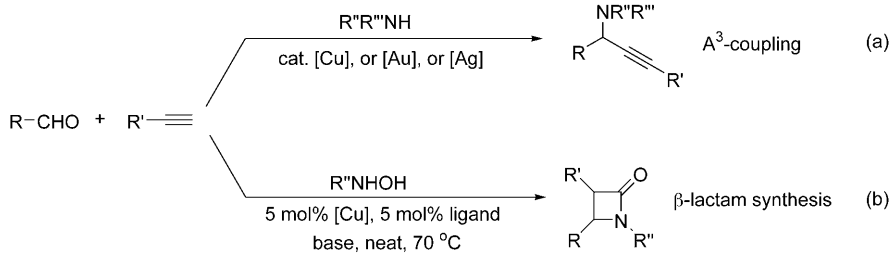


Scheme 1. Mechanism of the Kinugasa reaction proposed by Ding and Irwin.[14]

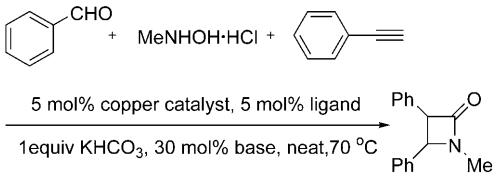


Scheme 2. Coupling of aldehydes and alkynes with amines and *N*-alkyl hydroxylamines.

pling).[16] As part of our continued interest in extending the scope of the aldehyde–alkyne–amine couplings, herein we report a one-pot synthesis of β-lactams through the multicomponent coupling[17] of *N*-alkyl hydroxylamines, aldehydes, and alkynes catalyzed by copper under mild conditions (Scheme 2, route b). Interestingly, replacement of the amine by an *N*-alkyl hydroxylamine led to a different product of the A^3-coupling: β-lactams. The required *N*-methylhydroxylamine used in the current study was conveniently generated in situ from the combination of its HCl salt with $KHCO_3$ (1 equiv).

Results and Discussion

In our initial study, we found that CuCl effectively catalyzes β-lactam formation from *N*-methylhydroxylamine, benzaldehyde, and phenylacetylene in 37% yield in 18 h at 70°C (Scheme 3). Various solvents were examined for the reaction, and the optimal yield was obtained under neat conditions. The addition of another base (30 mol%) was found to



Scheme 3. Formation of β-lactam from coupling of benzaldehyde, *N*-methylhydroxylamine, and phenylacetylene, catalyzed by CuCl.

be beneficial for the reaction. Subsequent to these preliminary investigations, the effects of catalyst, ligand, and base on the three-component reaction were examined (Table 1). Among the various copper salts that we examined (Table 1, entries 1–5), CuCl provided the desired product in the best yield, with 2,2′-bipyridine as the ligand and NaOAc as the base. The use of $KHCO_3$ instead of NaOAc as the base led to a poorer yield of the product (Table 1, entry 6). On the other hand, the same results were obtained with K_3PO_4 and NaOAc as bases (Table 1, entries 3 and 7). Surprisingly, almost no desired product was observed when either triethylamine or DBU were used as the bases (Table 1, entries 8 and 10), whereas the products were obtained in lower yields when using $(i\text{Pr})_2\text{NEt}$ and K_2CO_3 (Table 1, entries 9 and 11). The use of pyridine (Table 1, entry 12), 1,10-phenanthroline (Table 1, entry 13), and phosphines (Table 1, entries 14 and 15) as ligands also decreased the yield of the desired product. Thus, the combination of

Table 1. Optimization of the reactions.[a]

Entry	Catalyst	Ligand	Base	Yield [%][b]	*cis*/*trans*[c]
1	CuI	2,2′-bipyridine	NaOAc	77	74:26
2	CuBr	2,2′-bipyridine	NaOAc	83	81:19
3	CuCl	2,2′-bipyridine	NaOAc	97	80:20
4	CuOTf	2,2′-bipyridine	NaOAc	81	79:21
5	Cu_2O	2,2′-bipyridine	NaOAc	92	79:21
6	CuCl	2,2′-bipyridine	$KHCO_3$	57	76:24
7	CuCl	2,2′-bipyridine	K_3PO_4	97	80:20
8	CuCl	2,2′-bipyridine	NEt_3	trace	n.a.
9	CuCl	2,2′-bipyridine	$(i\text{Pr})_2\text{NEt}$	78	79:21
10	CuCl	2,2′-bipyridine	DBU	trace	n.a.
11	CuCl	2,2′-bipyridine	K_2CO_3	85	82:18
12	CuCl	pyridine[d]	NaOAc	31	72:28
13	CuCl	1,10-phenanthroline	NaOAc	89	78:22
14	CuCl	PPh_3[d]	NaOAc	49	76:24
15	CuCl	dppp[e]	NaOAc	24	83:17

[a] Reaction conditions: MeNHOH·HCl (0.2 mmol), benzaldehyde (0.3 mmol), phenylacetylene (0.4 mmol), $KHCO_3$ (0.2 mmol), catalyst (5 mol%), and ligand (10 mol%) were used unless otherwise noted, and all reactions were carried out under a N_2 atmosphere for 18 h. [b] Yields were based on MeNHOH·HCl and determined by NMR spectroscopy by using an internal standard. [c] The ratio of the two diastereomers was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Ligand: 10 mol%. [e] dppp = 1,2-bis(diphenylphosphanyl)propane.

Abstract in Chinese:

在氯化亚铜/联吡啶的催化下，氮上取代的羟胺，醛和苯乙炔可以在无溶剂条件下反应生成β-酰胺。在优化条件下，芳香醛，杂芳香醛和烷基醛都适用于此反应。与此同时，我们也研究了醛上的电子效应对该反应的影响。对于氮甲基羟胺，富电子的醛活性高于贫电子的醛。对于氮苄基羟胺，醛上的电子效应对反应没有明显的影响。

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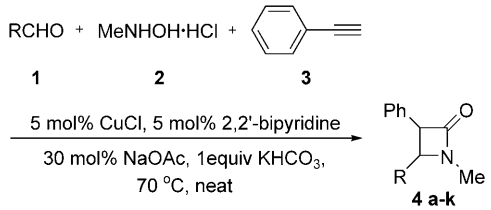
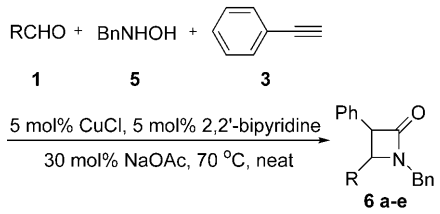
CuCl as the catalyst, 2,2′-bipyridine as the ligand, and NaOAc as the base was used as the standard conditions for the three-component synthesis of the β-lactams.

Various aldehydes were coupled with *N*-methylhydroxylamine and phenylacetylene under the optimized conditions, and the products were obtained in good to excellent yields in all cases (Scheme 4 and Table 2). Benzaldehyde and electron-rich aromatic aldehydes gave higher yields than electron-deficient aromatic aldehydes in most cases. Halogen substituents such as bromine, chlorine, and fluorine atoms on the aromatic ring of the aldehyde survived the reaction conditions (Table 2, entries 4–6). Heteroaromatic 2-furaldehyde (Table 2, entry 3) and aliphatic aldehyde (Table 2, entry 11) also provided the corresponding β-lactams in excellent yields. Aliphatic alkynes are also effective under the present reaction conditions; however, in these cases the reaction generated a mixture of products, which are still under investigation.



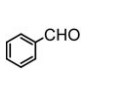
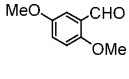
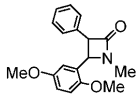
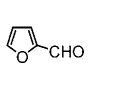
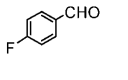
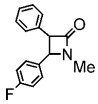
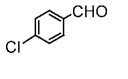
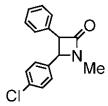
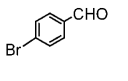
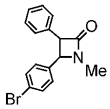
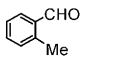
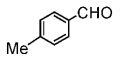
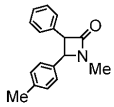
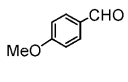
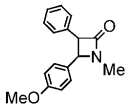
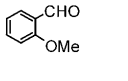
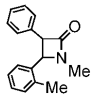
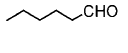
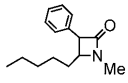
Scheme 4. Coupling of aldehydes with *N*-methylhydroxylamine and phenylacetylene.

Furthermore, *N*-benzylhydroxylamine is also highly effective for this three-component β-lactam formation (Scheme 5 and Table 3). Because the benzyl group on the β-lactam nitrogen atom can be removed readily by standard hydrogenolysis, the three-component reaction provides a very effective method for the synthesis of β-lactams that do not have any substituent on the nitrogen atom.[18] Interestingly, in these cases the electronic nature of the substituent on the aldehyde did not significantly influence the reaction (see Table 3).



Scheme 5. Formation of β-lactam from coupling of aldehydes, *N*-benzylhydroxylamine, and phenylacetylene.

Table 2. Synthesis of β-lactams through coupling of *N*-methylhydroxylamine, aldehydes, and phenylacetylene.[a]

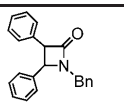
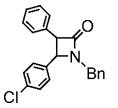
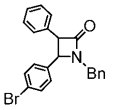
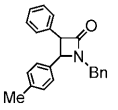
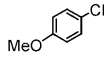
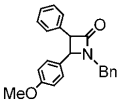
Entry	Aldehyde	Product		Yield [%][b]	*cis*/*trans*[c]
1			**4a**	97 (86)	80:20
2			**4b**	87 (55)	76:24
3			**4c**	85 (79)	63:37
4			**4d**	78 (70)[d]	78:22
5			**4e**	88 (83)[e]	80:20
6			**4f**	72 (70)	80:20
7			**4g**	88 (67)	84:16
8			**4h**	99 (95)	89:11
9			**4i**	96 (69)	76:24
10			**4j**	93 (66)	75:25
11			**4k**	75 (55)	63:37

[a] Reaction conditions: MeNHOH·HCl (0.4 mmol), aldehyde (0.6 mmol), phenylacetylene (0.8 mmol), $KHCO_3$ (0.4 mmol), NaOAc (0.12 mmol), CuCl (5 mol%), and 2,2′-bipyridine (5 mol%) were used unless otherwise noted; all reactions were run under N_2 for 18 h. [b] Yields based on MeNHOH·HCl and determined by ^1H NMR spectroscopy by using an internal standard; yields of the two isolated diastereomers are given in parentheses. [c] The ratio of the two diastereomers were determined by NMR spectroscopy of the crude reaction mixture. [d] Ligand: 4,4′-dimethyl-2,2′-bipyridine (5 mol%). [e] Phenylacetylene (120 μL), preheated at 90 °C for 30 min to melt the reaction mixture.

Conclusions

A simple three-component method was developed to synthesize β-lactams from *N*-substituted hydroxylamine, aldehydes, and phenylacetylene catalyzed by copper. The reactivities of different *N*-substituted hydroxylamines and various aldehydes were examined. The method provided various *N*-alkyl β-lactam derivatives efficiently. The scope and application of this multicomponent is under investigation.

Table 3. Synthesis of β-lactams by coupling of *N*-benzylhydroxylamine, aldehydes, and phenylacetylene.[a]

Entry	Aldehyde	Product		Yield(%)[b]	*cis*/*trans*[c]
1			**6a**	85 (75)	78:22
2			**6b**	83 (75)	78:22
3			**6c**	79 (78)	80:20
4			**6d**	81 (80)	79:21
5			**6e**	80 (79)	79:21

[a] Reaction conditions: BnNHOH (0.4 mmol), aldehyde (0.6 mmol), phenylacetylene (0.8 mmol), NaOAc (0.12 mmol), CuCl (5 mol%), and 2,2′-bipyridine (5 mol%) were used; all reactions were performed under a N_2 atmosphere for 18 h. [b] Yields based on BnNHOH and determined by ^{1}H NMR spectroscopy by using an internal standard; yields of the two isolated diastereomers are given in parentheses. [c] The ratio of the two diastereomers was determined by ^{1}H NMR spectroscopy of the crude mixture.

Experimental Section

Chemicals were purchased from Aldrich Chemicals Company and Acros Chemicals and were used without further purification. All experiments were carried out under an atmosphere of N_2, unless otherwise noted. ^{1}H and ^{13}C NMR spectra were acquired at 400 MHz and 100 MHz or 300 MHz and 75 MHz, respectively (Varian Mercury), and referenced to the internal solvent. IR spectra were recorded on an ABB Bomem MB 100 interferometer. MS data were measured on a KRATOS MS25RFA mass spectrometer. HRMS-ESI measurements were performed at McGill University. *N*-Benzylhydroxylamine was prepared according to a literature method.[19]

4a: CuCl (2.0 mg, 0.02 mmol), 2,2′-bipyridine (3.2 mg, 0.02 mmol), NaOAc (10 mg, 0.12 mmol), $KHCO_3$ (40 mg, 0.40 mmol) and *N*-methylhydroxylamine hydrochloride (33 mg, 0.40 mmol) were added to a test tube, which was then sealed and flushed with nitrogen gas. Benzaldehyde (60 μL, 0.60 mmol) and phenylacetylene (85 μL, 0.80 mmol) were then added to the mixture through a syringe, and the test tube was heated at 70 °C for 18 h under N_2. The reaction mixture was cooled to room temperature and filtered through a short silica-gel column to remove the inorganic salts. The final product was obtained by thin-layer chromatography (TLC, hexanes/EtOAc 2:1): *cis* isomer: 65 mg (R_f = 0.2); *trans* isomer: 17 mg (R_f = 0.3), 86% overall yield). *cis*: IR (KBr): $\tilde{\nu}_{max}$ = 3061, 3026, 2918, 1756, 1419, 1189, 983, 768, 699, 584 cm^{-1}; 1H NMR (400 MHz, CD_3Cl): 7.15–6.98 (m, 10H; Ar-H), 4.95 (d, J = 5.6 Hz, 1H; C-H), 4.86 (d, J = 5.6 Hz, 1H; C-H), 2.91 ppm (s, 3H; NCH_3); ^{13}C NMR (100 MHz, CD_3Cl): 168.1, 134.6, 132.5, 128.4, 128.0, 127.8, 127.6, 127.0, 126.6, 62.0, 61.1, 27.3 ppm; MS (EI): *m/z* (%): 237 [M$^+$], 180 (100), 165, 152, 139, 118, 102, 90, 77, 63, 51; HRMS (ESI): calcd for [$C_{16}H_{15}NO$+H]$^+$: 238.1226; found: 238.1225; *trans*: IR (KBr): $\tilde{\nu}_{max}$ = 3061, 3026, 2918, 1757, 1497, 1457, 1388, 1068, 699, 631, 523 cm$^-$ cm^{-1}; 1H NMR (400 MHz, CD_3Cl): 7.44–7.24 (m, 10H; Ar-H), 4.44 (d, J = 2.0 Hz, 1H; C-H), 4.16 (s, 1H; C-H), 2.86 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.2, 137.2, 134.9, 129.1, 128.8, 128.6, 127.5, 127.2, 126.2, 65.7, 65.3, 27.1 ppm; MS (EI): *m/z* (%): 237 [M$^+$], 180 (100), 165, 152, 139, 118, 102, 89, 76, 63, 51; HRMS (ESI): calcd for [$C_{16}H_{15}NO$+H]$^+$: 238.1226; found: 238.1226.

4b: Prepared by following the same procedure as described for **4a**. Yield of the two diastereomers: 55%. *cis*: $\tilde{\nu}_{max}$ = 3061, 3030, 2998, 2940, 2834, 1753, 1591, 1498, 1464, 1452, 1387, 1280, 1218, 1047, 1025, 988, 699 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl): 7.04–6.96 (m, 5H; Ar-H), 6.57–6.50 (m, 3H; Ar-H), 5.22 (d, J = 6.0 Hz, 1H; C-H), 4.82 (d, J = 6.0 Hz, 1H; C-H), 3.64 (s, 3H; OCH_3), 3.61 (s, 3H; OCH_3), 2.96 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.8, 152.9, 151.0, 132.7, 128.4, 127.5, 126.6, 124.7, 113.1, 112.6, 110.6, 60.9, 57.4, 55.7, 55.4, 28.0 ppm; MS (EI): *m/z* (%): 297 [M$^+$], 266, 240, 225, 210, 197, 179, 164, 148 (100), 118, 104, 90, 77, 63, 51; HRMS-ESI: calcd for [$C_{18}H_{19}NO_3$+H]$^+$: 298.1438; found: 298.1437; *trans*: $\tilde{\nu}_{max}$ = 3069, 3027, 3004, 2935, 2835, 1748, 1506, 1388, 1270, 1219, 1045, 990, 858, 831, 745, 726, 104, 694, 633, 514 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl): 7.37–7.24 (m, 5H; Ar-H), 6.84 (s, 3H; Ar-H), 4.86 (d, J = 2.0 Hz, 1H; C-H), 4.20 (s, 1H; C-H), 3.78 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 2.86 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.7, 153.8, 151.6, 135.4, 128.5, 127.3, 127.2, 126.6, 113.5, 112.6, 111.9, 64.2, 59.6, 56.0, 55.8, 27.4 ppm; MS (EI): *m/z* (%): 297 [M$^+$], 266, 240 (100), 225, 210, 197, 180, 164, 148, 118, 104, 90, 77, 63, 51; HRMS (ESI): calcd for [$C_{18}H_{19}NO_3$+H]$^+$: 298.1438; found: 298.1437.

4c: Prepared by the same procedure as described for **4a**. Yield of the two diastereomers: 55%. *cis*: IR (KBr): $\tilde{\nu}_{max}$ = 3138, 3061, 3026, 2912, 1752, 1421, 1383, 1143, 1066, 763, 501 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl): 7.15–7.10 (m, 6H; Ar-H), 6.12 (dd, J = 3.2 Hz, 1.6 Hz, 1H; Ar-H), 6.01 (d, J = 3.6 Hz, 1H; Ar-H), 4.95 (d, J = 5.6 Hz, 1H; C-H), 4.79 (d, J = 5.6 Hz, 1H; C-H), 2.89 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.0, 149.1, 142.9, 133.0, 128.5, 128.2, 127.4, 110.5, 109.3, 61.0, 56.5, 27.66 ppm; MS (EI): *m/z* (%): 227 [M$^+$], 170, 141, 128, 118, 115, 110 (100), 90, 81, 63, 51; HRMS (ESI): calcd for [$C_{14}H_{13}NO_2$+H]$^+$: 228.1019; found: 228.1019; *trans*: IR (KBr): $\tilde{\nu}_{max}$ = 3061, 3026, 2918, 1758, 1497, 1388, 1152, 1070, 1014, 926, 729, 698, 598, 527 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl): 7.46 (s, 1H; Ar-H), 7.35–7.24 (m, 5H; Ar-H), 6.39 (s, 2H; Ar-H), 4.48 (s, 2H; 2×C-H), 2.82 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 167.8, 149.9, 143.2, 134.5, 128.7, 127.5, 127.2, 110.5, 109.2, 61.9, 58.0, 27.1 ppm; MS (EI): *m/z* (%): 227 [M$^+$], 170 (100), 141, 128, 118, 115, 110, 90, 77, 63, 51; HRMS (ESI): calcd for [$C_{14}H_{13}NO_2$+H]$^+$: 228.1019; found: 228.1020.

4d: Prepared by the same procedure described for **4a**, except that 4,4′-dimethyl-2,2′-bipyridine (5 mol%) was used as the ligand. Yield of the two diastereomers: 70%. *cis*: IR (KBr): $\tilde{\nu}_{max}$ = 3061, 3026, 2918, 1741, 1607, 1510, 1388, 1217, 1081, 983, 842, 703 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl): 7.06–6.93 (m, 7H; Ar-H), 6.82 (t, J = 8.8 Hz, 2H; Ar-H), 4.92 (d, J = 5.6 Hz, 1H; C-H), 4.85 (d, J = 5.6 Hz, 1H; C-H), 2.89 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.4, 163.6, 161.2, 132.7, 130.8, 130.8, 129.1, 129.0, 128.8, 128.3, 127.2, 115.6, 115.3, 61.9, 61.6, 27.7 ppm; MS (EI): *m/z* (%): 255 [M$^+$], 198, 183, 177, 170, 138, 118 (100), 109, 98, 90, 75, 63, 51; HRMS (ESI): calcd for [$C_{16}H_{14}NOF$+H]$^+$: 256.1132; found: 256.1132; *trans*: $\tilde{\nu}_{max}$ = 3063, 3030, 2910, 1756, 1603, 1509, 1426, 1388, 1225, 1157, 1069, 989, 841, 697, 509 cm^{-1}; ^{1}H NMR (300 MHz, CD_3Cl): 7.36–7.26 ppm (m, 7H; Ar-H), 7.12 (t, J = 8.7 Hz, 2H; Ar-H), 4.43 (d, J = 2.1 Hz, 1H; C-H), 4.13 (s, 1H; C-H), 2.85 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.3, 164.1, 161.6, 134.8, 133.1, 133.1, 128.9, 128.0, 127.9, 127.7, 127.3, 116.3, 116.1, 65.9, 64.7, 27.0 ppm; MS (EI): *m/z* (%): 255 [M$^+$], 198 (100), 183, 177, 170, 138, 118, 109, 98, 90, 75, 63, 51; HRMS (ESI): calcd for [$C_{16}H_{14}NOF$+H]$^+$: 256.1132; found: 256.1132.

4e: Prepared by the same procedure described for **4a**, except that the reaction mixture was heated at 90 °C for 30 min and then at 70 °C for another 18 h. Yield of the two diastereomers: 83%. *cis*: IR (KBr): $\tilde{\nu}_{max}$ = 3061, 3026, 2909, 1751, 1492, 1425, 1388, 1090, 1014, 985, 825, 721, 699, 468 cm^{-1}; ^{1}H NMR (300 MHz, CD_3Cl): 7.12–6.92 (m, 9H; Ar-H), 4.91 (d, J = 5.7 Hz, 1H; C-H), 4.86 (d, J = 5.7 Hz, 1H; C-H), 2.87 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 167.9, 133.4, 133.3, 132.2, 128.4, 128.3, 128.2, 128.0, 126.9, 61.5, 61.2, 27.3 ppm; MS (EI): *m/z* (%): 271 [M$^+$], 214, 179, 154, 118 (100), 90, 76, 63, 51; HRMS (ESI): calcd for [$C_{16}H_{14}NOCl$+H]$^+$: 272.0837; found: 272.0836; *trans*: IR (KBr): $\tilde{\nu}_{max}$ =

3061, 3026, 2918, 1757, 1491, 1424, 1388, 1090, 1013, 988, 840, 741, 699, 575, 498 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.39 (d, J=8.4 Hz, 2H; Ar-H), 7.30 (d, J=8.4 Hz, 2H; Ar-H), 7.27–7.24 (m, 5H; Ar-H), 4.42 (d, J=2.0 Hz, 1H; C-H), 4.12 (s, 1H; C-H), 2.85 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.0, 135.8, 134.6, 134.4, 129.3, 128.8, 127.6, 127.5, 127.2, 65.9, 64.7, 27.1 ppm; MS (EI): *m/z* (%): 271 [M^+], 214 (100), 179, 152, 118, 89, 76, 63, 51; HRMS (ESI): calcd for [$C_{16}H_{14}NOCl+H]^+$: 272.0837; found: 272.0835.

4f: Prepared by the same procedure described for **4a**. Yield of the two diastereomers: 70%. *cis*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3028, 2906, 1757, 1488, 1423, 1386, 1069, 1010, 837, 698, 575, 493; 1757 cm^{-1}; ^1H NMR (300 MHz, CD_3Cl): 7.27(d, J=8.1 Hz, 2H; Ar-H), 7.09–7.04 (m, 3H; Ar-H), 7.00–6.97 (m, 2H; Ar-H), 6.88 (d, J=8.1 Hz, 2H; Ar-H), 4.90 (d, J=5.4 Hz, 1H; C-H), 4.87 (d, J=5.4 Hz, 1H; C-H), 2.87 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.1, 134.0, 132.3, 131.3, 128.9, 128.5, 128.2, 127.1, 121.8, 61.6, 61.2, 27.3 ppm; MS (EI): *m/z* (%): 315 [M^+], 258, 198, 178, 152, 118 (100), 90, 76, 63, 51; HRMS (ESI): calcd for [$C_{16}H_{14}NOBr+H]^+$: 316.0331; found: 316.0330; *trans*: $\tilde{\nu}_{max}$=3061, 3028, 2907, 1754, 1423, 1386, 1070, 1010, 986, 821, 716, 699, 655, 512 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.56(d, J=8.4 Hz, 2H; Ar-H), 7.38–7.34 (m, 2H; Ar-H), 7.32–7.26 (m, 3H; Ar-H), 7.21 (d, J=8.4 Hz; 2H; Ar-H), 4.42 (d, J=2.4 Hz, 1H; C-H), 4.12 (s, 1H; C-H), 2.86 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.2, 136.4, 134.6, 132.4, 128.9, 127.9, 127.8, 127.3, 122.6, 65.8, 64.8, 27.1 ppm; MS (EI): *m/z* (%): 315 [M^+], 258, 198, 178 (100), 165, 152, 118, 89, 76, 63, 51; HRMS (ESI): calcd for [$C_{16}H_{14}NOBr+H]^+$: 316.0331; found: 316.0330.

4g: Prepared by the same procedure described for **4a**. Yield of the two diastereomers: 67%. *cis*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3029, 2949, 2903, 1757, 1458, 1424, 1390, 1339, 1202, 1080, 986, 773, 697, 667, 490 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.05–6.89 (m, 9H; Ar-H), 5.10 (d, J=5.6 Hz; 1H; C-H), 4.82 (d, J=5.6 Hz, 1H; C-H), 2.98 (s, 3H; NCH_3), 2.16 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.5, 135.2, 132.8, 132.0, 130.0, 128.6, 127.6, 127.2, 126.9, 125.6, 125.3, 61.1, 59.7, 28.0, 19.2 ppm; MS (EI): *m/z* (%): 251 [M^+], 236, 194, 179, 165, 152, 134, 118 (100), 96, 90, 77, 63, 51; HRMS (ESI): calcd for [$C_{17}H_{17}NO+H]^+$: 252.1383; found: 252.1382; *trans*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3026, 2918, 1757, 1654, 1388, 755, 698, 630 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.36–7.16 (m, 9H; Ar-H), 4.74 (d, J=2.0 Hz, 1H; C-H), 4.05 (s, 1H; C-H), 2.95 (s, 3H; NCH_3), 2.16 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.6, 135.8, 135.7, 135.1, 130.8, 128.8, 127.8, 127.6, 127.3, 126.6, 124.0, 65.7, 62.2, 27.6, 19.5 ppm; MS (EI): *m/z* (%): 251 [M^+], 236, 194 (100), 179, 165, 152, 134, 118, 96, 90, 77, 63, 51; HRMS (ESI): calcd for [$C_{17}H_{17}NO+H]^+$: 252.1383; found: 252.1383.

4h: Prepared by the same procedure described for **4a**. Yield of the two diastereomers: 95%. *cis*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3026, 2918, 1757, 1424, 1385, 1080, 816, 700, 511 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.06–6.98 (m, 5H; Ar-H), 6.92 (d, J=7.6 Hz, 2H; Ar-H), 6.87 (d, J=7.6 Hz, 2H; Ar-H), 4.90(d, J=5.6 Hz, 1H; C-H), 4.82 (d, J=5.6 Hz, 1H; C-H), 2.87 (s, 3H; NCH_3), 2.19 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.6, 137.8, 133.1, 131.9, 129.1, 128.9, 128.2, 127.5, 127.0, 62.4, 61.4, 27.6, 21.5 ppm; MS (EI): *m/z* (%): 251 [M^+], 194 (100), 179, 165, 152, 134, 118, 105, 96, 89, 77, 63, 51; HRMS (ESI): calcd for [$C_{17}H_{17}NO+H]^+$: 252.1383; found: 252.1383; *trans*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3026, 2918, 1757, 1514, 1423, 1387, 1069, 698, 592, 517 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.32 (d, J=6.0 Hz, 2H; Ar-H), 7.28–7.21 (m, 7H; Ar-H), 4.40 (d, J=2.0 Hz, 1H; C-H), 4.13 (s, 1H; C-H), 2.83 (s, 3H; NCH_3), 2.38 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.3, 138.5, 135.0, 134.1, 129.7, 128.7, 127.5, 127.2, 126.1, 65.7, 65.2, 27.0, 21.3 ppm; MS (EI): *m/z* (%): 251 [M^+], 236, 194, 179, 165, 152, 134 (100), 118, 105, 96, 90, 77, 63, 51; HRMS (ESI): calcd for [$C_{17}H_{17}NO+H]^+$: 252.1383; found: 252.1382.

4i: Prepared by the same procedure described for **4a**. Yield of the two diastereomers: 69%. *cis*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3026, 2922, 2834, 1735, 1612, 1513, 1391, 1245, 1173, 984, 830, 700 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.07–6.98 (m, 5H; Ar-H), 6.89 (d, J=8.4 Hz, 2H; Ar-H), 6.50 (d, J=8.4 Hz, 2H; Ar-H), 4.89 (d, J=5.6 Hz, 1H; C-H), 4.81 (d, J=5.6 Hz, 1H; C-H), 3.66 (s, 3H; OCH_3), 2.85 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.1, 158.8, 132.7, 128.3, 128.3, 127.8, 126.5, 126.4, 113.4, 61.6, 61.0, 55.0, 27.1 ppm; MS (EI): *m/z* (%): 267 [M^+], 210, 165, 150 (100), 118, 90, 77, 63, 51; HRMS (ESI): calcd for [$C_{17}H_{17}NO_2+H]^+$: 268.1332; found: 268.1332; *trans*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3026, 2918, 1752, 1611, 1513, 1388, 1249, 1175, 1031, 837, 698, 595, 520 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.35–7.23 (m, 7H; Ar-H), 6.94(d, J=8.4 Hz, 2H; Ar-H), 4.39 (d, J=2.4 Hz, 1H; C-H), 4.13 (s, 1H; C-H), 3.82 (s, 3H; OCH_3), 2.83 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.3, 159.7, 135.0, 128.9, 128.7, 127.4, 127.4, 127.2, 114.4, 65.7, 65.0, 55.4, 26.9 ppm; MS (EI): *m/z* (%): 267 [M^+], 210 (100), 195, 179, 165, 150, 118, 90, 82, 77, 63, 51; HRMS (ESI): calcd for [$C_{17}H_{17}NO_2+H]^+$: 268.1332; found: 268.1331.

4j: Prepared by the same procedure described for **4a**. Yield of the two diastereomers: 66%. *cis*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3026, 2938, 2837, 1752, 1492, 1465, 1388, 1243, 1111, 1027, 984, 751, 699, 594, 502 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.05–6.93 (m, 7H; Ar-H), 6.74 (t, J=7.2 Hz, 1H; Ar-H), 6.57 (d, J=8.0 Hz, 1H; Ar-H), 5.23 (d, J=5.6 Hz, 1H; C-H), 4.82 (d, J=5.6 Hz, 1H; C-H), 3.67 (s, 3H; OCH_3), 2.97 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.8, 156.6, 132.8, 128.4, 128.4, 127.4, 126.6, 126.4, 123.7, 119.7, 109.6, 61.0, 57.6, 54.9, 28.0 ppm; MS (EI): *m/z* (%): 267 [M^+], 210, 165, 150 (100), 118, 90, 77, 63, 51; HRMS (ESI): calcd for [$C_{17}H_{17}NO_2+H]^+$: 268.1332; found: 268.1331; *trans*: IR (KBr): $\tilde{\nu}_{max}$=3061, 3026, 2940, 1838, 1755, 1601, 1492, 1388, 1245, 1026, 986, 756, 697, 628, 527 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.38–7.24 (m, 7H; Ar-H), 7.01(t, J=7.6 Hz, 1H; Ar-H), 6.92 (d, J=8.0 Hz, 1H; Ar-H), 4.88 (d, J=2.0 Hz, 1H; Ar-H), 4.22 (s, 1H; C-H), 3.80 (s, 3H; OCH_3), 2.86 ppm (s, 3H; NCH_3); ^{13}C NMR (75 MHz, CD_3Cl): 169.1, 157.8, 135.9, 129.6, 128.8, 127.7, 127.5, 126.9, 125.8, 121.1, 111.0, 64.4, 60.1, 55.7, 27.7 ppm; MS (EI): *m/z* (%): 267 [M^+], 210 (100), 195, 179, 165, 150, 118, 90, 82, 77, 63, 51; HRMS (ESI): calcd for [$C_{17}H_{17}NO_2+H]^+$: 268.1332; found: 268.1331.

4k: Prepared by the same procedure described for **4a**. Yield of the two diastereomers: 55%. *cis*: $\tilde{\nu}_{max}$=2955, 2931, 2858, 1753, 1603, 1497, 1467, 1453, 1421, 1392, 1259, 1078, 1031, 733, 723, 700, 623, 616 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.32–7.17 (m, 5H; Ar-H), 4.49 (d, J=5.2 Hz, 1H; C-H), 3.70 (ddd, J=6.0 Hz, 6.0 Hz, 6.0 Hz, 1H; C-H), 2.89 (s, 3H; NCH_3), 1.44–0.88 (m, 8H; CH_2), 0.72 ppm (t, J=6.0 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.4, 133.1, 129.3, 128.3, 127.4, 58.6, 58.4, 31.5, 29.0, 27.2, 25.3, 22.1, 13.7 ppm; MS (EI): *m/z* (%): 231 [M^+], 174, 117, 104 (100), 91, 77, 65, 55; HRMS (ESI): calcd for [$C_{15}H_{21}NO_2+H]^+$: 232.1696; found: 232.1697; *trans*: $\tilde{\nu}_{max}$=2955, 2929, 2858, 1755, 1497, 1467, 1454, 1422, 1392, 1253, 1079, 731, 698, 573 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.35–7.23 (m, 5H; Ar-H), 3.89 (s, 1H; C-H), 3.47 (ddd, J=9.6 Hz, 4.8 Hz, 2.4 Hz, 1H; C-H), 2.87 (s, 3H; NCH_3), 1.94–1.89 (m, 1H; CH_2), 1.63–1.54 (m,1H; CH_2), 1.44–1.24 (m, 6H; CH_2), 0.89 ppm (t, J=8.0 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.1, 135.7, 128.8, 127.4, 127.3, 62.3, 60.9, 32.4, 31.8, 26.7, 25.4, 22.5, 13.9 ppm; MS (EI): *m/z* (%): 231 [M^+], 174, 131, 117 (100), 104, 91, 77, 65, 55; HRMS (ESI): calcd for [$C_{15}H_{21}NO_2+H]^+$: 232.1696; found: 232.1693.

6a: CuCl (2.0 mg, 0.02 mmol), 2,2′-bipyridine (3.2 mg, 0.02 mmol), NaOAc (10 mg, 0.12 mmol), and *N*-benzylhydroxylamine (50 mg, 0.40 mmol) were added to a test tube, which was then sealed and flushed with nitrogen gas. Benzaldehyde (60 μL, 0.60 mmol) and phenylacetylene (85 μL, 0.80 mmol) were then added to the mixture through a syringe. The test tube was heated at 70 °C for 18 h under N_2. The reaction mixture was filtered through a short silica-gel column to remove the inorganic salts, and the final product was obtained by TLC (hexanes/EtOAc 3:1). Yield of the two diastereomers: 75%. *cis*:[20] (R_f=0.3); ^1H NMR (400 MHz, CD_3Cl): 7.32–6.95 (m, 15H; Ar-H), 5.01 (d, J=14.8 Hz, 1H; C-H), 4.84 (d, J=5.6 Hz, 1H; C-H), 4.83 (d, J=5.6 Hz, 1H; C-H), 3.92 ppm (d, J=14.8 Hz, 1H; C-H); ^{13}C NMR (75 MHz, CD_3Cl): 168.1, 135.4, 134.6, 132.6, 128.8, 128.6, 128.1, 128.0, 127.8, 127.8, 127.4, 126.8, 60.9, 59.6, 44.6 ppm; MS (EI): *m/z* (%): 313 [M^+], 196, 180 (100), 165, 118, 91, 77, 65, 51; *trans* (corresponds to the inseparable mixture of two diastereomers): (R_f=0.3); $\tilde{\nu}_{max}$=3061, 3029, 2916, 1755, 1496, 1454, 1395, 1360, 1075, 1028, 941, 770, 753, 698, 595, 498 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.41–7.18 (m, 15H; Ar-H), 4.98 (d, J=15.0 Hz, 1H; C-H), 4.34 (d, J=2.4 Hz, 1H; C-H), 4.20 (d, J=2.4 Hz, 1H; C-H), 3.83 ppm (d, J=15.0 Hz, 1H; C-H); ^{13}C NMR (75 MHz, CD_3Cl): 168.2, 137.2, 135.6, 135.0, 129.1, 128.9, 128.8, 128.5, 127.8, 127.6, 127.4, 126.5, 65.2, 63.1, 44.6 ppm; MS (EI): *m/z* (%): 313 [M^+], 196, 180 (100), 165, 152, 118, 91, 77, 65, 51; HRMS (ESI): calcd for [$C_{22}H_{20}NO+H]^+$: 314.1539; found: 314.1534.

6b: Prepared by the same procedure described for **6a**. Yield of the two diastereomers: 75%. *cis*: $\tilde{\nu}_{max}$ = 3061, 3029, 2917, 1752, 1496, 1453, 1391, 1090, 1014, 824, 744, 721, 699, 599, 507 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.32–7.28 (m, 3H; Ar-H), 7.18 (dd, J = 8.0 Hz, 1.6 Hz, 2H; Ar-H), 7.08–6.97 (m, 7H; Ar-H), 6.88 (d, 8.4 Hz, 2H; Ar-H), 4.94 (d, J = 14.8 Hz, 1H; C-H), 4.80 (d, J = 5.6 Hz, 1H; C-H), 4.79 (d, J = 5.6 Hz, 1H; C-H), 3.89 ppm (d, J = 14.8 Hz, 1H; C-H); ^{13}C NMR (75 MHz, CD_3Cl): 167.8, 135.1, 133.6, 133.2, 132.2, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 127.8, 127.0, 60.8, 59.0, 44.7 ppm; MS (EI): *m/z* (%): 347 [M^+], 230, 214, 178, 118 (100), 91, 77, 65, 51; HRMS (ESI): calcd for $[C_{22}H_{19}NOCl+H]^+$: 348.1150; found: 348.1143; *trans*: $\tilde{\nu}_{max}$ = 3061, 3029, 2916, 1757, 1491, 1454, 1091, 1013, 751, 700, 503 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.39–7.18 (m, 14H; Ar-H), 4.96 (d, J = 16.0 Hz, 1H; C-H), 4.31 (d, J = 2.0 Hz, 1H; C-H), 4.16 (d, J = 2.0 Hz, 1H; C-H), 3.83 ppm (d, J = 16.0 Hz, 1H; C-H); ^{13}C NMR (75 MHz, CD_3Cl): 168.0, 135.7, 135.3, 134.6, 134.5, 129.3, 128.9, 128.9, 128.5, 127.9, 127.8, 127.8, 127.3, 65.2, 62.4, 44.7 ppm; MS (EI): *m/z* (%): 347 [M^+], 230, 214 (100), 178, 118, 91, 77, 65, 51; HRMS (ESI): calcd for $[C_{22}H_{19}NOCl+H]^+$: 348.1150; found: 348.1143.

6c: Prepared by the same procedure described for **6a**. Yield of the two diastereomers: 78%. *cis*: $\tilde{\nu}_{max}$ = 3061, 3029, 2917, 1757, 1496, 1488, 1454, 1390, 1070, 1010, 751, 699 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.32–7.28 (m, 3H; Ar-H), 7.25–7.22 (m, 3H; Ar-H), 7.18 (dd, J = 8.0 Hz, 1.6 Hz, 2H; Ar-H), 7.09–7.05 (m, 2H; Ar-H), 6.99–6.97 (m, 2H; Ar-H), 6.83 (d, 8.4 Hz, 2H; Ar-H), 4.95 (d, J = 14.8 Hz, 1H; C-H), 4.81 (d, J = 6.0 Hz, 1H; C-H), 4.77 (d, J = 6.0 Hz, 1H; C-H), 3.89 ppm (d, J = 14.8 Hz, 1H; C-H); ^{13}C NMR (75 MHz, CD_3Cl): 167.8, 135.1, 133.8, 132.2, 131.2, 129.1, 128.8, 128.6, 128.5, 128.2, 127.9, 127.1, 121.8, 60.8, 59.1, 44.7 ppm; MS (EI): *m/z* (%): 391 [M^+], 274, 258, 178, 165, 152, 118 (100), 91, 65, 51; HRMS (ESI): calcd for $[C_{22}H_{19}NOBr+H]^+$: 392.0644; found: 392.0638; *trans*: $\tilde{\nu}_{max}$ = 3061, 3029, 2917, 1757, 1496, 1488, 1454, 1412, 1391, 1070, 1010, 751, 699, 597, 499 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.52 (d, J = 8.4 Hz, 2H; Ar-H), 7.32–7.25 (m, 7H; Ar-H), 7.19–7.17 (m, 3H; Ar-H), 7.15 (d, J = 8.4 Hz, 2H; Ar-H), 4.96 (d, J = 16.0 Hz, 1H; C-H), 4.28 (d, J = 2.0 Hz, 1H; C-H), 4.15 (d, J = 2.0 Hz, 1H; C-H), 3.82 ppm (d, J = 16.0 Hz, 1H; C-H); ^{13}C NMR (75 MHz, CD_3Cl): 168.0, 136.3, 135.3, 134.6, 132.3, 128.9, 128.9, 128.5, 128.1, 127.9, 127.8, 127.3, 122.6, 65.2, 62.5, 44.7 ppm; MS (EI): *m/z* (%): 391 [M^+], 274, 258 (100), 178, 165, 152, 118, 91, 65, 51; HRMS (ESI): calcd for $[C_{22}H_{19}NOBr+H]^+$: 392.0644; found: 392.0639.

6d: Prepared by the same procedure described for **6a**. Yield of the two diastereomers: 80%. *cis*: $\tilde{\nu}_{max}$ = 3062, 3031, 2926, 1735, 1513, 1495, 1433, 1396, 1345, 1267, 1183, 820, 750, 700, 604, 518 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.35–7.30 (m, 3H; Ar-H), 7.22–7.20 (m, 2H; Ar-H), 7.11–7.03 (m, 5H; Ar-H), 6.94 (d, J = 8.0 Hz, 2H; Ar-H), 6.87 (d, J = 8.0 Hz, 2H; Ar-H), 5.01 (d, J = 14.8 Hz, 1H; C-H), 4.83 (d, J = 5.6 Hz, 1H; C-H), 4.81 (d, J = 5.6 Hz, 1H; C-H), 3.90 (d, J = 14.8 Hz, 1H; C-H), 2.21 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.1, 137.5, 135.4, 132.8, 131.4, 128.8, 128.7, 128.6, 128.5, 127.9, 127.7, 127.4, 126.7, 60.7, 59.4, 44.4, 21.0 ppm; MS (EI): *m/z* (%): 327 [M^+], 312, 224, 210 (100), 194, 179, 165, 118, 91, 77, 65, 51; HRMS (ESI): calcd for $[C_{23}H_{22}NO+H]^+$: 328.1696; found: 328.1689; *trans* (corresponds to the inseparable mixture of two diastereomers) : $\tilde{\nu}_{max}$ = 3062, 3029, 2924, 1752, 1496, 1454, 1395, 1355, 1043, 820, 750, 700, 604 cm^{-1}; ^1H NMR (300 MHz, CD_3Cl): 7.32–7.03 (m, 14H; Ar-H), 4.96 (d, J = 15.0 Hz, 1H; C-H), 4.31 (d, J = 2.1 Hz, 1H; C-H), 4.18 (d, J = 2.1 Hz, 1H; C-H), 3.89(d, J=15.0 Hz, 1H; C-H), 2.38 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, CD_3Cl): 168.3, 138.5, 135.6, 135.1, 134.1, 129.8, 128.8, 128.5, 127.5, 127.3, 126.5, 65.1, 62.9, 44.4, 21.2 ppm; MS (EI): *m/z* (%): 327 [M^+], 312, 224, 210 (100), 194, 179, 165, 118, 91, 77, 65, 51; HRMS (ESI): calcd for $[C_{23}H_{22}NO+H]^+$: 328.1696; found: 328.1689.

6e: Prepared by the same procedure described for **6a**. Yield of the two diastereomers: 79%. *cis* (corresponds to the inseparable mixture of two diastereomers):[21] ^1H NMR (400 MHz, CD_3Cl): 7.33–7.29 (m, 3H; Ar-H), 7.23–7.20 (m, 3H; Ar-H), 7.11–7.03 (m, 4H; Ar-H), 6.89 (d, J = 8.8 Hz, 2H; Ar-H), 6.65 (d, J = 8.8 Hz, 2H; Ar-H), 4.97 (d, J = 14.8 Hz, 1H; C-H), 4.81 (d, J = 5.6 Hz, 1H; C-H), 4.80 (d, J = 5.6 Hz, 1H; C-H), 3.89 (d, J = 14.8 Hz, 1H; C-H), 3.68 (s, 3H; OCH_3) ppm; MS (EI): *m/z* (%): 343 [M^+], 226 (100), 210, 195, 178, 165, 152, 134, 118, 104, 91, 77, 65, 51; *trans* isomer (corresponds to the inseparable mixture of two diastereomers) : $\tilde{\nu}_{max}$ = 3062, 3026, 2920, 2839, 1747, 1614, 1514, 1394, 1360, 1303, 717 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl): 7.33–7.03 (m, 12H; Ar-H), 6.94 (d, J = 8.8 Hz, 2H; Ar-H), 4.95 (d, J = 14.8 Hz, 1H; C-H), 4.32 (d, J = 2.0 Hz, 1H; C-H), 4.19 (d, J = 2.0 Hz, 1H; C-H), 3.82 (s, 3H; OCH_3), 3.81 ppm (d, J = 14.8 Hz, 1H; C-H); ^{13}C NMR (75 MHz, CD_3Cl): 168.2, 159.8, 135.6, 135.0, 128.8, 128.8, 128.4, 127.7, 127.4, 126.3, 114.4, 65.0, 62.6, 55.2, 44.3 ppm; MS (EI): *m/z* (%): 343 [M^+], 226 (100), 210, 195, 178, 165, 152, 134, 118, 104, 91, 77, 65, 51; HRMS (ESI): calcd for $[C_{23}H_{22}NO_2+H]^+$: 344.1645; found: 344.1637.

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[1] a) *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, New York, **1996**, chap. 1.18–1.20; b) *The Chemistry of β-Lactams* (Ed.: M. I. Page), Blackie Academic & Professional, New York, **1992**; c) *Chemistry and Biology of β-Lactam Antibiotics, Vol. 1–3* (Eds.: R. B. Morin, M. Gorman), Academic Press, New York, **1982**; d) I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377; e) I. Ojima, *Acc. Chem. Res.* **1995**, *28*, 383; f) P. A. Magriotis, *Angew. Chem.* **2001**, *113*, 4507; *Angew. Chem. Int. Ed.* **2001**, *40*, 4377.

[2] a) Synthesis of β-Lactam Antibiotics: Chemistry, Biocatalysis and Process Integration (Ed.: A. Bruggink), Kluwer, Dordrecht, **2001**.

[3] For reviews on the synthesis of β-lactams, see: a) *Synthesis of β-Lactam Antibiotics: Chemistry, Biocatalysis and Process Integration* (Ed.: A. Bruggink), Kluwer, Dordrecht, **2001**; b) *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), VCH, New York, **1997**; c) *The Organic Chemistry of β-Lactams* (Ed.: G. I. Georg), VCH, New York, **1993**; d) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Synlett* **2001**, 1813; e) B. Alcaide, P. Almendros, *Synlett* **2002**, 381, f) B. Alcaide, P. Almendros, *Chem. Soc. Rev.* **2001**, *30*, 226.

[4] H. Staudinger, H. W. Klever, P. Kober, *Justus Liebigs Ann. Chem.* **1910**, *374*, 1.

[5] J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.* **1955**, *77*, 1067.

[6] G. J. McGarvey, M. Kimura, *J. Org. Chem.* **1985**, *50*, 4655.

[7] a) J. C. Sheehan, A. K. Bose, *J. Am. Chem. Soc.* **1950**, *72*, 5158; b) J. C. Sheehan, A. K. Bose, *J. Am. Chem. Soc.* **1951**, *73*, 1761; c) G. Simig, G. Doleschall, G. Hornyak, J. Fetter, K. Lempert, J. Nyitral, P. Huszthy, T. Gizur, M. Kajtar-Peredy, *Tetrahedron* **1985**, *41*, 479; d) J. Fetter, K. Lempert, M. Kajtar-Peredy, G. Simig, G. Hornyak, J. Horvath, *J. Chem. Res. (S)* **1985**, 368.

[8] T. Kawabata, K. Sumi, T. Hiyama, *J. Am. Chem. Soc.* **1989**, *111*, 6843.

[9] a) A. Commercon, G. Ponsinet, *Tetrahedron Lett.* **1983**, *24*, 3725; b) H. Takahata, Y. Ohnishi, T. Yamazaki, *Heterocycles* **1980**, *14*, 467; c) R. F. Abdulla, J. C. Williams Jr., *Tetrahedron Lett.* **1980**, *21*, 997; d) S. Sebti, A. Foucaud, *Tetrahedron* **1984**, *40*, 3223; e) D. M. Floyd, A. W. Fritz, J. Plusec, E. R. Weaver, C. M. Cimarusti, *J. Org. Chem.* **1982**, *47*, 5160.

[10] a) M. Kinugasa, S. Hashimoto, *J. Chem. Soc. Chem. Commun.* **1972**, 466; b) D. K. Dutta, R. C. Boruah, J. S. Sandhu, *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **1986**, *25B(4)*, 350; c) J. Marco-Contelles, *Angew. Chem.* **2004**, *116*, 2248; *Angew. Chem. Int. Ed.* **2004**, *43*, 2198.

[11] M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem.* **1995**, *60*, 4999.

[12] a) M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 4572; b) R. Shintani, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4216; *Angew. Chem. Int. Ed.* **2003**, *42*, 4082.

[13] M.-C. Ye, J. Zhou, Z.-Z. Huang, Y. Tang, *Chem. Commun.* **2003**, 2554.
[14] L. K. Ding, W. J. Irwin, *J. Chem. Soc. Perkin Trans. 1* **1976**, 2382.
[15] a) C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268; b) J. Zhang, C. Wei, C.-J. Li, *Tetrahedron Lett.* **2002**, *43*, 5731; c) C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473; d) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584; e) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**,1472; f) Z. Li, C. Wei, L. Chen, R. S. Varma, C.-J. Li, *Tetrahedron Lett.* **2004**, *45*, 2443; g) Y. Ju, C.-J. Li, R. S. Varma, *QSAR Comb. Sci.* **2004**, *23*, 891–894; h) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810; i) C. Wei, C.-J. Li, *Lett. Org. Chem.* **2005**, *2*, 410; j) Y. Luo, Z. Li, C.-J. Li, *Org. Lett.* **2005**, *7*, 2675. For the related work on A^3- and AA^3-coupling from other groups, see: k) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; l) H. Dube, N. Gommermann, P. Knochel, *Synthesis* **2004**, 2015; m) N. Gommermann, P. Knochel, *Chem. Commun.* **2005**, 4175; n) N. Gommermann, P. Knochel, *Tetrahedron* **2005** *61*, 11418; o) S. Yasuike, C. C. Kofink, R. J. Kloetzing, N. Gommermann, K. Tappe, A. Gavryushin, P. Knochel, *Tetrahedron: Asymmetry* **2005**, *16*, 3385; p) N. Gommermann, A. Gehrig, P. Knochel, *Synlett* **2005**, 2796; q) N. Gommermann, P. Knochel, *Synlett* **2005**, 2799; r) C. Fischer, E. M. Carreira, *Org. Lett.* **2001**, *3*, 4319; s) T. F. Knoepfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 6097; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971; t) C. Fischer, E. M. Carreira, *Synthesis* **2004**, 1497.
[16] C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638; C. Wei, J. T. Mague, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5749; Z. Li, C.-J. Li, *Org. Lett.* **2004**, *6*, 4997.
[17] For references on multicomponent reactions, see: a) D. Alexander, *Chem. Rev.* **2006**, *106*, 17; b) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; c) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321; d) D. J. Vugts, H. Jansen, R. H. Schmitz, F. J. J. de Kanter, R. V. A. Orru, *Chem. Commun.* **2003**, 2594; e) R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth, M. Zeller, *Synlett* **2003**, 1536; f) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51; g) G. Dyker, K. Breitenstein, G. Henkel, *Tetrahedron: Asymmetry* **2002**, *13*, 1929; h) R. Gamez-Montano, E. Gonzalez-Zamora, P. Potier, J. P. Zhu, *Tetrahedron* **2002**, *58*, 6351; i) R. Zimmer, A. Ziemer, M. Gruner, I. Brudgam, H. Hartl, H. U. Reissig, *Synthesis* **2001**, 1649; j) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.
[18] D. A. Evans, E. B. Sjogren, *Tetrahedron Lett.* **1985**, *26*, 3783, 3787.
[19] H. Maskill, W. P. Jencks, *J. Am. Chem. Soc.* **1987**, *109*, 2062.
[20] T. Sheradsky, D. Zbaida, *J. Org. Chem.* **1980**, *45*, 2169.
[21] B. Alcaide, P. Almendros, C. Aragoncillo, N. R. Salgado, *J. Org. Chem.* **1999**, *64*, 9596.

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